The Effect of Giving Salak Fruit Skin Extract (*Salacca zalaca*) on Liver Function and Histopathology of the Liver of Male Wistar White Rats with Diabetes Mellitus

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ABSTRACT

This study was conducted to test the effect of salak fruit skin extract (Salacca zalaca) on liver function and histopathological features of the liver of male white rats with diabetes mellitus. This study used 24 Wistar rats as experimental animals, divided into 4 groups, namely the control group and treatment (P1, P2, P3) with different treatments. The results of phytochemical testing of salak fruit skin extract contained secondary metabolites such as saponins, tannins, flavonoids, alkaloids, and steroids. On the 14th day of observation, the results showed that administering salak fruit skin extract (Salacca alpaca) at 600 mg/kg BW effectively improved liver function in white rats (Rattus norvegicus) with diabetes mellitus. This improvement can be seen through the SGOT and SGPT levels and the rat liver's histological structure, which is close to the expected results. The data analysis test on the normality test using Kolmogorov Smirnov showed that the significance results in the SGOT examination were 0.677> 0.05 and SGPT 0.551> 0.05, so the data was normally distributed. The homogeneity test results for the variables of group P0, group P1, P2, and P3 were homogeneous.

Keywords: Salak Skin, Liver, SGOT, SGPT, Diabetes Mellitus

INTRODUCTION

Diabetes Mellitus is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin performance, or both. One of the main signs of diabetes is impaired insulin secretion or impaired insulin function in target organs, especially the liver and muscles. The liver breaks down toxins and produces proteins involved in digestion. Insulin and glucagon are responsible for metabolizing carbohydrates, proteins, and fats. These two hormones affect even blood sugar balance. This liver function

test aims to determine the liver's overall condition and the possibility of liver disease. SGOT and SGPT are two types of enzymes produced by liver cells used for liver function tests. Salak fruit skin (Salacca zalaca) is a plant from India and several Asian countries that has been used for a long time to help cure various health problems of people in India, China, and Southeast Asia. The study results showed that salak fruit skin (Salacca zalaca) is used as a traditional medicine because of its properties as an antibiotic, antifungal, and antioxidant. Based on several previous studies, the author wants 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 salak fruit skin extract (Salacca Palace)

LITERATURE REVIEW

High blood sugar levels indicate a chronic disease known as diabetes mellitus (DM). This disease is caused by the ineffective use of the body's insulin production or the body's inability to produce the insulin hormone. According to the article (Widyawati, 2021), diabetes is the most common long-term disease that appears today and is one of the ten most common causes of death in the world. Diabetes Mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia that occurs due to abnormalities in insulin secretion, insulin function, or both. Chronic hyperglycemia in DM is closely related to dysfunction or failure of several body organs (Spătărelu and Popa, 2021). Increasing blood glucose levels above typical values is the main sign of this disease. (Ministry of Health of the Republic of Indonesia, 2018). In its category, diabetes has two types, namely type 1 and type 2 diabetes. In type 1 diabetes, the body cannot produce the insulin hormone that helps absorb sugar in the blood into energy (Willcox, A., & Gillespie, 2015).

The liver plays a critical role in maintaining metabolic homeostasis and overall health. This can often cause the liver to become the target of toxins. This is because toxic substances enter the body through the gastrointestinal system, which is then absorbed and carried by the portal vein to the liver (Huda MN, 2017). The liver consists of vascular pathways, some connective tissues, and lobes. This process can easily cause liver cells to experience changes in cell structure or impaired function. If these toxic substances are too much in the liver, they can certainly cause various types of liver damage, such as necrosis or liver degeneration (Rosita Y, 2011). The liver maintains the body's overall health by performing various tasks, including breaking down toxins in the blood, producing proteins, and aiding in the digestive process (Polyzos SA, 2019).

Salak, or Salacca zalaca, is an exotic fruit from Southeast Asian countries such as Indonesia, Malaysia, Thailand, and Brunei Darussalam. Included in the palm group, its family is Arecaceae. The fruit's skin is scaly like a salak and reddish brown with a honey-like taste. Salak is an excellent source of antioxidants (Ismail, 2018). The antioxidant content in plants can be used to ward off free radicals and make the body stronger in warding off other disease viruses (Syaputri, 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). Compared with ethanol and water fractions of 70%, the ethyl acetate fraction showed the highest antioxidant activity of all the skin extract fractions containing high phytochemicals and antioxidants (Ismail, 2018).

