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Hepatoprotective Effects Of Several Doses Of Nanoherbal Andaliman Extract (Zanthoxylum Acanthopodium) On Liver Function And Histopathology In Streptozotocin-Induced Diabetic Male Wistar Rats For 2 Weeks

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Abstract : Background: Diabetes particularly type 2 can increase the risk of developing Non-Alcoholic Fatty Liver Disease (NAFLD) through key mechanisms such as insulin resistance. Insulin resistance, where the body is unable to use insulin effectively, leads to increased levels of glucose and fat in the blood. This condition promotes the accumulation of fat in the liver, which

in turn leads to inflammation and damage to liver cells. The andaliman nanoherbal has antioxidant properties that can affect the body. Objective: This study aimed to evaluate the impact of andaliman nanoherbal on liver function and histopathological features of the liver. Methods: The study was conducted with an experimental approach using a post-test-only control group design on 30 male Wistar rats induced with streptozosin. The rats were divided into 6 groups, with andaliman nanoherbal as the test material. Results: There was no significant difference in liver function (SGOT and SGPT) between the groups that received andaliman and those that did not, with p values of 0.183 and 0.449 ($p>0.05$). However, there was a significant difference in liver histopathological features between the two groups with a p value of 0.03 ($p<0.05$), indicating that the group receiving andaliman had liver degeneration. Conclusion: The andaliman nanoherbal exhibits antioxidant effects that serve as hepatoprotectors, but also contains substances that can potentially cause damage to liver cells. The authors recommend increasing the number of samples, conducting pre-test and post-test examinations, and analyzing the effects of steroids and terpenoids in andaliman on liver cells

Keywords: Andaliman, Nanoherbal, SGOT, SGPT, Liver Histopathology

INTRODUCTION

Diabetes mellitus is a chronic disease characterized by high levels of sugar (glucose) in the blood. Diabetes occurs when the body is unable to produce enough insulin (a hormone produced by the pancreas) or is unable to use insulin effectively. Insulin plays an important role in helping glucose enter the body's cells to be used as energy.[1,2] Data in 2018, the prevalence of diabetes in men in Indonesia increased to 8.5%, while the prevalence of diabetes mellitus in North Sumatra province increased from 1.8% in 2013 to 2.0% in 2018. In the liver of

[1] Perkeni, P. E. I., 2021. Pedoman Pengelolaan Dan Pencegahan Diabetes Melitus Tipe 2 Dewasa Di Indonesia 2021. S.L.:Pb. Perkeni.

[2] ADA, A. D. A., 2018. Standards of Medical Care in Diabetes - 2018. The Journal of Clinical and Applied Research and Education, Volume 41.

diabetic patients, changes occur called Non-Alcoholic Fatty Liver Disease (NAFLD), where steatosis, fibrosis, and inflammation occur in the liver lobules.[3]

Andaliman (Zanthoxylum acanthopodium) is a spice plant widely found in North Sumatra, Indonesia, and originates from Dairi Regency in North Sumatra Province. Andaliman is known to have antimicrobial effects and can inhibit bacterial growth, its effects as an antioxidant and hepatoprotective. Andaliman extract contains alkaloids, steroids, and terpenoids that have antioxidant and antimicrobial effects.[4] Andaliman (Zanthoxylum acanthopodium) has great potential in the treatment of diabetes. The bioactive compounds in Andaliman may help lower blood sugar levels by increasing insulin sensitivity or slowing glucose absorption. In addition, Andaliman has hepatoprotective properties that may protect vital organs, such as the liver, from diabetes-induced damage by reducing inflammation and oxidative stress. Andaliman can also help prevent diabetic complications, such as nerve damage, heart disease and kidney problems, thanks to its antioxidant and anti-inflammatory properties.[5]

Nanotechnology is a solution to help optimize the use of Andaliman as a medicine for diabetes, nanotechnology has the advantage of being able to produce herbal medicine preparations on a smaller scale, with a size range of 10 - 100 nm. Nanotechnology plays an important role in increasing the effectiveness of drug active ingredients by improving the bioavailability, absorption, and distribution of active substances in the body.[6] With nanotechnology, active ingredients can be converted into nano-sized particles, which allows for better absorption through biological membranes and increases the ability of active

[3] RISKESDAS, B. P. d. P. K. K. R. I., 2018. Riset Kesehatan Dasar (RISKESDAS) 2018. s.l.:s.n.

