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The Effect of Bay Leaf Extract Nanoemulsion Preparation (*Syzygium Polyanthum*) on Reducing Myeloperoxidase (Mpo) and Histamine Levels in Kidney Pathology in Wistar Rats with Diabetes Melitus

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ABSTRACT

Sudy aimed to evaluate the effect of bay leaf (Syzygium polyanthum) extract nanoemulsion on reducing myeloperoxidase (MPO) levels in Wistar rats with diabetes mellitus. The rats were divided into control and treatment groups, where the treatment group received bay leaf extract nanoemulsion. The results showed that treatment with nanoemulsion significantly reduced MPO levels compared to the control group. Administration of bay leaf extract nanoemulsion Bay leaves (*Syzygium polyanthum)* at a concentration of 5% were effective in improving kidney function in Wistar white rats (*Rattus norvegicus*) with diabetes mellitus. This improvement was evident through MPO levels and the histopathological structure of the kidneys, which improved and resembled the control group . The results of histopathological observations of kidney tissue in treatment group 3 were as follows: nanoemulsion extract Bay leaves (*Syzygium Polyanthum)* with a concentration of 5% experienced the most significant improvement and were closer to the control group compared to the other groups. Nanoemulsion extract Bay leaves (*Syzygium Polyanthum)* contain secondary metabolites in the form of saponins, tannins, flavonoids, and triterpenoids which help repair liver cells that experience fatty liver and necrosis due to diabetes mellitus. Furthermore, histopathological examination of the kidneys showed improvements in kidney tissue, indicating the potential of bay leaf extract in reducing oxidative stress and inflammation. This study concluded that bay leaf extract nanoemulsion preparation could be an effective therapy for managing kidney complications in diabetes mellitus.

Keywords: *Nanoemulsi Leaf Greetings, MPO, DM*

INTRODUCTION

Increasing prevalence of diabetes mellitus (DM) in several country develop like Indonesia a lot associated with increasing level life public as well as change pattern life especially in cities big . Research in 3 villages (Sangsit , Pedawa And Ceningan) in Bali, with amount population of 1,070 people, aged over 13 years , obtained amount glucose fast disturbed (Impaired Fasting Glucose/IFG) and diabetes respectively by 15.5% and 6.4%.1 In Indonesia with assumptions prevalence of DM is 4%, based on pattern increase resident like moment this , it is estimated on in 2020 will There is a total of 178 million Indonesian population aged over 20 years , so that estimated will 7 million people have DM . According to the World Health Organization (WHO) in 1998, estimated the number of people with DM in Indonesia will increase almost 250 % from 5 million in 1995 to 12 million in 2025 .

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One of complications chronicle from DM is angiopathy diabetic , consequences occurrence damage endothelium that is affected vessels blood , good vessels blood large (macroangiopathy) or vessels blood small (microangiopathy). Quality vessels blood is determinant quality life a diabetes sufferers . Abnormalities vascular This Can about brain , eyes , heart , kidneys , each of which the incidence varies.3Hyperglycemia can increase production of Reactive Oxygen Species (ROS) through enzymatic processes that is reaction oxygenation And phosphorylation (ox- phos) and ADPH-Oxidase reaction , besides That Also through non- enzymatic processes with form gluco -oxidant and AGE which then experiencing auto- oxidation . ROS is oxidative stress that can activates Nuclear Factor-κB (NF- κB) in core cell so that can express various kinds of genes and pro- inflammatory cytokines (IL-1 and TNF-α), as well as chemokines like C-Reactive Protein (CRP) and monocyte chemoattractant protein-1 (MCP-1), with manifestation clinical in the form of reaction inflammation And cause damage endothelium vessels blood .

Myeloperoxidase (MPO) is hemoprotein (Heavy Molecule 140 kDa) which consists of from chain heavy And light , stored in granules *azurophilic* including neutrophils And macrophages , functioning For catalyze change chloride And hydrogen peroxide become hypochloride . *Myeloperoxidase* is released to fluid extracellular And circulation during the inflammatory process . Enzymes This involved in HDL oxidation (Apple *et al.*, 2005). MPO accumulation is proatherogenic Which potent . *Myeloperoxidase* Also involved in oxidation cholesterol LDL, with method multiply *uptake* by macrophages And form formation cell *foam* . *Myeloperoxidase* activate *metalloproteinase* And increase instability And rupture surface plaque atherosclerosis (Baldus *et al.*, 2003).

