INTERNATIONAL CONFERENCE
ON LIFESTYLE DISEASES AND NATURAL MEDICINE (ICOLIFEMED)
Nomor ISSN: 3124-1115

Effectiveness Test of Mangosteen Peel Extract (Garcinia Mangostana L) Nanoemulsion Preparation on the LevelsGDP,HbA1c, MDAAnd Histopathological Image of the Pancreas of Alloxan-Induced Diabetes Mellitus Rats

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ABSTRACT

A bad lifestyle can cause diabetes.Mostly, diabetes mellitus is caused by uncontrolled food consumption or side effects from the use of certain drugs.This research was conducted to see howThe effectiveness of nanoemulsion preparation of mangosteen peel extract (Garcinia mangostana L.) on GDP, HbA1c and MDA levels and histopathological features of the pancreas of alloxan-induced diabetic rats. The study usedA sample of 20 mice in 5 groups (positive control, negative, treatment 1, 2 and 3) where the extract preparation in the treatment was in the form ofnanoemulsion of skin extractmangosteen peel extract (Garcinia Mangostana L)onconcentration of F1 (1%), F2 (2%), and F3 (3%). The results of the GDP levels of groups P1, P2 and P3 are105.5 mg/dL, 92 mg/dL, 86.5 mg/dL. For blood sugar levelsHbA1c levels were 5.3%, 4.8%, and 4.6%, respectively, and MDA levels were 3.22%.nmol/mL, 2.6 nmol/mL and 2.25 nmol/mL. Administration of mangosteen peel extract nanoemulsion (Garcinia Mangostana L)effective in healing pancreatic cells that suffer from diabetes mellitus andadministration at a concentration of 3% extract showed that pancreatic cells no longer experienced necrosis.

Keywords: *Mangosteen Peel, Nanoemulsion, Level GDP, HbA1c, MDA, Pancreas*

INTRODUCTION

According to 2021 data from the International Diabetes Federation (IDF), Indonesia has the fifth-highest number of diabetes mellitus (DM) sufferers in the world, with 19.5 million cases. This number is expected to rise to 28.6 million by 2045 if prompt treatment is not available. According to the Ministry of Health, the prevalence was 11.7% in 2023 and continues to rise.(Litha, 2024).

Diabetes is the second most common disease in Indonesia after stroke and heart disease. In the next ten years, the number of people suffering from diabetes is estimated to increase two to threefold. Poor lifestyle choices, such as excessive carbohydrate consumption, excessive sugary drinks, and inactivity, can contribute to diabetes.(Drg. Widyawati, 2021).Blood glucose levelsAbnormal levels can indicate pancreatic problems, including diabetes, because the pancreas produces insulin to control blood sugar. High insulin concentrations cause insulin receptors to self-regulate by reducing the number of receptors.(S, 2014)This results in decreased receptor responsiveness and further leads to insulin resistance. Diabetes mellitus is mostly caused by uncontrolled food consumption or side effects from certain medications.

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Routine HbA1c testing can be performed to measure glycemic levels and is associated with the risk of DM complications. Oxidative stress plays a key role in the pathogenesis and complications of DM. One biomarker of lipid peroxidation is malondialdehyde (MDA), whose levels have been found to be elevated in patients with diabetes mellitus.(Anita Rosari Dalimunthe, 2023).

Alloxan significantly increases blood sugar levels in rats. Research has shown that several chemical compounds can be used as diabetes mellitus inducers, such as streptozotocin, ferric nitrite, dithizone, alloxan monohydrate, and anti-insulin serum. Among these compounds, alloxan monohydrate is the most commonly used inducer. This induction compound can be administered parenterally, such as intravenously, intraperitoneally, or subcutaneously.(Ashok, 2007).

The hyperglycemia of type 2 diabetes mellitus can cause cell death in both pancreatic β cells and other cells. Preventing this cell death is necessary to prevent complications in type 2 diabetes mellitus. One way to prevent this is through the consumption of antioxidants. Antioxidants are compounds that function to repair damage to cells in the body caused by free radicals.(Sri Lestari Ramadhani Nasution, 2022).