METHODS

This research method controls all external variables that can affect the experimental activities. The research was conducted at the Laboratory of the Department of Pharmacology and Therapeutics, Faculty of Medicine, Universitas Sumatera Utara in May - July 2024. Ethical studies supervised by Health Research Ethics Commission (KPEK) Universitas Prima Indonesia. This study used a post-test-only group design to determine and analyze the effects of salak fruit skin extract (Salacca zalaca) on liver function and liver histopathology in male Wistar rats (Rattus norvegicus) with diabetes mellitus. The sample in this study was 24 male rats, which were divided into 4 groups. Control group (P0) treatment 1,2,3 (P1, P2, P3), were each given salak fruit skin extract at 200mg/kgBW, 400mg/kgBW, and 600mg/kgBW. Then, test the phytochemical content of salak fruit skin extract. SGOT and SGPT are used as standard indicators of liver function in research. To conduct liver function tests (SGOT-SGPT) on rats that have been declared diabetes mellitus after being induced by alloxan. After that, the process was observed for 14 days, after which the extract was given, the histopathology of the rat liver was observed, and the liver was scored. The data will be presented descriptively, with the data normality test analyzed using the Kolmogorov-Smirnov approach ($p > 0.05$). Significance testing between trial groups was carried out using the one-way variance analysis technique or One Way ANOVA at a 95% confidence level ($p < 0.05$) (Ghozali, 2018).

RESULTS

This study used male rats (Rattus norvegicus) of the Wistar strain weighing 160-200 grams and aged 2-3 months with the use of the number of research samples, namely 24 male rats, which will be divided into 4 groups where each group consists of 6 rats. Male white rats weighing 160 to 200 grams were adapted to the environment for one week, then given a dose of alloxan to make the rats hyperglycemic, namely 150 mg/kg BW intraperitoneally. Diabetic rats were taken and grouped into 4 groups, each with 6 experimental diabetic rats. Three days after alloxan induction, blood glucose levels were measured. Rats showed hyperglycemic glucose levels if the levels were ≥ 300 mg/DL and were declared diabetes mellitus.

The entire group had diabetes mellitus. The group that experienced the most drastic increase was in treatment group 1 (P1), with an average of 391 mg/DL. This indicates a reaction to increased glucose levels in rats induced by alloxan, so the rats experienced diabetes mellitus. Then, while looking at the rats' blood glucose levels, the researchers also monitored the weight of the rats before and after being induced by alloxan and after being given a treatment extract of salak fruit skin (Salacca zalaca). The group that experienced the most drastic increase was the control group (P0), with an average of 208.6 gr. This shows a reaction to increased body weight in rats that have experienced diabetes mellitus

Before treatment, secondary metabolite testing was carried out using a phytochemical test. The results of the extract of salak fruit skin (Salacca zalaca) were positive for containing active compounds such as alkaloids, flavonoids, and saponins. So, it can be said that this extract has many benefits for the skin because it has antioxidant content.

After the rats had diabetes mellitus, the extract treatment was given according to the respective doses, namely the control group (P0) without treatment, treatment 1,2,3 (P1, P2, P3), which each would be given salak fruit skin extract at a dose of 200mg/kgBW, 400mg/kgBW and 600mg/kgBW. The normal SGPT range in rats is 17.5-30.2 (IU/L), while the standard SGOT value in rats is 45.7-80.8 (IU/L). The examination showed that all groups of rats experienced abnormal liver function because the SGPT and SGOT values were above normal levels when the rats had diabetes mellitus. The highest average SGOT value before administering salak fruit skin extract (Salacca zalaca) was in group P0, with an average value and standard deviation of 215.17±16.4. Then, the highest SGPT value was in group P1, with an average value of 118.8±41.8.

Liver function for rats can be seen in Table.1 After 14 days, the treatment was given. In the control group, the rats were only given distilled water. While in the treatment group, the rats were given salak fruit skin extract (Salacca alpaca) with different doses with the results of the SGOT values that had shown expected results were in treatment group 2 (P2) with a value of 79.6 ± 12.8 then in treatment group 3 (P3) with a value of 58.17 ± 7.2. For group P1, the SGOT value exceeded the normal limit and got an average value and standard deviation of 87.6 ± 19.05. The SGPT value with the average results and standard deviation that got typical values was in group P2, 24.3 ± 3.61, then group P3, with a value of 20.17 ± 3.6. Meanwhile, group P1 had not yet obtained the expected results with a value of 30.6 ± 5.27, and group P0 had not yet obtained normal liver function results with SGOT values of 117.6 ± 11.2 and SGPT 48.33 ± 4.32.