MPO is enzymes produced by cells immune , especially neutrophils , and play a role in the inflammatory process . High MPO levels can show existence prolonged inflammation , which often happen on diabetes mellitus patients . Study show that improvement MPO levels can relate with complications of diabetes, such as neuropathy And disease cardiovascular . High MPO levels can become indicator risk For development complications This on diabetes mellitus patients . MPO involved in production species oxygen reactive (ROS), which can cause damage oxidative on cells And network . This contribute on pathogenesis of diabetes and complications , including damage on cells pancreas And network other . MPO levels can used as a biomarker for monitor inflammation And risk complications on diabetes patients . Study more carry on required For determine mark diagnostic And prognostic from MPO levels in context of diabetes mellitus .

One herbal plant that can be used as a substitute for medication for diabetes is the bay leaf (Syzygium *polyanthum).* (Wight) Walp.) is a plant that is widely used as a spice supplement. cooking. Apart from being used as a complement [cooking] spices , are also known to have properties cure diarrhea and stomach ulcers, lowering cholesterol levels, treating hypertension and lower blood sugar levels in people with diabetes mellitus (Dafriani, 2016). The chemical content of bay leaves is tannins, essential oils, citral, eugenol, dyes and flavonoids (Widyawati P. S, 2016). Compounds flavonoids contained in bay leaves is one of the groups of compounds that can lower blood glucose levels (Rizki Pebrian Pratama, 2020). Flavonoid compounds in bay leaves has an effect as an antioxidant.

One herbal plant that can be used as a substitute for diabetes medication is the bay leaf (*Syzygium polyanthum).* The medicinal properties of the bay leaf are found in all parts of the plant, including the bark, roots, fruit, and leaves (Wijayakusuma, 2022). However, the leaves possess far more medicinal properties than any other part.

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A study has been conducted on the formulation of bay leaf extract nanoemulsion as an active ingredient in the manufacture of antioxidant serum (Yusuf, 2022). The stages of this study include: (1) extraction using maceration and *Microwave-Assisted Extraction* (MAE) techniques; (2) Characterization and identification of the extract including phytochemical tests, DPPH tests, shear reagent tests, and compound identification using LC-MS; (3) formulation of nanoemulsion preparations using the *Self-Nanoemulsifying Drug Delivery System* (SNEDDS) method; (4) Nanoemulsion testing: stability test, antioxidant activity test using the DPPH method, and irritation test, (5) characterization of nanoemulsions including particle size, transmittance, pH, and viscosity.

Based on the above background, the researcher aims to evaluate the effect of bay leaf extract nanoemulsion preparation (*Syzygium polyanthum*) on reducing myeloperoxidase (mpo) levels in Wistar rats with diabetes mellitus and kidney histology.

Objective from study This namely knowing the process of making bay leaf extract (*syzygium polyanthum)* in nanoemulsion preparations , knowing the content of active substances in bay leaf extract (*syzygium polyanthum),* knowing the effect of administering bay leaf nano extract preparations (*syzygium polyanthum*) with doses of 2%, 3% and 5% on reducing Myeloperoxidase (MPO) levels in Wistar rats with diabetes mellitus and analyze the histopathological picture of the kidney; after the treatment period, as for hypothesis his research There is an effect of bay leaf extract nanoemulsion preparation (*Syzygium polyanthum*) on reducing myeloperoxidase (MPO) levels in Wistar rats with diabetes mellitus and kidney histology. The conceptual framework in this study is as follows:

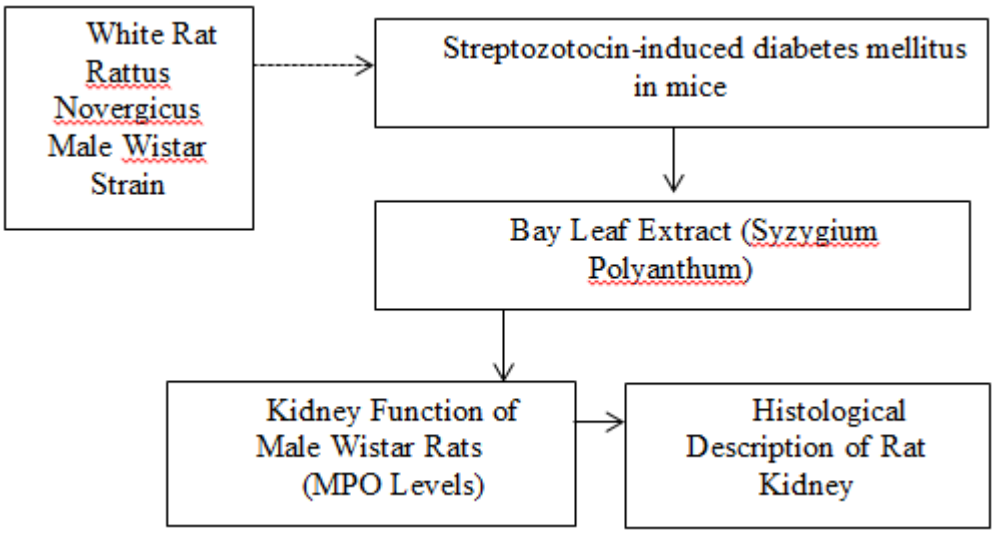

Figure 1. Conceptual Framework

METHODS

This research is a True experimental research, with the research design used is *Post Test Only Control Group Design* , which is a type of research that only observes the control and treatment groups after being given an action. The research design uses *a post-test with control group design* or controls the sample based on the treatment group to analyze the activity test of bay leaf extract nanoemulsion (*syzygium polyanthum*) on myeloperoxidase (mpo) levels in wistar strain rats with diabetes mellitus. This research was conducted in the Laboratory of the Department of Pharmaceutical Pharmacology, Faculty of Medicine, University of North Sumatra and the Anatomical Pathology Laboratory of the University of

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s, Ethical Clearance will be submitted to the Health Research Ethics Commission (KPEK) of Prima Indonesia University with No. 174/KEPK/UNPRI/VI/2025 . Based on the sample calculation above, each group must have a minimum of 6 test animals. In this study, researchers used 6 Wistar rats for each group, resulting in a total of 24 test animals. The test animals were randomly assigned to 4 test groups.

Acclimatization is the process of adjusting to a new environment. All male Wistar rats underwent acclimatization for seven days in the Laboratory of the Department of Pharmaceutical Pharmacology, Faculty of Medicine, University of North Sumatra before receiving treatment. The rats had sufficient time to adjust to their new environment, food, and water. The rats were fed and watered according to their standard needs (*ad libitum*) . After 14 days of adaptation, on the first day of the experiment, an injection was given. streptozotocin 55 mg/kgBW intraperitoneally in mice. After injection streptozotocin, in time 24 O'clock mouse given sucrose 10% through probe And given Eat Which Enough For prevent hypoglycemic conditions . Then, body weight measurements were taken every 2 days, namely on the 3rd day and blood glucose measurements were taken every 6 days, namely on the 7th day, for determine mouse diabetes mellitus with criteria level glucose >300mg/dl. Before making the nanoemulsion, bay leaves must first be converted into an extract using a maceration method. 2 kg of the collected bay leaves are then taken to be used as an extract. The collected bay leaves are then cleaned and dried. Once the bay leaves are dry, they are ground to a fine powder (simplicia) of 600 g. Next, the powdered simplicia is mixed with 96% ethanol in a ratio of 1:10, then left for 24 hours and stirred every 6 hours. The maceration results are separated and the previous steps are repeated with the same amount of 96% ethanol. The resulting macerate is then placed in *a rotary vacuum evaporator* and evaporated to obtain a crude extract. Next, take 0.2 ml of the extract into vial and add 5 ml of 75 µM 2,2-Diphenyl-1-Picrylhydrazyl (DPPH) solution. Then, let the mixture stand for 30 minutes in a light-free room.

Bay leaf nanoemulsion was obtained using the *water-titration method* . The oil phase was made from a mixture of virgin coconut oil *and* Tween 80 as a surfactant, and *polyethylene glycol* 400 (PEG 400) as a co-surfactant in a ratio of 1:8.5:0.5. Then, water at a temperature of 70 $^{\circ}$C was added to the oil phase by titration, stirring continuously until a homogeneous nanoemulsion was obtained. The nanoemulsion was then assessed through organoleptic tests, pH, stability, and particle size. In addition, the nanoemulsion was also assessed physically through color, aroma, and several homogeneity parameters. The particle size used in this study was 33 nm (Hanifah *et al.* , 2021).

