



Noni (*Morinda Citrifolia*) Ethanol Extract Lowered Blood Glucose Levels, Increased Glutathione Peroxidase Activity, And Decreased Malondialdehyde in White Rats Model of Diabetes

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Abstract: Diabetes mellitus can increase oxidative stress and damage cells. Noni fruit has antibacterial, antifungal, antitumor, analgesic, hypotensive, and anti-inflammatory benefits, can boost immunity, and has antioxidant content. Noni contains phenolic compounds (anthraquinones, acutities, asperulosides, and scopoletin), organic acids (capric and caprylic acids), and alkaloids (xeronine). The effect of noni ethanol extract can significantly reduce blood glucose ($P < 0.05$) of the T2 group (177.00 ± 137.78) and T3 (159.40 ± 86.53) when compared to the C+ group (511.00 ± 131.45). The T1 group (387.40 ± 170.06) had no significant difference ($P > 0.05$) when compared to the C+ group (511.00 ± 131.45), but there was a decrease in the average yield at T1 (387.40 ± 170.06). Serum malondialdehyde (MDA) examination showed a significant decrease ($p < 0.05$) in T1 (1188.32 ± 93.41), while in T2 (1385.35 ± 38.65) and T3 (1460.32 ± 42.51) was not significant ($p < 0.05$). Examination of serum glutathione peroxidase (GPX) showed a significant decrease in T1 (119.97 ± 37.45), there was a decrease in GPX levels, while in the T2 group (236.14 ± 6.05) and T3 (185.24 ± 43.07), there was no decrease. Noni ethanol extract can lower blood glucose levels, reduce Malondialdehyde levels, and prevent increased activity of the enzyme glutathione peroxidase. Flavonoid compounds in noni ethanol extract can avoid increased blood glucose and reduce free radicals formed due to hyperglycemia conditions.

Keywords: Blood Glucose; Diabetes Mellitus; Flavonoids; Glutathione Peroxidase; Metabolic; Malondialdehyde

Introduction

Diabetes Mellitus is a metabolic disease characterized by increased glucose levels in the blood (Cho et al., 2018; Wardani, 2023). Diabetes consists of several types, namely type 1 diabetes mellitus, type 2 diabetes, and gestational type diabetes. People with diabetes increased from 108 million in 1980 to 422 million in 2014. Diabetes mellitus caused the death of 1.6 million people in 2015, and almost half of these deaths occurred at the age of under 70 years (Basit et al., 2018).

Type 2 diabetes is the most common type of diabetes, where type 2 diabetes mellitus is an increase

in blood sugar levels due to insulin resistance (Chatterjee et al., 2017). Insulin resistance can be caused by pancreatic beta cell dysfunction, an unhealthy lifestyle is the cause of type 2 diabetes mellitus (Mentari et al., 2023).

Lack of physical activity can affect the number of insulin receptors so that it can affect the speed of GLUT-4 (glucose transporter-4), which decreases and can be a factor causing an increased risk of type 2 diabetes (Sayem et al., 2018).

In the condition of diabetes mellitus, glucose cannot be absorbed, so that it can cause the body's response to convert glucose into sorbitol with aldose reductase

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enzyme pranan (Fatmawati et al., 2023). Changes in glucose molecules require NADPH, which is converted into NADP. This mechanism can cause the use of NADPH and cause NADPH deficiency, which can contribute to oxidative stress, this is because NADPH is the primary raw material for endogenous antioxidant enzymes such as Glutathione peroxidase (GPX) to convert hydrogen peroxide radicals (H_2O_2) into water (H_2O) and oxygen (O_2) molecules (Dahlan et al., 2023; Yan, 2018). Increased production of free radicals due to hyperglycemic conditions, causing oxidative stress conditions this condition causes endogenous antioxidants unable to neutralize the free radicals formed, where which can cause an increase in the oxidation process so that it can cause lipid peroxidation and produce mutagenic products, namely malondialdehyde (MDA). Free radicals can also react with cell components so that they can cause cell damage (Decroli et al., 2019).