High blood glucose levels and diabetes mellitus can be treated with antihyperglycemic drugs, which are generally taken throughout the patient's life. However, synthetic drug therapy has side effects, so to minimize these side effects, herbal remedies can be an alternative option for diabetes mellitus sufferers. Mangosteen rind is one type of plant used in the treatment of diabetes mellitus as an alternative medicine. Xanthones found in mangosteen rind have antioxidant, antidiabetic, anticancer, anti-inflammatory, hepatoprotective, immunomodulatory, aromatase inhibitor, antibacterial, and other functional properties. Mangosteen rind (Garcinia mangostana.L.)(Lina, NWM, 2017)beneficial for health because it contains anthocyanins, tannins, phenol/polyphenol compounds, epicatechin, and xanthones. According to research, the compounds found in mangosteen peel (Garcinia mangostana L) consist of 8-hydroxykudraxanthone, gartanin, garcinon E, garcinone D, α mangostin, α-mangostin, α-mangostin, mangostinon, smeathxanthone, and tovophyllin A. The compounds with the highest activity are α mangostin, α-mangostin, and garcinone D(Jung HA, 2006).

Based on this background, the researcher is interested in conducting research with the title "testing the effectiveness of mangosteen peel extract nanoemulsion preparations (Garcinia mangostana L) on GDP, HbA1c and MDA levels and histopathological features of the pancreas of alloxan-induced diabetic rats".

LITERATURE REVIEW

In people without diabetes, the pancreas produces more insulin whenever blood glucose levels rise, such as after a meal, and insulin signals the body's cells to take up glucose. However, in people with diabetes, the pancreas' ability to produce insulin or the cells' response to insulin changes.(Willcox, A., & Gillespie, 2015)The pancreas is an organ in the digestive system responsible for two main functions: producing digestive enzymes (exocrine function) and producing hormones (endocrine function). The pancreas is located in the upper left quadrant of the abdomen, with its head attached to the duodenum. Enzyme products enter the duodenum through the main pancreatic duct.(Scanlon et al, 2007).The pancreas is located in the upper left quadrant of the abdomen or stomach and its caput/head is attached to the duodenum organ. Enzyme products will be channeled from the pancreas to the duodenum through the main pancreatic duct.(Alex, 2024).

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A pancreatic blood test measures important markers such as amylase, lipase, and blood glucose to assess pancreatic health and function. A pancreatic blood test involves drawing blood to measure a number of markers that can indicate the health and function of the pancreas. Diseases such as pancreatitis (inflammation of the pancreas), pancreatic cancer, diabetes, and other inflammatory conditions can be detected through this test.(Apollo Hospitals, 2025).

Mangosteen is known as the "queen of fruits" because of its delicious, sweet and slightly sour taste. Mangosteen not only tastes good, but is also known to contain high levels of antioxidants, such as xanthones, which are thought to have numerous health benefits. Xanthones found in mangosteen rind have antioxidant, antidiabetic, anticancer, anti-inflammatory, hepatoprotective, immunomodulatory, aromatase inhibitor, antibacterial, and other functional properties. Mangosteen rind (Garcinia mangostana.L)(Lina, NWM, 2017)beneficial for health because it contains anthocyanins, tannins, phenol/polyphenol compounds, epicatechin, and xanthones.

METHODS

This study uses an experimental quantitative research type, namely by using a true experiment or laboratory experimental design where this study was conducted to test the effectiveness of mangosteen peel extract nanoemulsion preparations (Garcinia Mangostana L) on GDP, HbA1c and MDA levels and the histopathological features of the pancreas of alloxan-induced diabetic rats.The research design uses a post-test with control group design or controls the sample based on the treatment group.*post test*was carried out to see the success of the extract in reducing GDP, HbA1c and MDA levelsin mice that had experienced diabetes mellitus after being inducedalloxan which was then carried out histopathological observations on the pancreas of mice in each treatment group.

