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Effectiveness of Ginger (Zingiber Officinale) Extract Nanoemulsion Preparation on Blood Glucose Levels, Lipid Profiles, Hba1c and Liver Histopathology in Male Rats Induced by Streptozotocin

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ABSTRACT
Study This aim For evaluate effectiveness stock nanoemulsi extract ginger (*Zingiber officinale*) against level glucose blood , lipid profile , and HbA1c in mouse induced male streptozotocin , as well as For analyze description histopathology heart . Results study show that stock nanoemulsi extract ginger in a way significant lower level glucose blood , repair lipid profile , and lower level glucose blood , lipid profile , and HbA1c were compared with group control. Administration of ginger extract nanoemulsion (*zingiber officinale*) at a dose of 200 mg/kgBW had an effect on reducing HbA1c levels, indicating an effect on long-term glycemic control. The results of the ANOVA test showed a significant difference between groups ($p < 0.05$) . Histopathology of ginger extract nanoemulsion (*zingiber officinale*) at a dose of 200 mg/kgBW showed a microscopic picture of the liver of mice in treatment group 3 (P3). It looked normal, no inflammation was seen, the cells began to improve, no looks necrosis and fatty. And scoring For this picture is 1 that is normal. Conclusion from study This is that stock nanoemulsi extract ginger effective in control level glucose blood And lipid profile as well own potential as therapy addition for diabetes mellitus , with effect positive on health heart.

Keywords: *Nanoemulsi ginger , KGD, Lipid profile , HbA1c.*

INTRODUCTION
Diabetes Mellitus is a chronic metabolic disorder characterized by high blood sugar levels and impaired carbohydrate, lipid, and protein metabolism, resulting from insufficient insulin utilization. Insufficiency of insulin function can be caused by impaired or insufficient insulin production by the beta cells of Langerhans in the pancreas, or by a lack of responsiveness of body cells to insulin (Lestari, 2022). In addition to controlling blood glucose levels, managing lipid profiles and HbA1c levels is also important to prevent long-term complications. Controlling high blood glucose levels can lead to various complications, such as nerve damage, heart disease, and impaired kidney function. Blood glucose control can be achieved through various approaches, including diet, exercise, and the use of antidiabetic medications. Diabetes is also often accompanied by changes in lipid profiles, including increased triglyceride and LDL cholesterol levels, and decreased HDL cholesterol levels. Lipid profile management is crucial because the risk of cardiovascular disease increases in diabetic patients. Dietary interventions, physical activity, and hypolipidemic medications can assist in this management. HbA1c levels reflect average blood glucose levels over the past 2-3 months. HbA1c measurement is important for assessing glycemic control and the risk of diabetes complications. The

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generally recommended HbA1c target is below 7%, but this target can vary depending on the individual's condition. Effectively controlling blood glucose levels, lipid profiles, and HbA1c levels can reduce the risk of diabetes complications, improve quality of life, and extend life expectancy.

The use of streptozotocin (STZ) in experimental animals induces research on the occurrence of diabetes mellitus. Streptozotocin (STZ) has properties as a diabetogenic agent that can trigger increased production of excess free radicals and cause oxidative stress. Munjiati et al. (2021) explained that STZ works by targeting βpancreatic cells, which results in decreased insulin levels in the blood, causing hyperglycemia. Research by Saputra et al. (2018) related to the administration of STZ to white rats (Rattus norvegicus) can cause experimental diabetic hyperglycemia within 3 days. Streptozotocin (STZ) forms free radicals that can damage pancreatic beta cells, thereby disrupting insulin production. STZ enters pancreatic beta cells through glucose transporter 2 (GLUT 2) and causes DNA alkylation.

Diabetes management often involves the use of medications, but there is also growing interest in herbal-based therapies, one of which is ginger (*Zingiber officinale*). Ginger (*Zingiber officinale*) is a spice plant abundant in the Toba Samosir and North Tapanuli Regencies, North Sumatra (Asbur, 2019). Ginger's active compounds are believed to contribute positively to human health, namely flavonoids, alkaloids, saponins, and terpenoids. Flavonoids have antioxidants and inhibitors of the α-glucosidase enzyme, which in vitro have antidiabetic activity. Saponins can regenerate the pancreas, causing an increase in the number of pancreatic β cells and islets of Langerhans, thus increasing insulin secretion.