Research on noni fruit (*Morinda citrifolia*) as a diabetes treatment is important, because noni fruit has been used traditionally for its potential health benefits, including its anti-diabetic properties. Diabetes is a common and challenging health condition in Indonesia, and alternative treatments are needed to complement existing therapies (Dahlan et al., 2023). Research on noni fruit can provide valuable insight into its potential as a natural remedy for diabetes, thereby contributing to the development of new and effective treatments (Nindatu et al., 2023). Increasing interest in natural and traditional medicines, research on noni fruit could help bridge the gap between traditional knowledge and modern scientific evidence, potentially leading to the development of new anti-diabetic drugs or supplements (Hamzah et al., 2023). The traditional use of noni fruit in Indonesia and its potential health benefits require scientific investigation to validate its efficacy as an antidiabetic agent. This kind of research could contribute to the development of new and effective diabetes treatments, providing potential benefits for individuals living with this condition (Adiaksa et al., 2023).

Noni fruit (*Morinda citrifolia*) is an herbal plant that grows in many landmarks of Asia including Indonesia. Based on the results of previous studies, noni fruit has benefits for antibacterial, antifungal, antitumor, analgesic, hypotensive, and anti-inflammatory, can increase immunity, and has antioxidant content. Noni contains phenolic compounds (anthraquinones, aucubittins, asperulosides, and scopoletins), organic acids (caproic and caprylic acids), and alkaloids (xyronin) which are very good for the body to help improve body health (Hasri et al., 2018) (Rajivgandhi et al., 2020). Noni fruit has the potential to be developed as

an herbal medicine.

Herbal medicines from natural plants have the advantage that they are safer and have fewer side effects compared to the use of modern medicine (Mishra et al., 2020; Yulianti, Mercuriani, Sugiyarto, & Huang, 2023). Noni fruit is a fruit that is rich in antioxidants and has other benefits that are good for the health of the body; researchers are interested in further examining the use of noni fruit to be developed as a candidate for antidiabetic drugs in the future.

Materials and Methods

This research is experimental research with a post-test-only control group design. The total number of experimental animals used was 40, divided into five treatment groups. This research has received ethical approval with Number 117/EC-03/FK-06/UNIZAR/XII/2022.

Method

The research materials used were noni ethanol extract, aqua dest, newspaper as a base for disposal of rat feces, indomethacin, 0.9% saline solution, citrate buffer pH 4.5, split syringe 3 ml, ethylene diamine tetraacetic (EDTA) (Merck), rat blood, ELISA reagent kit (Cell Biolabs, INC).

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Preparation of Animal Models of Diabetes with Streptozotocin

The dose of indomethacin given to rats was 55 mg/kg body weight of rats. The average weight of the rats was ± 200 grams. Before being delivered to mice, rats were injected with nicotinamide at a dose of 230 mg/kg body weight; after 30 minutes, the rats would be injected with STZ. Experimental animals were divided into five treatment groups: negative control, positive control, treatment 1 with a dose of 30mg / 200gBB, treatment 2 with 60mg / 200gBB, and Treatment 3 with a dose of 120mg / 200gBB.