The kidney function parameter in this study was a decrease in myeloperoxidase (MPO) levels. Myeloperoxidase (MPO) levels can be used as a parameter in kidney examinations, especially to evaluate inflammatory conditions and kidney damage. Scoring data was then created from histopathological observation data through microscopic examination. The data obtained from the study were tabulated, then analyzed regarding the changes found, and finally presented descriptively. Furthermore, the research data were analyzed using the Statistical Package for Social Sciences (SPSS) 25.0 for Windows. To assess data normality, the Kolmogorov-Smirnov test was used ($p > 0.05$). In addition, the significance between the trial groups was tested using One Way ANOVA or one-way analysis of variance at a 95% confidence level. Further analysis or testing was carried out using the Post Hoc Test and LSD techniques.

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RESULTS AND DISCUSSION

This chapter will outline and describe the results of the research data collection and processing. This will then be followed by a discussion, beginning with a general overview of the research subjects and continuing with the analysis and interpretation of the research data. The description of the research results will also illustrate how the research problems were addressed and conclusions drawn.

Measurement of Body Weight and Blood Glucose Levels of Rats

The data shows that the average initial body weight of all groups of mice fell within the research weight criteria, namely 200-300 grams. Furthermore, glucose levels in all groups were within the normal range of 6.97-97.89 **mg/dL** . study to be continued with give induction streptozotocin for 14 days monitoring to group P1 , P2 and P3. Then given bay leaf extract nanoemulsion for 14 days And return seen results the examination in day to 28.

From the table it can be seen that there was a decrease in average body weight in the treatment groups (P1, P2 and P3) after being induced by streptozotocin which was observed on the 14th day, it was seen that group P1 had an average body weight of 186.1 gr, P2 with an average of 190.6 gr and P3 with an average of 184.1 gr. So that the administration of diabetes induction can cause weight loss in test animals because streptozotocin can damage pancreatic beta cells which are responsible for producing insulin. However, there was a drastic increase in blood sugar levels in mice with group P1 331 mg / dL, group P2 with 336.1 mg / dL and group P3 with 333 mg / dL. So that streptozotocin induction can increase glucose levels in mice in the treatment group so that all groups were declared diabetes mellitus. The P0 group was the reference group because it was not given any treatment and the results in this group were a body weight of 213.3 grams and glucose of 91.5 mg/dL. Then, observations were made again on the body weight of the mice and glucose levels after administration of bay leaf extract nanoemulsion.

Then all groups were given treatment with bay leaf extract nanoemulsion (*Syzygium Polyanthum).* for 14 days and the final results were observed on the 28th day with treatment group 1 (P1) given bay leaf extract nanoemulsion with a concentration of 2% , Treatment 2 (P2) with a concentration of 3% , and treatment 3 (P3) with a concentration of 5% . The results showed an increase in body weight in the treatment group. The P0 group was the reference group with an average body weight of 218.5 grams and glucose of 93.5 mg/dL. For group P1, the average body weight was 217.6 grams and glucose of 110 mg/dL, the results of body weight were normal but glucose levels were seen above the normal threshold. In group P2, the average body weight was 214.7 grams and glucose of 96 mg/dL, the results of body weight had returned to normal and glucose levels were within normal limits. In group P3, the average body weight was 213.5 grams and glucose of 86.5 mg/dL, the results of body weight had returned to normal and glucose levels had returned to normal. And it can be seen that the results of groups P2 and P3 in the test group showed normal results on the 28th day of testing.

In group P0, diabetes induction treatment was not given so that this group had stable glucose levels, whereas in groups P1, P2 and P3, this group was induced by streptozotocin so that post-induction observations showed that all groups had glucose levels >300 mg/dL, but after being given the extraction treatment Bay leaf extract nanoemulsion (*Syzygium Polyanthum)* was seen to reduce blood glucose levels in mice until groups P2 and P3 entered the normal blood glucose criteria for mice.

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Making Nanoemulsion of Bay Leaf Extract (*Syzygium Polyanthum)*

The results of the bay leaf extract nanoemulsion production were analyzed for organoleptic, pH, stability, and particle size. Furthermore, the nanoemulsion was also physically evaluated for color, aroma, and several homogeneity parameters.