Ginger (*Zingiber Officinale*) is a plant that can live in tropical areas, for example Indonesia (Agoes, 2012). Ginger has the potential to lower blood pressure in hypertensive patients, because of the many contents of red ginger that can affect the renin-angiotensin-aldosterone system (SRAA), one of which is flavonoids (Alva Nadia, 2020). Based on previous research conducted by (Arman, 2016) traditional medicine that has been recorded for hundreds of years for treatment is ginger, which has traditionally been used to treat rheumatism, asthma, stroke, toothache, infection, muscle pain, throat, cramps, hypertension, nausea, fever and diabetes The main content of ginger is essential oil (1-5%), sesquiterpenoids and monoterpenoids, gingerols, shogaols, paradols and zingerones. Most of the therapeutic effects of ginger as anti-inflammatory, analgesic, hypotensive and diabetes are related to gingerols and shogaols which are abundant in fresh ginger and dried ginger,

Flavonoids are one of the phytochemical compounds found in herbal plants, one of which is ginger (*Zingiber Officinale*). Flavonoids are useful as analgesics, antitumor, antioxidants, anti-inflammatory, antibiotics, anti-allergic and diuretics (Yuliningtyas *et al.* , 2019). Several previous studies also stated that ginger and its compounds can affect blood pressure. Based on research conducted by Alva Nadia (2020), it explains that ginger contains chemical compounds such as gingerol, zingerone, flavonoids, potassium and essential oils that have benefits in lowering blood pressure. The same study also stated that the mechanism is by influencing the renin-angiotensin-aldosterone system by inhibiting ACE activity. Research by Akinyemi *et al.* (2014), shows that ginger has an antihypercholesterolemic role with an ACE inhibition mechanism, so it can also be used as a therapy for hypertension and other cardiovascular diseases.

Nanoemulsion preparation is a technology that can increase the bioavailability of active compounds in ginger extract. With smaller particle size, nanoemulsion can improve the absorption and distribution of active substances in the body, thereby increasing therapeutic effectiveness. The use of nanoemulsion in ginger preparations is expected to

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provide a more significant effect in reducing blood glucose levels in streptozotocin-induced mice. This study aims to evaluate the effect of ginger extract nanoemulsion preparation on blood glucose levels in streptozotocin-induced male mice. This mouse model is used to mimic the condition of type 2 diabetes, allowing researchers to observe the effects of the treatment more clearly.

In a previous study examining red ginger nanoemulsion on blood pressure and ACE levels, it was stated that red ginger nanoemulsion with a nanoparticle size of 32.8 nm and a polydisperity index of 0.268 at a dose of 360 mg/200 g of mice was more effective in lowering blood pressure and suppressing ACE levels in mice with UUO induction compared to red ginger nanoemulsion with a dose of 540 mg/200 g (Hanifah *et al.* , 2021). In the sub-acute phase, red ginger extract has a toxic effect on the liver, this was proven in a study conducted by Putu Dewi & Ma'ruf (2023), in mice (*Mus musculus*) with a dose of 400 mg/kgBW red ginger extract produced a toxic test score of 3, which can be interpreted as hydropic degeneration. At a dose of 800 mg/kgBW the score showed 4, which means necrosis occurred.

This study aims to determine the effect of ginger nanoemulsion preparations in reducing blood glucose levels, blood glucose profiles. Lipid and HbA1c levels in male rats . To demonstrate these benefits, this study will assess changes in values in rats induced by streptozotocin to develop diabetes mellitus.

The conceptual framework in this study is as follows:

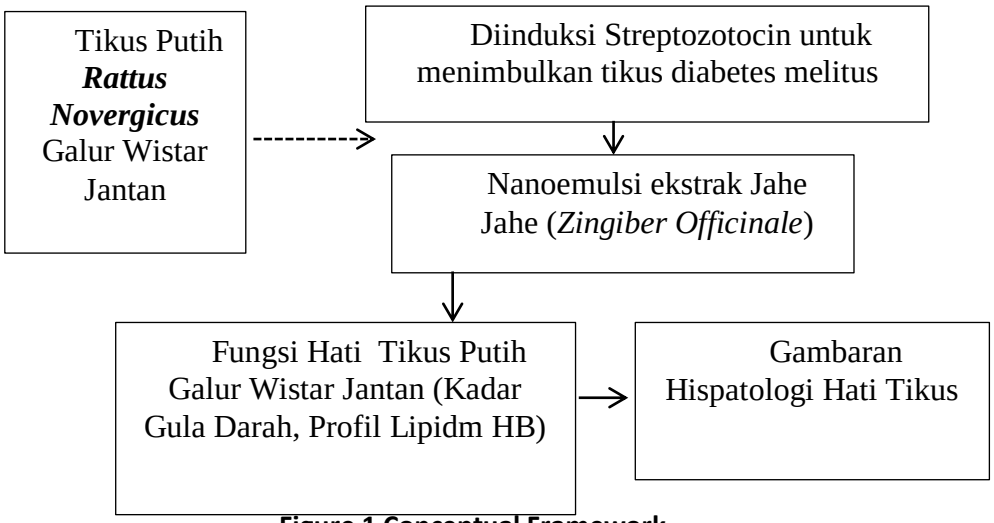

Figure 1 Conceptual Framework

METHODS

This research uses an experimental quantitative research type, namely by using a true experiment or laboratory experimental design where this research was conducted. to examine the effectiveness of administering ginger (zingiber officinale) extract nanoemulsion on blood glucose levels, lipid profiles and HBA1C in streptozotocin-induced male rats and liver histopathology images The research design uses a post-test with control group design or controls the sample based on the treatment group. post test done For see success extract in reduce blood glucose levels, lipid profiles and HBA1C in mice that have experienced diabetes mellitus, then histopathological observations were carried out on the livers of mice in each treatment group. The research location is the Laboratory of the Department of Pharmacology and Therapeutics Faculty Medical

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University Sumatra North on Month June- August 2025. Ethical Clearance is still in process by Health Research Ethics Commission (KPEK) of Prima Indonesia University.
Acclimatization is the process of adjusting to a new environment, climate, condition, or atmosphere. Before administering treatment, all male Wistar rats underwent a 7-day acclimatization process in the Laboratory of the Department of Pharmacology and Therapeutics, Faculty of Medicine, University of North Sumatra. The rats were given time to adapt to the new environment, as well as their food and drink. The rats were fed and watered according to their standard needs (ad libitum). In another study, different doses of streptozotocin (40 mg/kg, 50 mg/kg, and 60 mg/kg) were tested to determine the optimal dose that was most effective in inducing diabetes. The results showed that a dose of 50 mg/kg provided the highest success rate in producing diabetes in Sprague Dawley rats by injection 3 times a week via intraperitoneal (Munjiati, 2021).

To calculate the dose, you can use the following formula:

Dose (mg) = Dose per kg (mg/kg) x Rat body weight (kg)

For example, if the study uses a dose of 50 mg/kg for mice weighing 0.25 kg (250 grams), then the dose given is: Dose = 50 mg/kg x 0.25 kg = 12.5 mg.

Before making the nanoemulsion, ginger rhizomes must first be converted into an extract using the maceration method. 2 kg of ginger rhizomes were then collected and used to make the extract. The collected ginger rhizomes were then cleaned and cut into 1-2 mm pieces, then dried. After the ginger rhizomes were dried, the ginger was ground to obtain 600g of ginger powder (simplicia). The simplicia powder was then mixed with 96% ethanol in a ratio of 1:10 and left for 24 hours, stirring every 6 hours. The maceration results were separated and the previous steps were repeated with the same amount of 96% ethanol. The resulting macerate was then placed in a rotary vacuum evaporator and evaporated to obtain a crude extract. Next, 0.2 ml of the extract was taken into a 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 . Ginger 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). Determination of ginger nanoemulsion dosage based on previous ginger nanoemulsion research using doses of 180mg/200g and 360mg/200g (Fillah, 2024). This study tested the effect of 50% of the effective doses in previous studies, namely 100mg/kgBW, 150mg/kgBW and 200mg/kgBW on blood glucose levels, lipid profiles and hba1c in male rats induced by streptozotocin).

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RESULTS AND DISCUSSION

Making Nanoemulsion of Ginger Extract (Zingiber officinale)

The results of the ginger extract nanoemulsion production were analyzed for organoleptic properties, 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	- Aroma	- Smell Typical
	- Color	- Yellow
	- Form	- Emulsion
	- Homogeneity	- Homogeneous
P2	- Aroma	- Smell Typical
	- Color	- Yellow brownish
	- Form	- Emulsion
	- Homogeneity	- Homogeneous
P3	- Aroma	- Smell Typical
	- Color	- Yellow Brownish
	- Form	- Emulsion
	- Homogeneity	- Homogeneous

The results of the pH measurement table above, it can be concluded that the nanoemulsion of ginger extract with a dose of 100 mg/kgBW obtained pH measurement results with an average of 6.90, the nanoemulsion of ginger extract with a dose of 130 mg/kgBW obtained pH measurement results with an average of 6.83 and the nanoemulsion of ginger extract with a dose of 100 mg/kgBW obtained pH measurement results with an average of 6.66.