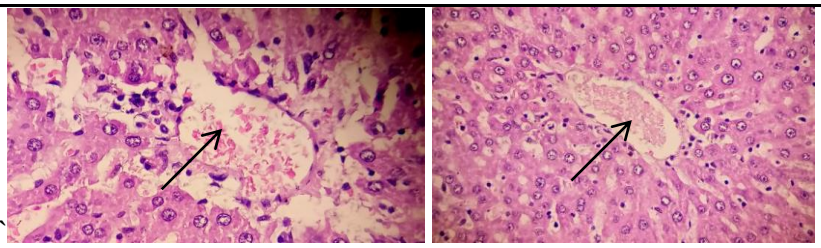
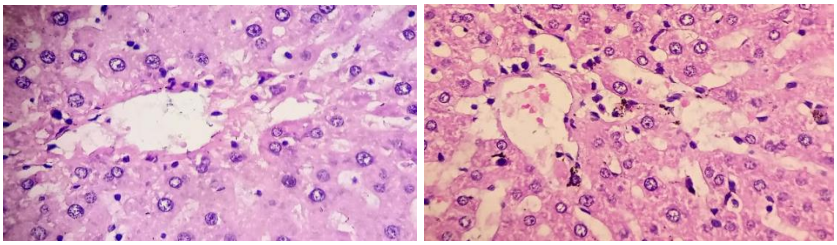
Table 1. Average Value of SGOT and SGPT

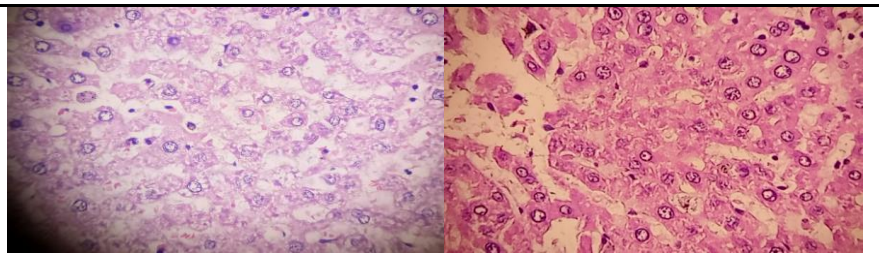
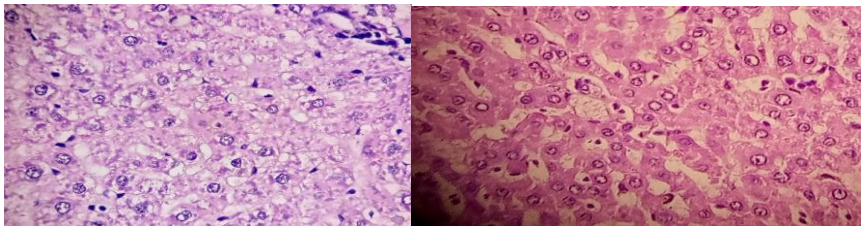
	Mean ±SD			
	H0		**H14**	
Group	**SGOT (U/L)**	**SGPT (U/L)**	**SGOT (U/L)**	**SGPT (U/L)**
P0	215.17±16.4	105±8.6	117.6±11.2	48.33±4.32
P1	205.83±31.5	118.8±41.8	87.6 ±19.05	30.6 ± 5.27
P2	204.5±16.5	106.17±9.6	79.6±12.8	24.3 ± 3.61
P3	185.8±21.9	105.3±10.09	58.17 ± 7.2	20.17 ± 3.6

From the table above, all groups of rats experienced abnormal liver function because the SGPT value was above 30.2 (IU/L) and the SGOT value was 80.8 (IU/L). So from the data above, it can be seen that the increase in values far above normal for SGOT and SGPT was found in all groups on day 0, which was precisely 14 days after the acclimatization period and was induced by alloxan which was given to the test animals so that they experienced diabetes mellitus. The highest average SGOT value before the treatment of salak fruit skin extract (Salacca zalaca) was in group P0 with an average value and standard deviation215.17±16.4. Then, the highest SGPT value was in group P1, with an average value of 118.8±41.8.