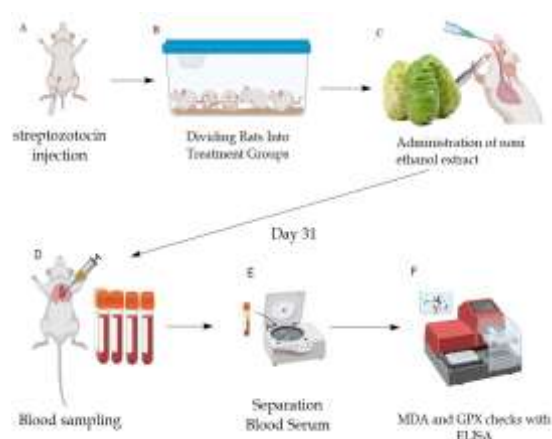


Figure 1. research flow on administering noni extract

Blood Sampling

Blood specimen collection of research subjects through heart function can be done as follows. Blood samples were taken on the 31st day after administration of noni ethanol extract. A blood draw (5 ml) was performed with a heart puncture after the rats were anesthetized with HCL ketamine. After blood collection, rats were sacrificed under anesthesia. The blood drawn is stored in a vacutainer tube. Blood samples will be taken on the 31st day, according to research conducted by Rao and Subramanian (2009) who gave noni extract for 30 days, and on the 31st day, the rat will be sacrificed first (Rao & Subramanian, 2009). Collection and storage of blood samples.

Glutathione peroxidase (GPX) examination in the serum of diabetic mouse models showed a significant decrease in T1 (119.97 ± 37.45), where there was a decrease in GPX levels, while in the T2 group (236.14 ± 6.05) and T3 (185.24 ± 43.07), there was no decrease, based on the results of the examination obtained normally distributed data presented in figure 1F.

Streptozotocin Administration

The induction of streptozotocin is a "chemical diabetes" that can make some species of experimental animals become diabetic, this induction can damage pancreatic beta cells impacting the body's insulin and blood glucose which will increase. The results of streptozotocin induction examination prove that streptozotocin is able to increase blood glucose levels, increase MDA levels, and increase GPX activity which can be seen in Figure 1.

Blood samples that have been accommodated in microtubes are centrifuged for 15 minutes at a speed of 3500 rpm. The plasma obtained is separated into 0.5 mL microtubes using appropriate micropipettes and tips. Microtubes that have been filled with plasma are labeled according to the sample code listed on the previous microtube. Statistical analysis to see the difference in

GPX activity and MDA levels of each group was carried out with the ANOVA test with a confidence interval value of 95%.

Noni ethanol extract reduces GDP levels

Induction of streptozotocin damaging pancreatic beta cells causes an increase in blood glucose, based on Table 1 and Figure 1A the effect of noni ethanol administration can significantly lower blood glucose levels in the T2 and T3 treatment groups. Noni fruit is reported to contain secondary metabolites, which are high in flavonoids that play a role in increasing the expression of GLUT (Glucose transporters 4) in muscle tissue, increasing GLUT4 involved in the process of glucose uptake into cells, and can prevent an increase in glucose outside the tissues and interstitial tissues that can cause a decrease in glucose in the blood (Wulandari, 2020).

This result is supported by research conducted by Royani, Hanafi, Julistiono, and Manaf (2023) where Noni fruit (*Morinda Citrifolia*) contains phenol and flavonoid compounds, secondary metabolite class compounds that are able to lower blood sugar levels. Flavonoid compounds can play an important role in increasing GLUT 4 expression, so as to maximize glucose absorption into cells and prevent increased glucose in the blood (Hajiaghaalipour et al., 2015).

Flavonoids are phenolic compounds that are widespread in the Plant Kingdom and are an essential component in the human diet. These compounds exhibit promising antidiabetic activity, including inhibition of α -amylase and α -glucosidase (Semaan et al., 2017). Flavonoid compounds can be inhibitors of α -Amylase and α -glucosidase have been shown to slow the release of glucose from starch and oligosaccharides, resulting in delayed glucose absorption and decreased postprandial blood glucose levels (Proença et al., 2022)

Result and Discussion

The results of noni ethanol extract on blood sugar levels, MDA, and GPX activity in white rats (*Rattus Norvegicus*) diabetes model which were divided into 5 treatment groups, below is a table of the average (mean) and standard deviation of each treatment. Table 1 attaches the results of fasting blood sugar levels, glutathione peroxidase, and malondialdehyde data figure 1 is the average curve and normality data results that have been obtained from the measurement results. Effects of noni ethanol extract can lower blood glucose in diabetic rat models. Figure 1A shows that there is a significant difference ($P < 0.05$) in the T2 group (177.00 ± 137.78) and T3 (159.40 ± 86.53) when compared to the C+ group (511.00 ± 131.45). The T1 group