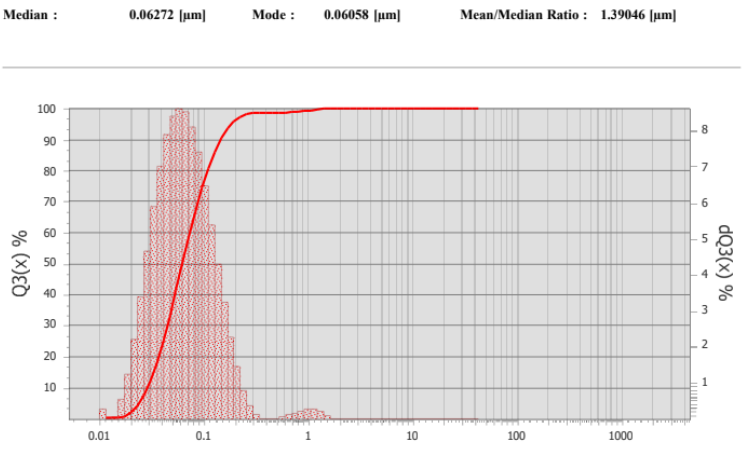

Table 4 Figure Measurement PSA Nanoemulsion Ginger Extract (* Zingiber Officinale *)

Zingiber officinale nanoemulsion are The average particle size is very small, which is around 60–63 nm, which indicates that this system is already in the ideal nanoemulsion category. The size distribution is narrow and uniform , because the mode ≈ median and

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the histogram shape is symmetrical. A Mean/Median Ratio higher than 1 indicates that there are still a small number of larger particles (possibly agglomerates), but not significant. Ginger nanoemulsion in this formulation shows very good particle distribution, with a dominant size below 100 nm. It is very suitable for pharmaceutical, cosmetic, or food applications because small particle size can increase physical stability **,** bioavailability and absorption by the body.

Phytochemical Test Results

Based on the results of the phytochemical tests carried out, it can be concluded that ginger extract (*zingiber officinale*) contains secondary metabolites in the form of flavonoids, saponins, tannin, alkaloids, And triterpenoid.

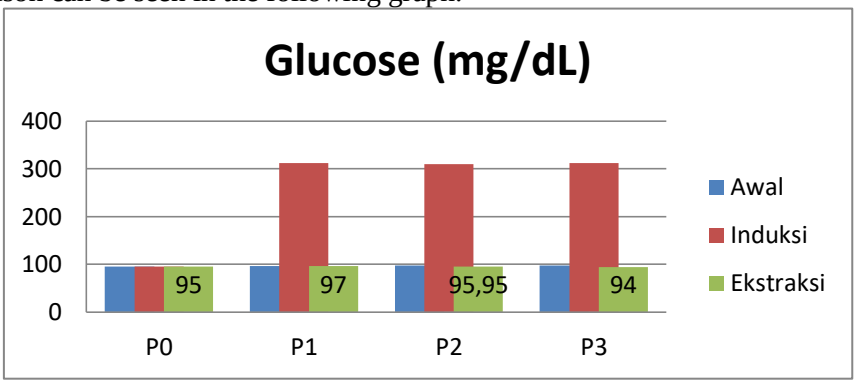
Table 3 Tests Phytochemicals

Secondary Metabolites	Color	Results
Flavonoid	Pink	+
Saponin	Yellow and foamy	+
Tannin	turquoise	+
Alkaloid	Yellow sediment	+
Steroids/Triterpenoids	Green	+

Information: (+) = Contain group compound Which tested
(-) = Does not contain the tested compound

Blood Sugar Level Observation Results

The test results above show the success rate of the ginger extract nanoemulsion (*zingiber officinale*). On reducing blood glucose levels in mice with diabetes mellitus. The comparison can be seen in the following graph:



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 ginger extract nanoemulsion (*zingiber officinale*) It was seen that there was a decrease in the blood glucose levels of the mice until groups P1, P2 and P3 entered the normal blood glucose criteria for mice.