[4] Sangeeta Kini, P. T. A. D. A., 2016. Histopathology of Liver in Diabetes Melitus Autopsy Study. International Journal of Scientific Study, 4(5), pp. 110-113.

[5] Hafiz Muhammad Bilal, F. R. K. M. A. S. M. R. S., 2016. Histological changes in the liver of diabetic rats: A review of pathogenesis of nonalcoholic fatty liver disease in type 1 diabetes mellitus. Cogent Medicine, Volume 3, pp. 1-9.

[6] Putri Cahaya Situmorang, S. I. S. H. R., 2019. Effect of Nanoherbal Andaliman (Zanthoxylum acanthopodium) and Extra Virgin Olive Oil Combination on Preeclamptic Rats Liver Histology. Macedonian Journal of Medical Sciences, 7(14), pp. 2226 - 2231.

ingredients to reach target organs more precisely. This technology can also help reduce the required dosage, minimize side effects, and improve the safety profile of drugs. In the context of using Andaliman as an herbal medicine, nanotechnology can be used to make Andaliman extract in nano form, so that the bioavailability and absorption of its active substances are increased, resulting in more effective therapeutic effects and fewer side effects for patients.[7]

Some previous studies have shown that andaliman nanoherbs can reduce liver cell degeneration and necrosis. There has been no research on the effect of andaliman nanoherbs on liver function and liver histopathology of STZ-induced male Wistar rats, so researchers are interested in examining this. Thus, the novelty of this study lies in exploring the effect of Andaliman nanoherbs on liver function and liver histopathology of male Wistar rats induced by streptozotocin (STZ), which has never been done before.

Previous research stated that manoemulsion of Andaliman fruit extract (Zanthoxylum acanthopodium DC) at a dose of 25 mg/KgBB was effective in improving triglyceride levels and increasing HDL in STZ-induced Wistar rats.[8] This nanoemulsion form is the most effective because it is able to reduce the amount of dosage needed compared to other dosage forms. The purpose of this study was to determine the effect of andaliman (Zanthoxylum acanthopodium) nanoherbs on liver function and liver histopathology picture of streptozocin-induced diabetic male Wistar rats.

LITERATURE REVIEW

Theoretical Foundations

Diabetes Mellitus (DM) is a metabolic disease with an increase in blood sugar levels or hyperglycemia caused by abnormalities in the secretion of the hormone insulin, its mechanism of action, and both.[9] In patients with DM, changes in the liver occur in *Non-Alcoholic Fatty Liver Disease* (NAFLD) with risk

[7] Berlian Hanutami N P, A. B., 2017. Review Artikel : Penggunaan Teknologi Nano Pada Formulasi Obat Herbal. Farmaka, 15(2), pp. 29 - 41.

[8] Tanessa, M., Praboswara, G. A., Chiuman, L., & Kotsasi, F. (2023). Efektivitas dari nanoemulsi ekstrak Andaliman. Gorontalo Journal Health and Science, 7(1), 27-34.

[9] Sangeeta Kini, P. T. A. D. A., 2016. Histopathology of Liver in Diabetes Melitus Autopsy Study. International Journal of Scientific Study, 4(5), pp. 110-113.

factors none other than DM, Obesity, and dyslipidemia. The underlying mechanism of NAFLD in patients with DM is caused by insulin resistance and oxidation of fatty acids resulting in fibrosis due to an increase in the amount of connective tissue in the liver and the process of *remodeling*. In addition, there can be steatosis, inflammation of the lobules and portal system.[10]

A liver function examination is a type of blood test to assess the condition of a person's liver. Those included in the liver function examination are SGOT (or AST, Aspartate Transaminase), derived from the cytoplasm and mitochondria of liver cells, and heart muscle or skeletal muscle as well as SGPT (or ALT, Alanine Transaminase), which comes from the cytoplasm of hepatic cells.[11] Elevated levels of SGOT and SGPT can indicate *cholestasis* or hepatocellular damage. In patients with DM, there is an increase in liver function, especially SGOT, and SGPT. This is due to the hepatotoxic effect of fatty acid accumulation due to the mechanism of insulin resistance in diabetic patients.[12]