(387.40±170.06) had no significant difference ($P>0.05$) when compared to the C+ group (511.00±131.45) but there was a decrease in the average yield at T1 (387.40±170.06). The effect of noni ethanol extract on serum malondialdehyde (MDA) examination showed a significant decrease ($p<0.05$) in T1 (1188.32±93.41) which can be seen in Figure 1C, the distribution of data from the results of MDA levels is normally distributed. While T2 (1385.35±38.65) and T3 (1460.32±42.51) did not show a significant decrease ($p<0.05$).

Table 1. Results of Examination of GDP, MDA, and GPX Levels

Group	GDP(Mean±SD)	GPX (Mean±SD)	MDA (Mean±SD)
Negative Control (C-)	151.60±13.24	107.138±29.97	216.78±97.53
Positive Control (C+)	511.00±131.45	239.10±95.38	1507±364.26
Treatment 1 (T1)	387.40±170.06	119.97±37.45	1188.32±93.41
Treatment 2 (T2)	177.00±137.78	236.14±6.05	1385.35±38.65
Treatment 3 (T3)	159.40±86.53	185.24±43.07	1460.32±42.51

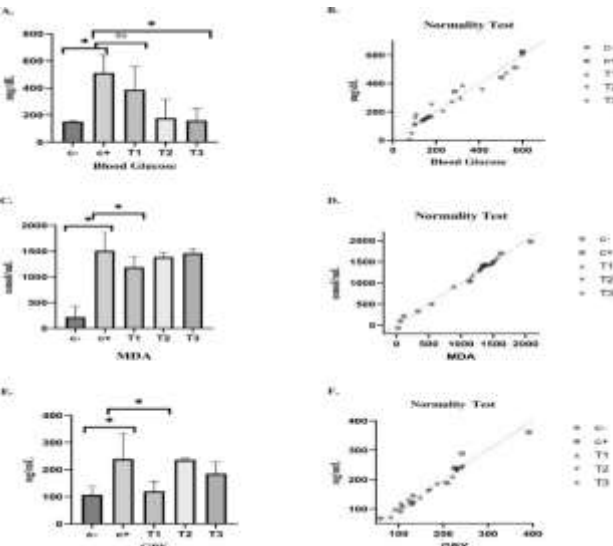


Figure 2. Average Graph and Data Normality

Administration Of Noni Ethanol Extract Increases MDA Levels

Malondialdehyde (MDA) is a mutagenic substance resulting from the reaction of free radicals with lipids, the role of free radicals has a major effect on the formation of MDA, the process of streptozotocin induction can cause the formation of free radicals (Martemucci et al., 2022). An increase in free radicals due to hyperglycemia conditions can lead to the

formation of Reactive OxygenSpecies (ROS) in Figure 2. The formation of NADPH oxidase reaction and glycation reaction electron chain can increase the formation of ROS. The production of superoxide anion radicals is able to react with lipids in cells and cause the formation of malondialdehyde (MDA) compounds (Sundaram et al., 2019).