Table 1. Test Evaluation Organoleptic nanoemulsi leaf regards

Testing		
P1 (1%)	- Aroma	- Smell Typical
	- Color	- Green pale
	- Form	- Emulsion
	- Homogeneity	- Homogeneous
P2 (3%)	- Aroma	- Smell Typical
	- Color	- Green concentrated
	- Form	- Emulsion
	- Homogeneity	- Homogeneous
P3(5%)	- Aroma	
	- Color	- Smell Typical
	- Form	- Green concentrated
	- Homogeneity	- Emulsion
		- Homogeneous

The results of the pH measurement table above, it can be concluded that the bay leaf extract nanoemulsion with a concentration of 2% obtained pH measurement results with an average of 6.55, the bay leaf extract nanoemulsion with a concentration of 3% obtained pH measurement results with an average of 6.41 and the bay leaf extract nanoemulsion with a concentration of 3.5% obtained pH measurement results with an average of 6.25.a

Figure 2. Photo of 2%, 3% and 5% Nanoemulsion Preparations

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Phytochemical Test Results

Table 3. Phytochemical Test

Secondary Metabolites	Color	Results
Flavonoid	Red	+
Saponin	Yellow and foamy	+
Tannin	turquoise	+
Alkaloid	Yellow	+
Steroid	Green	+

Description: (+) = Contains the tested compound group
(-) = Does not contain the tested compound

Phytochemical testing was conducted to examine the secondary metabolite compounds contained in bay leaf extract (*Syzygium polyanthum)* . Phytochemical testing included flavonoids, saponins, tannins, alkaloids, and steroids/triterpenes.

Description of MPO Level Results

Table 5. MPO Level Results

	Group (n=4) Mean-standard deviation			
Group	K	P1	P2	P3
Initial MPO levels	125±18.84	115.5±11.15	131±11.90	121.5±8.58
MPO levels after streptozotocin induction	132.5±13.11	405.17±60.79	429.67±96.78	445±71.37
MPO levels after treatment	136±10.23	143.83±9.57	156.33±9.48	142.83±8.91

Table in on show that The average MPO (malondialdehyde) level will increase under streptozotocin (STZ) induction conditions. Streptozotocin is a compound used to induce diabetes mellitus in experimental animal models, and this induction process will trigger oxidative stress characterized by increased MPO levels. This is seen in the average and deviation in the control group 132.5 ± 13.11, treatment 1 405.17 ± 60.79, treatment 2 429.67 ± 96.78 and treatment 3 445 ± 71.37. After being induced by streptozotocin, the mice were then treated with bay leaf nanoemulsion to reduce MPO levels for 2 weeks and after that they would be observed again. From the table it can be concluded that MPO levels decreased in treatment group 1 with the administration of 2% bay leaf extract nanoemulsion with a mean and standard deviation of 143.83 ± 9.57, treatment group 2 with the administration of 3% bay leaf extract nanoemulsion with a mean and standard deviation of 156.33 ± 9.48 and treatment group 3 with the administration of 5% bay leaf extract nanoemulsion with a mean and standard deviation of 142.83 ± 8.91.

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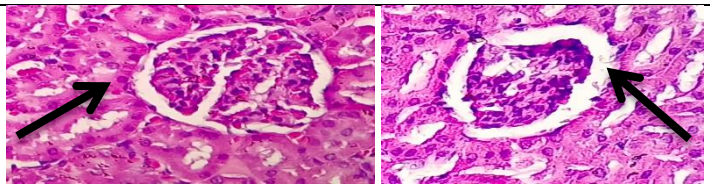
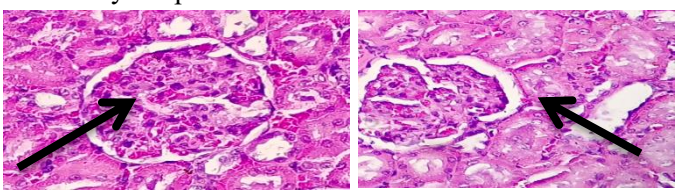
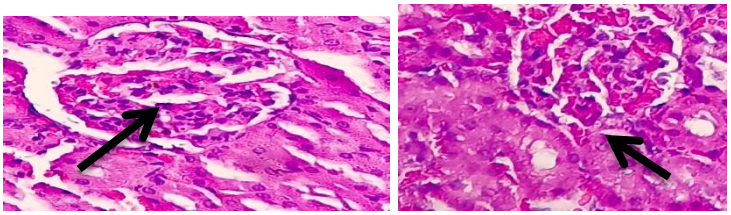
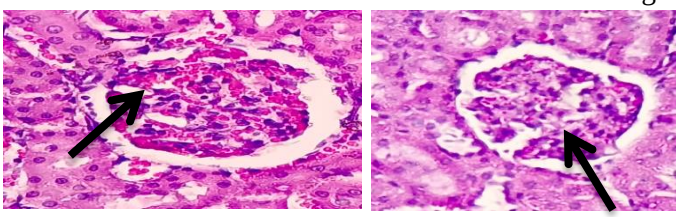
Histopathological Observation Results