Andaliman (*Zanthoxylum acanthopodium*) is a spice plant that is generally used as a cooking spice in the North Sumatra Province area. Currently, andaliman has begun to be used as a natural preservative, medicine, and supplement, as well as as a pesticide ingredient. Andaliman is known to have an antimicrobial effect and can inhibit the growth of bacteria such as *Escherichia coli, Bacillus cereus,* and *Staphylococcus aureus* as well as fungi such as *Pseudomonas fluorescens* and *Aspergillus flavus*. Andaliman also has an antioxidant effect, which is played by N-butanol compounds and terpenoids from andaliman fruit extract. Andaliman also contains glycoproteins that have an effect as antioxidants and

[10] Hafiz Muhammad Bilal, F. R. K. M. A. S. M. R. S., 2016. Histological changes in the liver of diabetic rats: A review of pathogenesis of nonalcoholic fatty liver disease in type 1 diabetes mellitus. Cogent Medicine, Volume 3, pp. 1-9.

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[12] Christofora Hanny Wijaya, F. I. N. V. K. &. S. I., 2019. A review of the bioactivity and flavor properties of the exotic spice "andaliman: (Zanthoxylum acanthopodium DC).. Food Reviews International, 35(1), pp. 1 - 19.

hepatoprotective agents. Andaliman contains alkaloids, flavonoids, and terpenoids that act as anti-inflammatory and antioxidants.[13]

Nanotechnology is a process that can change the size of herbal medicine molecules to a smaller size in the range of 10 – 100 nm.[14] Nanotechnology is also one of the solutions for increasing the bioavailability, absorption, and distribution of active substances in the blood to increase the efficacy of herbal medicines.[15] The process of making andaliman nanoherbs begins with Andaliman fruits that have been cleaned and dried, then mashed and processed with *High Energy Milling* (HEM) for 2 hours, where andaliman particles will be converted into smaller molecules. The molecular size of the nano herbal andaliman was then analyzed using a *Particle Size Analyzer* (PSA) so that the desired dose was obtained.[16]

RESEARCH METHODS

This study uses an experimental method with *the post test-only control group design* using random sampling. The research was carried out at the FK UNPRI Laboratory for two months starting from October to December 2022. The study was conducted on test animals, namely white rats (*Rattus noverticus*) male Wistar strain aged 6 to 8 weeks who had a body weight of 160-200 grams in 30 animals, with chemicals namely Nanoemulsion Andaliman 5%, Metformin, Streptozotocin, and Ethanol 96%. The tools used in this study were *ovens, evaporators, blenders,* 40 *mesh* sieves, spectrophotometers, digital scales, *Buchner*

[13] iwa Aulia Ahmad, I. A. A. K. F. H. M. L. L., 2021. ANTIINFLAMASI NANOPARTIKEL BUAH ANDALIMAN (ZANTHOXYLUM ACANTHOPODIUM DC.) PADA ATEROSKLEROSIS : INTERAKSI ENDOTELIAL HSP70. Jurnal Ilmiah Simantek, 5(2), pp. 137 - 142.

[14] P C Situmorang, S. I. S. H., 2019. Effect of Combination of Nano Herbal Andaliman (Zanthoxylum acanthopodium DC.) and Extra Virgin Olive Oil (EVOO) to Kidney Histology of Preeclampsia Rats. IOP Conf. Series: Earth and Environmental Science, Volume 305, pp. 1 - 6.

[15] P C Situmorang, S. I. S. H., 2019. Effect of Combination of Nano Herbal Andaliman (Zanthoxylum acanthopodium DC.) and Extra Virgin Olive Oil (EVOO) to Kidney Histology of Preeclampsia Rats. IOP Conf. Series: Earth and Environmental Science, Volume 305, pp. 1 - 6.