The sample of this study was male Wistar rats (Rattus norvegicus) weighing 160-250 grams and aged 2-3 months. The number of test animals was 4 per group. In this study, researchers used 20 Wistar rats for each experimental group: the negative control group (K-), positive control group (K+), Treatments 1, 2, and 3 (P1, P2, P3). The test animals were acclimatized for 7 days in the laboratory of the Department of Pharmacology and Therapeutics, Faculty of Medicine, University of North Sumatra.Nanoemulsion of Mangosteen Peel Extract (Garcinia Mangostana L)with the methodextraction process using the maceration methodand made in nanoemulsion preparations with adjusted particles where the size of the nanoemulsion particles is carried out using a Particle Size Analyzer (Horiba Scientific, Nanoparticle Analyzer SZ-100) and the results will be given to rat samples once a day for 14 days. Treatment was given to treatment groups 1, 2 and 3 using the concentration of the nanoemulsion extract preparation.mangosteen peel with concentrations of F1 (1%), F2 (2%), and F3 (3%). Measurement of blood glucose in mice by looking at GDP, HbA1c and MDA levels and using a blood glucose meter with Easy Touch GCU which is taken through the mouse's tail and seen the comparison before and after being given the extract. For the histopathological description of the mouse pancreas using pancreatic observations using a 400x magnification myxopsis. Diabetes mellitus mouse model with alloxan induction within 14 days of induction. Then the data from the research results were tabulated and analyzed with the help of SPSS (Statistics of Package for Social Science).

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RESULT

In the characterization test of mangosteen peel extract nanoemulsion(Garcinia Mangostana L) the characterization results are: particle size of 159nm indicates the emulsion is stable and has good particle distribution, Polydispersity Index (PDI) 0.2 so that the particle size distribution is homogeneous and physically stable, particles are round and evenly distributed without clumping, pH 5.2 which is suitable for topical application and safe for the skin, viscosity test with relatively low results and shows good fluid properties so that it facilitates application and penetration into the skin. So that the presentation of the extract in nanoemulsion is appropriate and can be used in research.

Phytochemical testing revealed the following compounds in the extract: xanthones, flavonoids, alkaloids, terpenoids, tannins, saponins, and steroids. Therefore, the extract is rich in bioactive compounds that can have various pharmacological effects, such as antioxidant, antimicrobial, and anti-inflammatory activity.

Before being given to test animals,Previously, all groups of mice were acclimatized for 7 days and before the study was carried out, the mice were fasted for 12 hours and then their blood glucose was measured before induction.alloxanwith a dose of 60 mg/kgbb to induce diabetes mellitus, the treatment was given by injection 3 times a week intraperitoneally. After 14 days, the mice's glucose levels were measured again. And in the initial measurement, it was known that all groups were at normal glucose levels, namely <97.89 mg/dL. The study was carried out again with the administration of alloxan induction. After being induced and re-examined, the mice's glucose levels (FBG) were first fasted for 12 hours before blood samples were taken, and re-examined for the observation of FBG 1 (after alloxan induction) and FBG 2 (after being given treatment with nanoemulsion extract of mangosteen peel extract (Garcinia Mangostana L).

Then, histopathological observations were carried out using a light microscope with a magnification of 400x. The purpose of this observation was to see the structure and morphology of the cells in each pancreatic tissue specimen in the control group and the treatment group given mangosteen peel extract nanoemulsion.

Reporting Research Results

The administration of nanoemulsion extract of mangosteen rind (Garcinia Mangostana L) was given for 14 days so that the total of this study was 28 days. The dosage of extract administration for each group was different, namely the negative control group (K-) mice induced by alloxan but not given any treatment, the positive control group (K+) mice induced by alloxan and given metformin at a dose of 200 mg/kgbb, treatment group 1 (P1) was given nanoemulsion extract of mangosteen rind (Garcinia Mangostana L) with a concentration of 1%, Treatment 2 (P2) with a concentration of 2%, and treatment 3 (P3) with a concentration of 3%.