From the table above, it can also be seen after 14 days and the treatment given. For the control group, the rats were only given distilled water. While in the treatment group, the rats were given salak fruit skin extract (Salacca zalaca) with different doses with the results of SGOT values that showed expected results in treatment group 2 (P2) with values79.6 ± 12.8 then in treatment group 3 (P3) with a value of 58.17 ± 7.2. For group P1, the SGOT value has exceeded the normal limit and gets an average value and standard deviation of 87.6 ± 19.05. while the SGPT value with an average result and standard deviation that gets a typical value is in group P2 24.3 ± 3.61, then group P3 with a value of 20.17 ± 3.6. Group P1 did not obtain expected results with a value of 30.6 ± 5.27, and group P0 did not obtain normal liver function results with SGOT values of 117.6 ± 11.2 and SGPT 48.33 ± 4.32. thus, the extract-salak fruit skin extract (Salacca zalaca), which is given to male Wistar rats (Rattus norvegicus) for 14 days of treatment, obtained significant results to restore liver function to normal after the test animals underwent an acclimatization period and were induced by alloxan to develop DM for 14 days.

Table 2. Histopathological Description of Rat Liver Function

Group	Histopathological Image Results of Rat Liver Function
Control (PO)	
Treatment P1	

P2 Treatment	
P3 Treatment	

Histopathologic results from Table 2 describe control group 1, a microscopic image of the liver of Wistar rats in the Control group (P0). Fatty degeneration (white arrow), necrotic congestion, and inflammatory cell infiltration are visible. The score is 4, which means necrosis is seen in the liver cells. Group P1 treatment shows a microscopic picture of the liver of rats in treatment group 1 (P1). In this group, there was a picture of quite a lot of fatty liver degeneration, which was spread, parenchymatous degeneration or bleeding in the liver cells, and inflammatory cell infiltration. The score in this group was 3, which means there were changes in the form of hydropic degeneration. Group P2 treatment shows a microscopic image of rats' livers in Treatment Group 2 (P2). The liver shows fatty degeneration, congestion, and inflammatory cell infiltration. The scoring for this group is 2. Group P3 treatment shows a microscopic image of the liver of rats in treatment group 3 (P3). It looks normal; no inflammation is seen, cells are starting to improve, and no necrosis and fatty deposits are seen. The scoring for this image is 1, which is normal. After conducting histopathological descriptions, the researchers analyzed the liver function data results by testing the data on the SPSS for Windows application for data analysis.

Table 3. Normality Test for SGPT and SGOT value

One-Sample Kolmogorov-Smirnov Test			
		SGOT	SGPT
N		24	24
Normal Parametersa,b	Mean	85.79	30.88
	Std. Deviation	25.205	11,678
Most Extreme Differences	Absolute	.147	.162
	Positive	.147	.162
	Negative	-.103	-.117
Kolmogorov-Smirnov Z		.720	.796
Asymp. Sig. (2-tailed)		.677	.551

Normality test in **Table.3**, 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 SGOT examination 0.677> 0.05 and SGPT 0.551> 0.05 so the data is normally distributed.

Table 4. Results for *ANOVA test*

		df	**Mean Square**	**F**	**Sig.**
SGOT	Between Groups	3	3640.375	19,727	.000
	Within Groups	20	184,542		
	Total	23			
SGPT	Between Groups	3	924,597	50,965	.000
	Within Groups	20	18,142		
	Total	23			

From the test results in **table.4** the significance value at a 95% confidence level (p <0.05) is 0.00 for SGOT liver function and a significant value of 0.00 for SGPT liver function. So that there is a significant difference in each average value between sample groups. The conclusion obtained is that there is or there is a significant difference in the average (mean) percentage of liver 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.
SGOT	2,850	3	20	.063
SGPT	.435	3	20	.730

The results in **Table.5** show a variance of the research data for the variables of group P0, group P1, P2 and group P3 is homogeneous or comes from a population that has the same variance, namely 0.063 (p>0.05) for the analysis data of SGOT liver function on the 14th day during the treatment of salak fruit skin extract and the significance of SGPT 0.730 (p>0.05) for the analysis of SGPT liver function on the 14th day during the treatment of salak fruit skin extract (*Salacca zalaca*).