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Lipid Level Observation Results

In this study, lipid levels that are often observed include: total cholesterol : Measuring total cholesterol in the blood and LDL (Low-Density Lipoprotein) cholesterol known as "bad cholesterol," which can clog arteries. which helps remove cholesterol from the arteries.

Description Total iroll level

Ssecond parameter to confirm rat test animal levels , serum collected from mice for after induction streptozotocin and given treatment nanoemulsi ginger extract (*zingiber officinale*) with a dose of 100mg /kgBW , 150mg/kgBW And 29 0mg/kgBW . Total cholesterol levels in normal mice typically range from 50 to 100 mg/dL . After being induced with certain factors (such as a high-fat diet, drugs, or chemicals), total cholesterol levels in mice can increase significantly. In many studies, total cholesterol levels in induced mice can reach to 300 mg/dL or even more, depending on the type of induction and duration of treatment. presented in the following :

Table 4 Average Total Cholesterol Levels / Dl) of Rats Before and After Streptozotocin Induction and Ginger Extract Treatment

Group	Initial Cholesterol Levels (H0)	Cholesterol Level (mg/dL) After Streptozotocin Induction (H14)	Cholesterol Level (mg/dL) After being given extract treatment (H28)
Control	52.4 ±0.84	55.92±1.13	55.55±1.68
Treatment 1 (P1)	52.19±1.26	158.25 ± 0.97	58.22±7.33
Treatment 2 (P2)	52.45±0.61	158.6±0.98	56.7 ±0.58
Treatment 3 (P3)	97.80	157.83±0.97	54.78 ±2.62

From the table above, it can be seen that the average blood cholesterol of mice decreased after 14 days of streptozotocin induction . Then, a drastic increase in the average and standard deviation of cholesterol levels in mice was seen with group P1 being 158.25 ± 0.97 mg/dl, group P2 being 158.6 ± 0.98 mg/dl, and group P3 being 157.83 ± 0.97 mg/dl. So that streptozotocin induction increased glucose in the mice in the treatment group so that all groups of mice were declared to have hyperglycemia.

Then all groups P1, P2 and P3 were given treatment with ginger extract (*zingiber officinale*) for 14 days and the final results were observed on the 28th day with treatment group 1 (P1) given nanoemulsion of ginger extract (*zingiber officinale*) with a dose of 100mg/kgBW , Treatment (P2) with a dose of 150mg/kgBW , and treatment 3 (P3) with a dose of 200mg/kgBW The results showed a decrease in total cholesterol levels in groups P1, P2 and P3 on average and standard deviation of total blood cholesterol 58.22±7.33 mg/dl, 56.7±0.58 mg/dl 54.78±2.62 mg/dl as for these results the total cholesterol levels had returned to normal .

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Thesis LDL Levels

The parameter examination levels the blood test animals to the condition of in . Hype rkole ste role mia i.e. if LDL levels high category . Normal LDL levels in mice are 7-27.2mg/dl, it is said to be high if it >27.2 mg/dl. Below data on levels in before And se is high kole ste rol se rta se te lah dibe ri pe rlakuan .

From the table, it can be seen that the average LDL in the blood of mice decreased after 14 days of streptozotocin induction . Then, a drastic increase in the average and standard deviation of cholesterol levels in mice was seen with group P1 being 29.71 ± 0.65 mg/dl, group P2 being 30.08 ± 0.99 mg/dl, and group P3 being 29.55 ± 0.78 mg/dl. So, streptozotocin induction increased cholesterol in the mice in the treatment group so that all groups of mice were declared to have hyperglycemia.

Then all groups P1, P2 and P3 were given treatment with ginger extract (*zingiber officinale*) for 14 days and the final results were observed on the 28th day with treatment group 1 (P1) given nanoemulsion of ginger extract (*zingiber officinale*) with a dose of 100mg/kgBW , Treatment (P2) with a dose of 150mg/kgBW , and treatment 3 (P3) with a dose of 200mg/kgBW. The results showed a decrease in LDL levels in groups P1, P2 and P3 with an average and standard deviation of blood LDL of 23.48±1.60. mg/dl, 22.76 ±0.99 mg/dl 18.63 ±1.42 mg/dl, with these results the LDL levels have returned to normal.