As fornormal GDP levels in mice are 80-120 mg/dL, the normal valueHbA1c is 3.5 – 5.5%, and the normal value of serum MDA is 1.5 – 3.5 nmol/mL. The following are the research results and data analysis:

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Table 1. Results of GDP Level Observations (mg/dL),HbA1c (%) and MDA (nmol/mL)

	Group (n=4) Mean ± Standard Deviation					Normality	Homogeneity	P Value
Variables	**K -**	**K +**	**P1**	**P2**	**P3**	***Shapiro Wilk***	***Levene Test***	
GDP 1	275.5±4.35	272.2±11.5	270.2±11.9	260±12.19	272 ±7.78	All Groups p>0.05	0.414	0.287
GDP 2	286.7± 6.23	123 ±8.04	105.5±6.24	92±5.16	86.5±2.38	All Groups p>0.05	0.164	0,000
HbA1c	11.6±0.21	5.9±0.28	5.3±0.21	4.8±0.18	4.6±0.84	All Groups p>0.05	0.171	0,000
MDA	9.4±0.47	3.4±0.22	3.22±0.95	2.6±0.17	2.25±0.12	All Groups p>0.05	0.101	0,000

Note: GDP1 = after Alloxan Induction, GDP 2 = After Extraction Treatment

The variable data of GDP levels after alloxan induction (GDP 1) obtained an average GDP result in all groups > 200 mg / dL, where all groups have been declared hyperglycemia and suffering from diabetes mellitus, while the group with the highest average is in the negative control group (K-) with GDP results of 275.5 ± 4.35. So that alloxan induction successfully caused diabetes mellitus in mice. After data analysis, the normality test using the Shapiro Wilk test showed a p value > 0.05, the homogeneity test using the Levene test produced p > 0.05. It can be concluded that GDP 1 data is normally distributed and homogeneous. Continued one-way ANOVA testing showed a p value = 0.287 where p > 0.05 so it can be concluded that there is no significant difference between treatment groups.

GDP variable data afterfor 14 days of treatmentnanoemulsion of mangosteen peel extract (GDP 2) showed an average GDP result in the negative control group (K-) with a result of 286.7 ± 6.23, so the mice in this group were declared to remain diabetic mellitus with glucose results> 200 mg / dL and far from the normal GDP level limit in mice. In the positive control group (K +) with a result of 123 ± 8.04, a decrease in glucose levels was seen so that metformin used in diabetes treatment was tested to be able to reduce blood glucose levels in mice even though these levels were still above the normal GDP limit in mice. In treatment group 1 (P1) with a result of 105.5 ± 6.24, treatment 2 (P2) with a result of 92 ± 5.16 and treatment group 3 (P3) with a result of 86.5 ± 2.38, from the data it was seen that there was a decrease in glucose levels so that the administration of nanoemulsion of mangosteen peel extract at a concentration of 1%, 2% and 3% was able to reduce blood glucose levels in mice and glucose levels returned to normal. After data analysis, the normality test using the Shapiro Wilk test showed a p value > 0.05, the homogeneity test using the Levene test produced p > 0.05. It can be concluded that GDP 2 data is normally distributed and homogeneous. Continued one-way ANOVA testing showed a p value = 0.000 where p < 0.05 so it can be concluded that there are significant differences between treatment groups. The best order of effectiveness of administering mangosteen peel extract