[16] Putri C. Situmorang, S. I. S. H. R. R. D. M., 2020. Acute Toxicity Test and Histological Description of Organs After Giving Nano Herbal Andaliman (Zanthoxylum acanthopodium). Rasayan Journal Chem, 13(2), pp. 780 - 788.

funnels, filter paper, glassware and test tubes, 30G 1cc syringes, *scalpels* and *blades*, stirrers, *handscoons*, and equipment for documentation.

The process of making andaliman extract comes from andaliman fruit that has been dried and then mashed with a crushing machine before being sifted in a 40 mesh sieve. The material was crushed and then weighed by 700 grams and then extracted by maceration using methanol with a solvent ratio of 1:3 for 24 hours. Next, it will be concentrated using an evaporator with a temperature of 55°C until a concentrated extract is obtained.

The preparation of nanoemulsion from andaliman extract began by dissolving 0.2 g methylparaben and 0.1 g propyl paraben in 100 mL of heated distilled water, then cooling the solution. Next, Tween 80 was added to the cooled distilled water and stirred using a magnetic stirrer at 5000 rpm for 30 minutes, resulting in Mass 1. Mass 2 was prepared by mixing Polyethylene Glycol (PEG) 400 with andaliman extract, then stirring at 5000 rpm for 20 minutes. Mass 1 and Mass 2 were slowly combined using a drop pipette and stirred again at 5000 rpm for 8 hours. The process was concluded with sonication to optimize the particle size and stability of the nanoemulsion. Characterization of the nanoemulsion included particle size and distribution measurements using techniques such as Dynamic Light Scattering (DLS) as well as stability evaluation to ensure the nanoemulsion remained homogeneous and did not agglomerate.

The doses of Andaliman extract given to each treatment group were 25mg/kgBB, 50mg/kgBB, and 75mg/kgBB. The STZ dose given to test animals is 45mg/kgBB. The treatment carried out in the group is as follows:

(1) Group 1 (1-5) is a normal group that is only given standard food and drinks without any treatment.
(2) Group 2 (6-10) was a negative control that was given standard food and beverages without 5% Andaliman Nanoemulsion, and induced STZ 45mg/kgBB on the first day.
(3) Group 3 (11-15) is a positive control group that is given standard food and beverages without 5% Andaliman Nanoemulsion, induced STZ 45mg/kgBB, and Metformin according to the required dose

(4) Group 4 (16-20) is treatment group 1 which is given standard food and beverages with 5% Andaliman Nanoemulsion of 25mg/kgBB for 14 days and induced STZ 45mg/kgBB.
(5) Group 5 (21-25) is the 2nd treatment group which was given standard food and beverages with 5% Andaliman Nanoemulsion of 50mg/kgBB for 14 days and induced STZ 45mg/kgBB.
(6) Group 6 (26-30) is treatment group 3 which is given standard food and beverages with 5% Andaliman Nanoemulsion as much as 75mg/kgBB for 14 days and induced STZ 45mg/kgBB.

Data analysis of this study used Kruskal-Wallis and Chi-square tests to test for differences and associations in treatment outcomes. The Kruskal-Wallis test was applied to compare differences in liver function (SGOT and SGPT) among several treatment groups, given that the data were not normally distributed or ordinal in nature. This test is useful to determine whether there is a significant difference between groups given various doses of Andaliman nanoemulsion compared to the negative and positive controls. Meanwhile, the Chi-square test was used to analyze categorical data from liver histopathology examinations, to identify any differences or associations in histopathological conditions between treatment and control groups. The histopathology procedure involved removal of liver tissue from the test animals, fixation in formalin, processing with paraffin embedding, and thin tissue sectioning for preparation. These preparations were then stained with hematoxylin-eosin (H&E) stain and examined under a microscope to assess liver damage and histopathological changes that may have occurred because of the treatment.

RESULT AND DISCUSSION

RESEARCH RESULT

1. Characteristics of andaliman fruit extract

Andaman fruit is extracted using maceration to obtain methanol extract with its characteristics as in the table below:

Table 1 Characteristics of Andaliman Methanol Extract

Characteristic	Value
Fresh Simplisia Weight (g)	2kg

Weight of Dry Simplicia Powder (g)	700g
Solvent Volume (ml)	5000ml
Extract Weight (g)	75.3g
Rendemen (%)	10,76%

From 2kg of fresh andaliman fruit, 75.3g of extract was obtained which yielded 10.76% of the yield. Based on the results of phytochemical screening of methanol andaliman extract, compounds such as flavonoids, alkaloids, saponins, and glycosides were obtained.