DISCUSSION

The liver is an important organ of the body that is responsible for the metabolism of toxic substances. This can cause the liver to become a target for toxins often because toxic substances enter the body through the gastrointestinal system, which is then absorbed and carried by the portal vein to the liver (Huda MN, 2017). The liver takes up little space in the upper left abdomen due to its large size. The liver comprises a network of vessels, some connective tissue, and lobes. This process can easily cause liver cells to experience cell structure or dysfunction changes. If the toxic substance is too much in the liver, it can certainly cause various types of liver damage, such as necrosis or liver degeneration (Rosita Y, 2011).

This study used male rats (Rattus norvegicus) Wistar strain, namely 24 male rats, which will be divided into 4 groups, each consisting of 6 rats. Then, the rats were given a dose of alloxan to make the rats hyperglycemic, namely 150 mg/kg BW intraperitoneally. If the rat weighs 160-200 grams, then the alloxan given is 30 grams. Alloxan monohydrate powder was weighed as much as 1.2 grams and then dissolved with sterile injection, which equates to 100 mL. Then, the rats were given treatment with salak fruit skin extract (Salacca zalaca). Salak is an extraordinary source of antioxidants (Ismail, NA, & Abu Bakar, 2018). The salak fruit plant is thorny and can reach a height of six meters. It can produce fruit for fifty years. Salak fruit grows in damp and low places. The trunk is large and has shiny dark green pinnate leaves. At the base of the tree, many oval-shaped fruits are gathered. Inside the fruit, dark brown seeds are segmented (Ridho, A., Wathoni, N., Subarnas, A., & Levita, 2019).

Before being given the salak extract, the rats were first measured for weight and blood sugar during a two-week acclimation process. Then, the rats were induced with alloxan. Rats given a dose of alloxan to make rat hyperglycemia, which is 150 mg/kg BW intraperitoneally; if the rat's body weight is 160-200 grams, then the alloxan given is 30 grams, alloxan monohydrate powder is weighed as much as 1.2 grams then dissolved with sterile injection equates to up to 100 mL. Diabetic rats were taken and grouped into 4 groups, each with 6 experimental diabetic rats. After the rats were diagnosed with diabetes mellitus (DM)

The examination of the average blood glucose levels (KGD) in rats showed that the rats experienced an increase after 14 days of Alloxan induction. It can be seen that the entire group has experienced diabetes mellitus. The group that experienced the most drastic increase was treatment group 1 (P1), with an average of 391mg/dL. This shows a reaction to increased glucose levels in rats induced by alloxan so that the rats experience diabetes mellitus. Then, after being given the treatment of extract-salak fruit skin (Salacca zalaca), the group control (K) experienced an average increase with KGD results of 354.67mg/dL.

In contrast, in groups P1, P2, and P3, there was a decrease in blood sugar levels, and it was shown that they did not have diabetes mellitus. The lowest results were in group P3, with KGD 107.16mg/DL. Then, while observing the rats' blood glucose levels, the researchers also monitored the weight of the rats before and after being induced by alloxan and after being given treatment—salak fruit skin extract (Salacca zalaca). From the observation results, The group that experienced the most drastic increase was the control group (K) with an average of 208.6 gr. This shows a reaction to increased body weight in rats that have experienced diabetes mellitus. Then, after being given the extract treatments, fruit skin

(Salacca zalaca), as seen in the group control (K), experienced an increase in average body weight with a difference of 11.6 gr. At the same time, groups P1, P2, and P3 experienced a decrease in body weight of up to 34.8 gr on the average body weight of rats in group P3.

After observing the weight and glucose levels of the rats (KGD), the rats were tested again for SGPT and SGOT levels. The usual range of SGPT values in rats is 17.5-30.2 (IU/L), while the expected value of SGOT in rats is 45.7-80.8 (IU/L). The observation results showed that all groups of rats experienced abnormal liver function because they obtained values above the standard threshold. The highest average SGOT value before the treatment of salak fruit skin extract (Salacca zalaca) was in group P0 with an average value and standard deviation of215.17±16.4. Then, the highest SGPT value was in group P1, with an average value of 118.8±41.8.