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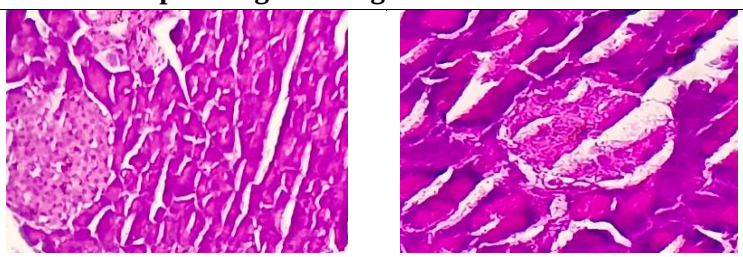
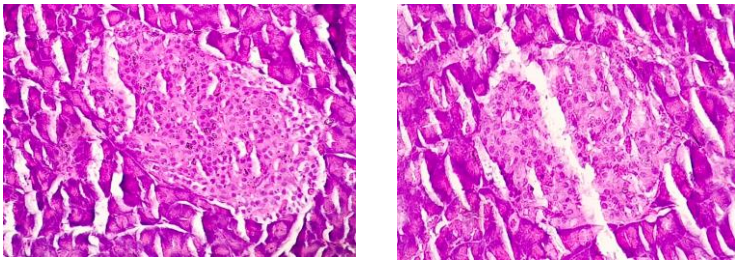
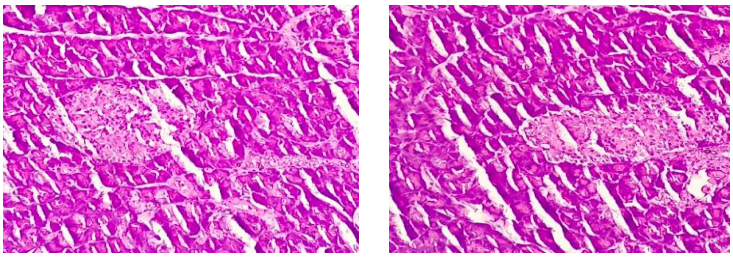
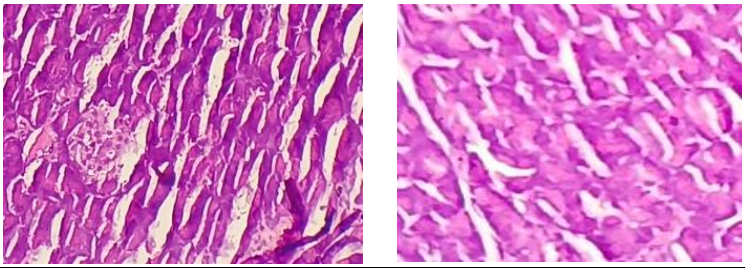
(Garcinia Mangostana L) nenoemulsion to reduce glucose levels in rats in groups P3, P2 and P1 with concentrations of 3%, 2% and 1%.

LevelHbA1c (%) in each research group showed the highest average in the negative control group (K-) of 11.6±0.21, while the lowest average was in treatment group 3 (P3) which was 4.6±0.84. In the positive control group (K+) which was given metformin treatment, the average was 5.9±0.28 and this result had not reached normal levels. So the best order of effectiveness of administering mangosteen peel extract (Garcinia Mangostana L) nenoemulsion in the group that reduced HbA1c and reached normal values was in the treatment groups P3, P2 and P1 with concentrations of 3%, 2% and 1%.

LevelMDA (nmol/mL) in each research group showed the highest average in the negative control group (K-) of 9.4±0.47, while the lowest average in treatment group 3 (P3) was 2.25±0.12. In the positive control group (K+) which was given metformin treatment, the average was 3.4±0.22 and this result had reached normal levels. So the best order of effectiveness of administering mangosteen peel extract (Garcinia Mangostana L) nenoemulsion in the group that reduced MDA and reached normal values in the treatment groups P3, P2, P1 with concentrations of 3%, 2% and 1% and followed by the positive control group (K+) with metformin administration of 200 mg/kgbb.