2. SGOT and SGPT Examination Results

Table 2 Results of SGOT and SGPT Examination

Treatment Groups	The function of the Liver	
	SGOT (U/L)	SGPT (U/L)
Usual	183 (48 – 481)	221 (38 – 565)
Negative Control	73 (54 – 96)	100 (34 – 262)
Positive Control	147 (75 – 209)	148 (44 – 241)
Nanoemulsion of andaliman extract 25mg/kgBB	130 (81 – 159)	142 (121 – 166)
Nanoemulsion of andaliman extract 50mg/kgBB	69 (53 – 111)	73 (46 – 145)
Nanoemulsion of andaliman extract 75mg/kgBB	92 (58 – 142)	60 (55 – 372)
P value	0,304	0,504

Based on the normality test, abnormal distributed data ($p<0.05$) was obtained and the Kruskal Wallis test was carried out, both SGOT and SGPT values of $p>0.05$ were obtained so that there was no difference in liver function after the administration of andaliman nanoherbs in the group given andaliman nanoherbs and the group that was not given andaliman nanoherbs.

3. Results of Liver Histopathology Examination

Table 3 Results of Liver Histopathology Examination

Treatment Groups	Histopathology of the liver		P Value
	Normal	Degenerate	
Normal	5	0	0,03
Negative Control	5	0	
Positive Control	5	0	
Nanoemulsion of andaliman extract 25mg/kgBB	3	2	
Nanoemulsion of andaliman extract 50mg/kgBB	3	2	
Nanoemulsion of andaliman extract 75mg/kgBB	3	2	

Based on the normality test, abnormal distributed data ($p<0.05$) was obtained and the Chi-square hypothesis test was carried out, a value of $p<0.05$ was obtained so that there was a difference in the histopathological picture of the liver after the administration of andaliman nanoherbs in the group given andaliman nanoherbs and those who were not given andaliman nanoherbs.

DISCUSSION

Increased aminotransferase enzyme is one of the signs of liver damage and is commonly found in diabetic conditions, where this can be caused by liver cell damage due to streptozotocin induction. Nanoherbal andaliman has a higher antioxidant content than the form of andaliman extract.[17] Based on the results of the analysis of andaliman's phytochemical compounds, there are alkaloids, flavonoids, saponins, and glycosides that have antioxidant roles. This compound can inhibit free radicals and reduce oxidative stress which is thought to inhibit the body's cell damage process.[18]

[17] Norman D Salih, G. H. K. R. M. N. R. K. M., 2014. The effect of streptozotocin induced diabetes mellitus on liver activity in mice. Global Journal on Advances in Pure & Applied Sciences, Volume 3, pp. 67 - 75.

[18] Muhammad Zafar, S. N.-u.-H. N. M. A. &. Z. A. K., 2009. Altered Liver Morphology and Enzymes in Streptozotocin Induced Diabetic Rats. Int. J. Morphol., pp. 719 - 725.

Based on the results of SGOT and SGPT examinations, there was no significant difference between the group given nanoherbs and the group that was not given nanoherbs with a p-value of >0.05. According to Hartono, et al. the normal SGOT value in white rats was 45.7 – 80.8 U/L while the normal SGPT value in rats was 17.5 – 30.2 U/L.[19] However, based on the data distribution table, it appeared that the SGOT value of the test group given andaliman nanoherb was lower than that of the normal group and the control was positive, especially at a dose of 50mg/kgBB with a mean value of 69 U/L. Meanwhile, the SGPT value appeared lower in the group given 75mg/kgBB nanoherb with a mean value of 69 U/L. This is suspected to be due to the results of the examination that were not normally distributed in the normal and control groups, where the SGOT and SGPT values in the experimental animals exceeded the normal values.[20] The results of the examination of the sample could not be excluded due to the limited number of test animals, so the results of data analysis were obtained as follows. The results obtained are under previous research, where alkaloid compounds that are also found in andaliman nano herbs can function as hepatoprotective and help reduce SGOT and SGPT levels due to free radicals. Previous research has also stated that plant extracts containing flavonoid compounds can function as hepatoprotection and can reduce SGOT and SGPT levels. In contrast to other studies that state that the administration of nanoherbal andaliman increases the levels of SGOT and SGPT in Rats.[21]