Table 6. Histopathological Description of Kidney Tissue

No	Group	Histopathological Image of Kidney Tissue
1	Control (Aquades)	 The control group underwent observation without experiencing diabetes mellitus and was not given bay leaf extract nanoemulsion, only given standard pellet feed and distilled water during the study. From the micropsis observation, normal kidney histology structure was seen, so the score was 0. A score of 0 means there was 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 the other groups and as a comparison with the treatment group induced by streptozotocin and the extract nanoemulsion. Bay leaf.
2	Treatment 1	 This group of mice was induced with streptozotocin and then treated with a 2% bay leaf nanoemulsion extract. Micropsies showed multifocal (moderate) damage with a score of 2.
3	Treatment 2	 This group of mice was induced with streptozotocin to develop diabetes mellitus, then treated with a 3% bay leaf nanoemulsion. Micropsies showed focal (mild) damage; therefore, this group received a score of 1 due to the still-visible mild damage.
4	Treatment 3	 In this group, mice were induced with streptozotocin to develop hyperglycemia , then treated with a 5% concentration of bay leaf extract. Micropsies showed focal (mild) kidney abnormalities, giving them a score of 1, indicating normal results.

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Data analysis

Based on results test normality that has been done use *Kolmogorov-Smirnov Test.* obtained results significance of 0.7888 on all group on moment beginning acclimation mice , after induced 0.492 and after given treatment 0.340. Data said normally distributed if p value > 0.05. So from that , can concluded that the data is normally distributed . After the data is known to be normally distributed, a homogeneity test is carried out using the *Levene test* to determine whether each variant of the research population group is the same or homogeneous.

The results of the homogeneity test using Levene's test can be seen in the table above. The probability values in the significance column are 0.121, 0.123, and 0.947. The significance probability value obtained is greater than 0.05, so it can be concluded that the control group, treatment group 1, treatment group 2, and treatment group 3 come from populations that have the same variance, or are homogeneous. The results of the *One-Way ANOVA* test in the table above show that the significance value produced is 0.000 or <0.05. Based on these data, it can be concluded that there is a significant difference between the control group and the treatment group. The *Post Hoc LSD* test was used to determine whether the group had a significant difference from the other groups. The results of the analysis showed that the MPO levels at the beginning of the study in mice did not have differences in MPO levels, namely all mice had normal MPO (Myeloperoxidase) levels ranging from 50 to 200 ng/mL. MPO levels after streptozotocin induction had differences because all groups after induction experienced an increase in MPO levels . After being given treatment with bay leaf extract nanoemulsion, there was a significant difference in MPO levels between the control group and treatment group 1 (p = 0.000). While the control group and treatment group 2 (p = 0.030. While treatment group 3 did not have a significant difference (p = 0.272).

CONCLUSION

1. Administration of nanoemulsion extract Bay leaves (*Syzygium polyanthum)* at a concentration of 5% were effective in improving kidney function in Wistar rats (*Rattus norvegicus*) with diabetes mellitus. This improvement was evident in MPO levels and kidney histopathology, which improved and resembled the control group.
2. The results of histopathological observations of kidney tissue in treatment group 3, namely nanoemulsion extract Bay leaves (*Syzygium Polyanthum)* with a concentration of 5% experienced the most significant improvement and were closer to the control group compared to the other groups.
3. Nanoemulsion extract Bay leaves (*Syzygium Polyanthum)* contain secondary metabolites in the form of saponins, tannins, flavonoids, and triterpenoids which help repair liver cells that experience fatty liver and necrosis due to diabetes mellitus.

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