In histopathological observations of the mouse pancreas, the image below can be seen:

Table 2. Histopathological Description of Pancreatic Tissue

No	Group	Histopathological Image of Pancreatic Tissue
1	ControlNegative (K-)	
	Positive Control (K+)	
2	Treatment 1 (F1=1%)	
3	Treatment 2 (F2=2%)	

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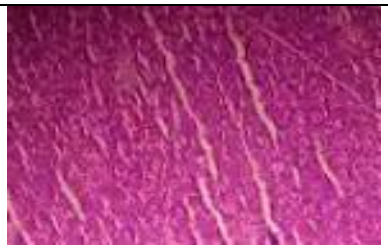
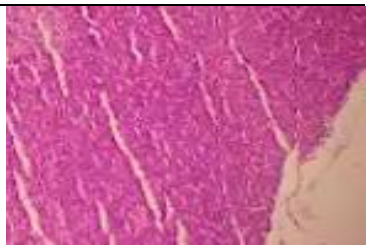
4	Treatment 3 (F3 =3%)		

Based on the cell morphology data above, there were differences in each group. The negative control group (K-), which was induced by alloxan but not given any treatment, received a score of 4 for pancreatic cell necrosis. The positive control group (K+), which was induced by alloxan and given 200 mg/kg of metformin, and treatment group 1 (P1), which was induced byalloxanand given treatment with mangosteen peel extract nanoemulsion with a concentration of 1% had histopathological features of the pancreas in the form of interstitial edema found between serous acini, leukocyte infiltration, mild vacuolization and pancreatic necrosis so that this group received a score of 3, namely there was ¾ of total pancreatic cell necrosis. In treatment group 2 (P2) which was inducedalloxanand given treatment with mangosteen peel extract nanoemulsion at a concentration of 2%, a significant difference was seen due to slight leukocyte infiltration and slight necrosis seen in pancreatic cells, so this group was given a score of 1, which is ¼ pancreatic cell necrosis. Meanwhile, in treatment group 3 (P3) which was inducedalloxanand given treatment with mangosteen peel extract nanoemulsion with a concentration of 3%, necrosis was no longer seen, but slight leukocyte infiltration was seen in the pancreatic cells so that this treatment group received a score of 0, meaning there was no pancreatic cell necrosis.

DISCUSSION

The pancreas is an organ located in the stomach that functions to produce a hormone called insulin, insulin is useful for helping glucose enter cells.(Spătărelu & Popa, 2021)Diabetes mellitus often begins with obesity due to overeating. To compensate, pancreatic β cells respond by secreting more insulin, increasing insulin levels (hyperinsulinemia). High insulin concentrations cause insulin receptors to self-regulate by decreasing the number of receptors.(S, 2014)Blood sugar tests are important for monitoring blood sugar levels and early detection of diabetes. FBG and HbA1c levels can be used as a reference for assessing a patient's blood sugar status. Routine HbA1c testing can be performed to measure glycemic levels and is associated with the risk of DM complications. Oxidative stress plays a key role in the pathogenesis and complications of DM. One biomarker of lipid peroxidation is malondialdehyde (MDA), whose levels have been found to be elevated in patients with diabetes mellitus.(Anita Rosari Dalimunthe, 2023).

This study aims to determineThe effectiveness of nanoemulsion preparation of mangosteen peel extract (Garcinia mangostana L) on GDP, HbA1c and MDA levels and histopathological features of the pancreas of alloxan-induced diabetic rats. With the results of the observationPhytochemical analysis of mangosteen peel extract with ethanol solvent shows that the extract is rich in bioactive compounds that can have various pharmacological effects, such as antioxidant, antimicrobial, and anti-inflammatory activities. because it contains compounds such asxanthones, flavonoids, alkaloids, terpenoids, tannins, saponins and steroids.