Based on the results of the examination of the histopathological picture of the liver, there was a significant difference between the group that was given nanoherbs and those who were not given nanoherbs andaliman with a p-value of

[19] Dina Sembiring, J. L., 2020. Hepatotoksisitas dan Aktivitas Hepatoprotektif Tanaman Malvaviscus. Farmaka, 17(3), pp. 142 - 150.

[20] Bambang Sujatmiko, W. D. I. P., 2021. Aktivitas Hepatoprotektor Dari Ekstrak Etanol Kerang Ale-Ale (Meretrix sp.). Jurnal Laut Khatulistiwa, 5(1), pp. 50 - 55.

[21] Putri Cahaya Situmorang, S. I. S. H. R. R., 2019. Effect of Nanoherbal Andaliman (Zanthoxylum acanthopodium) and Extra Virgin Olive Oil Combination on Preeclamptic Rats Liver Histology. Journal of Medical Sciences, Volume 7, pp. 2226-2231.

<0.05.[22] Where neither the positive nor negative control group found any degeneration or hepatic necrosis. In the test group, several samples were found to have degeneration and none had necrosis, with the highest number found in the group given nanoherbs 75mg/kgBB with 3 samples experiencing hepatic degeneration.[23] This is in line with previous studies that showed changes in the histopathology of the liver to degeneration, and damage to be aggravated in the group with larger doses, as well as increased hepatocyte damage. This is thought to be due to the presence of steroid compounds and terpenoids that can damage the liver.[24]

CONCLUSION

Based on the results of the study, there was no significant difference in liver function (SGOT and SGPT) between the group that was given andaliman nanoherbs and those who were not given andaliman nanoherbs. There was a decrease in SGOT and SGPT levels in the group given andaliman nanoherbs, andaliman is known to have an antioxidant effect that can be hepatoprotective. Meanwhile, there was a significant difference in the histopathological picture of the liver, whereas, in the test group given nanoherbal andaliman, there were samples that experienced hepatic degeneration. But in addition to antioxidants, other compounds such as steroids and terpenoids can damage liver cells. Therefore, the researchers concluded that the administration of nanoherbal andaliman can reduce SGOT and SGPT levels, but on the other hand, it can also cause liver cell degeneration.

The disadvantage of this study is the limited number of samples, so that when liver function is examined, and there are samples that have examination results outside the normal value cannot be excluded and affect the results of data

[22] Putri Cahaya Situmorang, S. I. S. H. R., 2019. Effect of Nanoherbal Andaliman (Zanthoxylum acanthopodium) and Extra Virgin Olive Oil Combination on Preeclamptic Rats Liver Histology. Macedonian Journal of Medical Sciences, 7(14), pp. 2226 - 2231.

[23] Putri C. Situmorang, S. I. S. H. R. R. D. M., 2020. Acute Toxicity Test and Histological Description of Organs After Giving Nano Herbal Andaliman (Zanthoxylum acanthopodium). Rasayan Journal Chem, 13(2), pp. 780 - 788.

[24] E Sabri, S. I. E. P., 2018. The effect of n-hexane extract of andaliman (Zanthoxylum acanthopodium DC.) fruit in the liver tissues of mice during post implantation of pregnancy. Journal of Physics, pp. 1 - 5.

analysis. This study also only conducted *a post-test* examination so that it could not compare the effects before and after the administration of andaliman nanoherbs. Based on the shortcomings that the author has explained above, it is recommended that researchers further consider an increase in the number of samples so that they can be excluded to minimize abnormally distributed data, conduct pre-test and post test examinations to compare conditions before and after the administration of andaliman nanoherbs, and further analyze the effects of steroid and trepenoid compounds contained in andaliman to find out further effects on histopathological changes in hepatic cells. The author would like to express his gratitude to all parties who have helped in this research process so that the research can be completed properly

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