Meanwhile, in the treatment group, rats were given salak fruit skin extract (Salacca zalaca) with a dose of P0 group, P1, P2, and P3 with alloxan induction, and 200 mg/kgBW, 400 mg/kgBW, 600 mg/kgBW and were given salak fruit skin extract /day/head orally using a probe, for 14 days showed SGOT results with normal results in treatment group 2 (P2) with a value of 200 mg/kg BW, 400 mg/kgBW, 600 mg/kg BW and were given salak fruit skin extract /day/head orally using a probe, for 14 days.79.6 ± 12.8 then in treatment group 3 (P3) with a value of 58.17 ± 7.2. For group P1, the SGOT value has exceeded the normal limit and gets an average value and standard deviation of 87.6 ± 19.05. Moreover, the SGPT value with the average and standard deviation results that get normal values are in group P2 24.3 ± 3.61 then group P3 with a value of 20.17 ± 3.6. Group P1 did not obtain normal results with a value of 30.6 ± 5.27, and group P0 did not obtain normal liver function results with SGOT values of 117.6 ± 11.2 and SGPT 48.33 ± 4.32. thus, the extract-salak fruit skin extract (Salacca zalaca), which is given to male Wistar rats (Rattus norvegicus) for 14 days of treatment, obtained significant results to restore liver function to normal after the test animals underwent an acclimatization period and were induced by alloxan to develop DM for 14 days.

In line with that, the histological picture shows that the Control group (P0) shows a picture of fatty degeneration (white arrow), necrotic congestion, and inflammatory cell infiltration. The scoring is 4, namely necrosis in liver cells. Treatment group 1 (P1) shows a picture of fatty degeneration in the liver that is quite widespread, parenchymatous degeneration or bleeding in liver cells, and inflammatory cell infiltration; the scoring in this group is 3. Namely, there are changes in the form of hydropic degeneration. Treatment group 2 (P2). The picture of the

liver experiencing fatty degeneration, congestion, and inflammatory cell infiltration, the scoring for this group is score 2. Treatment group 3 (P3). It looks normal. No inflammation is seen, cells are starting to improve, and no necrosis and fatty deposits are seen. The scoring for this picture is 1, namely regular. The secondary metabolite content found in salak fruit skin extract (Salaca Zalacca) can repair damaged cell tissue due to induction and diabetes mellitus conditions experienced by white rats of the Wistar strain. This is in line with previous research (Muharli Qadri Kanon, 2019) which successfully tested salak skin's effectiveness in lowering blood sugar in sucrose-induced rats and was successful. So, salak skin extract is potent against lowering blood sugar levels in rats with diabetes mellitus. Moreover, in line with the research (Nuralifah 2022), which has the results of research on the liver function of rats experiencing diabetes Mellitus, it began to improve after being given traditional red gedi plant extracts. If diabetes mellitus can be restored, the liver function of rats will also improve.

In data analysis testing the normality test using Kolmogorov Smirnov analysis, the 2-tailed significance results for the SGOT examination were 0.677 > 0.05 and SGPT 0.551 > 0.05, so the data was normally distributed. Homogeneity test results for the variable group P0, group P1, P2, and group P3 are homogeneous or come from a population that has the same variance, namely 0.063 (p> 0.05) for the analysis data of SGOT liver function on the 14th day during the treatment of salak fruit skin extract and the significance of SGPT 0.730 (p> 0.05) analysis of SGPT liver function on the 14th day during the treatment of salak fruit skin extract (Salacca zalaca). Moreover, in the one-way ANOVA significance test, the significance value at a 95% confidence level (p <0.05) is 0.00 for SGOT liver function and a significant value of 0.00 for SGPT liver function. So, sample groups have a significant difference in each average value. This means that Ho is rejected, so the conclusion is that there is or is a significant difference in the average (mean) percentage of liver function in the three groups.

CONCLUSION

This study, it was found that there was an effect of giving salak fruit skin extract (Salacca zalaca) on liver function and histopathological features of the liver of male Wistar strain white rats with diabetes mellitus with the results of improved liver function in rats as measured by SGOT and SGPT levels which had improved. Salak fruit skin extract (Salacca zalaca) 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. Administration of salak fruit skin extract (Salacca zalaca) at 600mg/KgBB effectively improves liver function in white rats (Rattus norvegicus) Wistar strain with diabetes mellitus. This improvement can be seen through SGOT and SGPT levels and the rat liver's histological structure, which is close to the expected results. The results of histopathological observations of kidney tissue in treatment group 3, namely salak fruit skin extract (Salacca zalaca) at a dose of 600mg/KgBB, experienced the most significant improvement and was close to normal.

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