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On examinationGDP levels after alloxan induction (GDP 1) obtained an average GDP result in all groups > 200 mg/dL, where all groups were declared hyperglycemic and suffering from diabetes mellitus, while the group with the highest average was the negative control group (K-) with a GDP result of 275.5±4.35. Afterfor 14 days of treatmentnanoemulsion of mangosteen peel extract (GDP 2) showed treatment group 1 (P1) with results of 105.5 ± 6.24, treatment 2 (P2) with results of 92 ± 5.16 and treatment group 3 (P3) with results of 86.5 ± 2.38, from the data it can be seen that there is a decrease in glucose levels so that the administration of nanoemulsion of mangosteen peel extract at concentrations of 1%, 2% and 3% is able to reduce blood glucose levels in mice and glucose levels return to normal. And the average GDP results in the negative control group (K-) with results of 286.7 ± 6.23 then the mice in this group are declared to remain diabetes mellitus with glucose results> 200 mg / dL and far from the normal GDP level limit in mice. In the positive control group (K +) with results of 123 ± 8.04 there is a decrease in glucose levels so that metformin used in the treatment of diabetes is tested to be able to reduce blood glucose levels in mice even though these levels are still above the normal GDP limit in mice. So the best order of effectiveness of administering mangosteen peel extract (Garcinia Mangostana L) nenoemulsion to reduce glucose levels in mice in groups P3, P2 and P1 with concentrations of 3%, 2% and 1%.

In histopathological examination of the pancreas of mice,in treatment group 3 (P3) which was inducedalloxanand given treatment with nanoemulsion of mangosteen peel extract with a concentration of 3%, necrosis was no longer seen, but slight leukocyte infiltration was seen in the pancreatic cells, so that this treatment group received a score of 0, meaning there was no pancreatic cell necrosis. Therefore, administration of nanoemulsion of mangosteen peel extract (Garcinia Mangostana L.)effective in healing pancreatic cells that suffer from diabetes mellitus andadministration at a concentration of 3% extract showed that pancreatic cells no longer experienced necrosis so that the score was 0. This is inseparable from the properties of mangosteen peel (Garcinia Mangostana L) which has properties from bioactive compounds that can have various pharmacological effects, such as antioxidant, antimicrobial, and anti-inflammatory activity. which can repair damaged cell tissue due to diabetes mellitus experienced by white rats (Rattus norvegicus) Wistar strain.

Based onPrevious research, compounds found in mangosteen peel (Garcinia mangostana L) consist of 8-hydroxykudraxanton, gartanin, garcinon E, garcinone D, α mangostin, α-mangostin, α-mangostin, mangostinon, smeathxanton, and tovophyllin A. The compounds with the highest activity are α mangostin, α-mangostin, and garcinone D.(Jung HA, 2006). And based on research that has been done, it also proves that the Xanthone content found in mangosteen peel has antioxidant, antidiabetic, anticancer, anti-inflammatory, hepatoprotective, immunomodulatory, aromatase inhibitor, antibacterial, and other functional properties, mangosteen peel (Garcinia mangostana.L)(Lina, NWM, 2017).

CONCLUSION

1. The compounds in mangosteen peel extract that were tested through phytochemical testing were compoundsxanthones, flavonoids, alkaloids, terpenoids, tannins, saponins and steroids
2. After being given nanoemulsion of mangosteen peel extract at concentrations of 1%, 2% and 3%, the GDP levels of groups P1, P2 and P3 were105.5 mg/dL, 92 mg/dL, 86.5 mg/dL. For blood sugar levelsHbA1c levels were 5.3%, 4.8%, and 4.6%, respectively, and MDA levels were 3.22%.nmol/mL, 2.6 nmol/mL and 2.25 nmol/mL.

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3. administration of nanoemulsion of mangosteen peel extract (Garcinia Mangostana L)effective in healing pancreatic cells that suffer from diabetes mellitus andAdministration of the extract at a 3% concentration showed that pancreatic cells no longer experienced necrosis. At a 2% concentration, a significant difference was observed, as there was slight leukocyte infiltration and minimal necrosis in pancreatic cells. At a 1% concentration, histopathological features of the pancreas included interstitial edema between serous acini, leukocyte infiltration, mild vacuolation, and pancreatic necrosis.

ACKNOWLEDGEMENT

This final assignment was completed thanks to the assistance and support of various parties. The author would like to express his gratitude to the Rector of Universitas Prima Indonesia, my academic supervisors, my beloved family, and my colleagues who have assisted me throughout the research process.

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