HbA1c Level Observation Results

The increase in HbA1c in the treatment group is likely related to increased body fat levels, which can trigger insulin resistance. However, other factors such as low physical activity, diet, and genetic predisposition can also influence HbA1c levels in a multifactorial manner. HbA1c values in normal rats usually range between 4% - 6%. After induction with streptozotocin (STZ), HbA1c values can increase significantly, often reaching 6% - 12% or more, depending on the dose of STZ used and the duration of observation. The increase in HbA1c in the treatment group is more closely associated with the toxic effects of streptozotocin, which disrupts pancreatic beta cell function, reduces insulin biosynthesis and secretion, and increases blood glucose levels.

From the table results, it can be seen that the average HbA1c levels in the blood of mice decreased after 14 days of streptozotocin induction . Then, a drastic increase in the average and standard deviation was seen in the HbA1c levels of mice with group P1 10.41% ± 0.007 , group P2 with 10.83% ± 0.005 and group P3 with 10.7% ± 0.005 . So that streptozotocin induction increased HbA1c in the treatment group mice so that all groups of mice were declared to have diabetes mellitus. Then all groups P1, P2 and P3 were given treatment with ginger extract (*zingiber officinale*) for 14 days and the final results were observed on the 28th day with treatment group 1 (P1) given nanoemulsion of ginger extract (*zingiber officinale*) with a dose of 100mg/kgBW , Treatment (P2) with a dose of 150mg/kgBW , and treatment 3 (P3) with a dose of 200mg/kgBW. The results showed a decrease in HbA1c levels in groups P1, P2 and P3 on average and standard deviation of blood HbA1c 5.8% ± 0.001, 5.4% ± 0001 and 5% ± 0.003 mg/dl, while these results showed that HbA1c levels had returned to normal.

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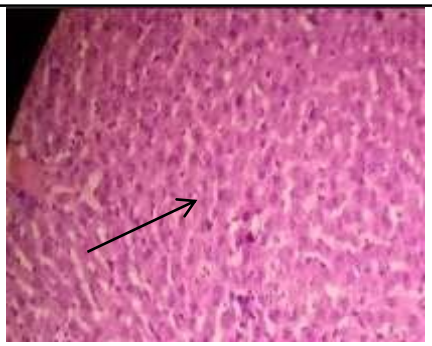
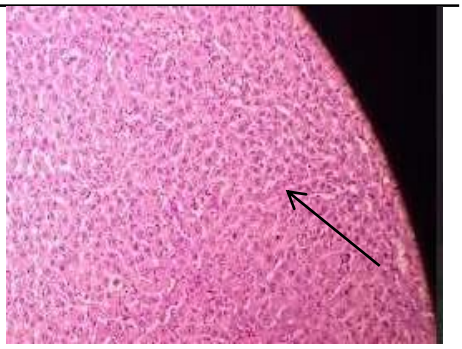
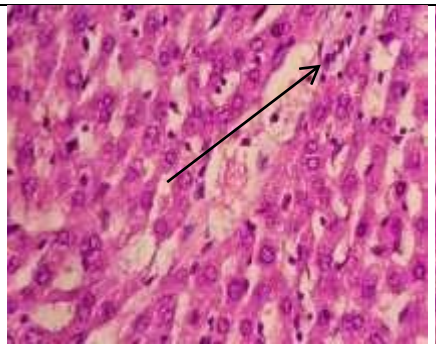
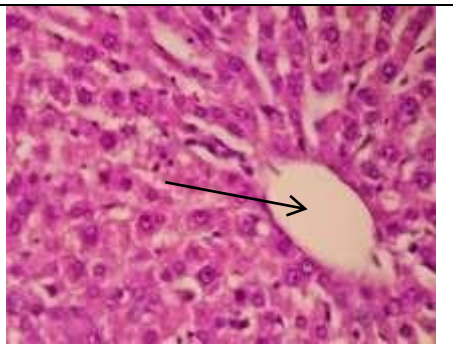
Histopathological Results

Table 9 Results Histopathology Rat Heart

Result Group	Description Histopathology Function Rat Heart
Kontrol (P0)	  Microscopic image of the liver of Wistar rats in the Control group (P0) showed no changes in the histological structure of the liver, no fatty liver or liver necrosis, so the score in this group was 1, namely normal .
Perlakuan P1	  Gambaran mikroskopik hati tikus kelompok perlakuan 1 (P1) pada kelompok ini tampak gambaran hati degenerasi melemak yang cukup banyak dan menyebar, degenerasi parenkimatosa ataupun perdarahan pada sel-sel hati, infitrasi sel radang skoring pada kelompok ini adalah 3 yaitu terdapat perubahan berupa degenerasi hidrofik.

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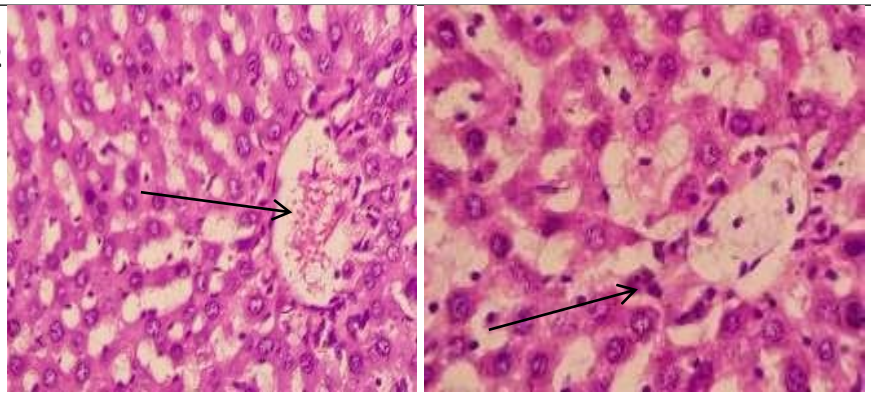
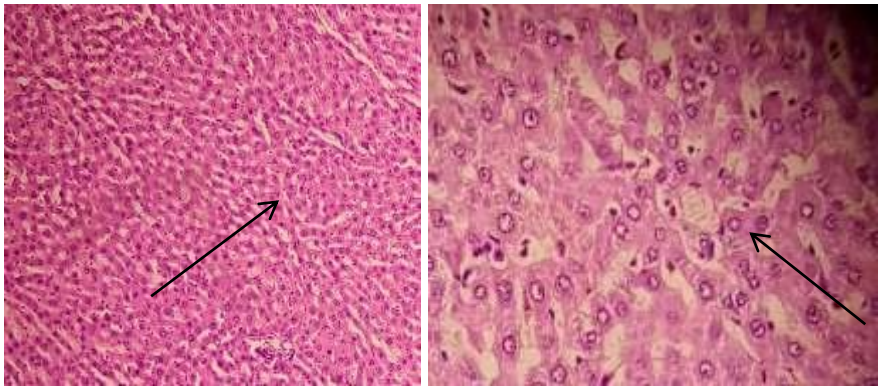
Perlakuan P2	 Microscopic image of the liver of mice in Treatment Group 2 (P2). The liver showed signs of fatty degeneration, congestion, and inflammatory cell infiltration. The score for this group was *2.*
Perlakuan P3	 Gambaran mikroskopik hati tikus kelompok perlakuan 3 (P3). Tampak normal tidak terlihat peradangan, sel sel mulai membaik, tidak tampak nekrosis dan perlemakan. Dan skoring untuk gambaran ini adalah 1 yaitu normal.

CONCLUSION

1. Phytochemical screening results on ginger (*Zingiber officinale*) extract revealed the presence of flavonoids, tannins, saponins, alkaloids, and polyphenols. These compounds act as natural antioxidants that support antidiabetic effects in test animals.
2. Treatment group 3 with a nanoemulsion of ginger extract (*zingiber officinale*) at a dose of 200 mg/kgBW experienced a greater reduction in total cholesterol compared to the other treatment groups, approaching the control

group. The ANOVA test showed a significant difference between groups ($p < 0.05$), which was confirmed by the results of the LSD test.

3. The average LDL level decreased significantly, especially in the treatment group 3 with ginger extract (*zingiber officinale*) at a dose of 200 mg/kgBW. The ANOVA test showed a significance value ($p < 0.05$), which means there was a significant difference between the treatment groups.
4. Administration of ginger (*Zingiber officinale*) nanoemulsion extract at a dose of 200 mg/kgBW was effective in reducing HbA1c levels, indicating an impact on long-term glycemic control. ANOVA results showed a significant difference between groups ($p < 0.05$).
5. Histopathology of nanoemulsion of ginger extract (*Zingiber officinale*) at a dose of 200 mg/kgBW shows a microscopic picture of the liver of mice in treatment group 3 (P3). It looks normal, no inflammation is visible, the cells are starting to improve, no... looks necrosis and fatty. And scoring For this picture is 1 that is normal.

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