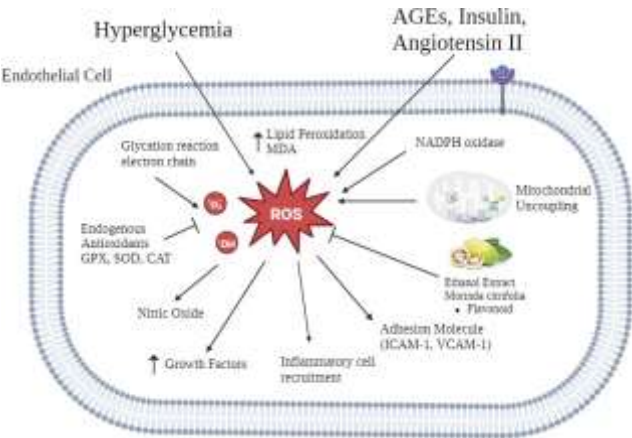


Figure 3. ROS Generation Mechanism

Hyperglycemia conditions can increase the xanthine oxidase reaction 3-fold so as to increase the radical production of superoxide anion (Matsumoto et al., 2003). The production of superoxide anion radicals able to react with lipids increases lipid peroxidase reactions in cells and causes the formation of malondialdehyde (MDA) compounds (Sundaram et al., 2019; Tandi et al., 2023).

The average result of noni ethanol extract at a dose of 150mg/kg body weight at T1 (1188.32±93.41) was able to reduce malondialdehyde (MDA) levels when compared to the positive control group (1507±364.26), based on the results of statistical tests it was found that there was a significant difference ($p < 0.05$) between treatment group 1 and positive control, this can occur because flavonoid compounds in noni fruit extract are able to reduce free radicals formed due to induction streptozotocin (Oteiza et al., 2021).

Research conducted by Landari, Kusumawati, Nursini, and Yogeswara (2023) looked at the profile of compounds in noni fruit (*Morinda citrifolia*), Noni fruit contains flavonoid compounds that can be used as free radical absorbers. Flavonoid compounds can play a role in providing electron donors to superoxide anion radical molecules so as to prevent lipid peroxidation and prevent an increase in malondialdehyde (MDA); this result is by research conducted by Ungur et al. (2022). Based on Figure 2, flavonoid compounds in noni can inhibit the increase in ROS and can prevent lipid peroxidation to prevent an increase in MDA (Qosimah et al., 2023; Ungur et al., 2022).

Hyperglycemia conditions can increase free radical production and cause ROS conditions (Lassie, Ashan, Triola, & Widiastuti, 2023). ROS conditions can cause inflammatory cell recruitment, affect adhesion molecules, ROS can increase MDA levels, flavonoid content can reduce free radicals formed from hyperglycemia conditions (Harun et al., 2023).

Administration of noni ethanol extract decreased GPX

Activity Glutathione peroxidase (GPX) enzyme examination showed an increase in GPX enzyme levels in the positive control group (C+) when compared to the negative control group (C-). Figure 1E shows that there is a difference in GPX enzyme activity with the noni extract administration group in the T1 group. Still, there is no significant difference in the noni ethanol extract administration group in the T2 and T3 groups. The increase in GPX activity in the positive control group (C+) can result from the response of the mouse body to compensate for the rise in free radicals caused by high blood sugar levels due to streptozotocin (STZ) injection to create a diabetic model mouse (Adhikary et al., 2021; Agustikawati et al., 2017).

Hyperglycemia conditions can cause increased formation of superoxide anion radicals, increased superoxide anion radicals can cause oxidative stress conditions, reactive superoxide anion radicals will be converted by the enzyme superoxide dismutase (SOD) into hydrogen peroxide which can react with iron and metal ions, causing a haber weis Fenton reaction which can cause the formation of hydroxyl radicals that are harmful to cells (Rolo et al., 2006).

Free radicals due to hyperglycemia conditions will respond to the expression of the glutathione peroxidase enzyme to reduce free radicals formed. The glutathione peroxidase enzyme can prevent the formation of hydroxyl radicals by converting hydrogen peroxide into water and oxygen molecules (Doroshov, 1995; Yariibeygi et al., 2019)

The results of noni extract (*Morinda citrifolia*) at T1 (119.97±37.45) Figure 1E were lower when compared to the positive control group (239.10±95.38) this difference can be caused by the content of secondary metabolite compounds found in noni fruit, flavonoid compounds in noni which can be electron donors to free radical molecules so as not to cause an increase in glutathione peroxidase expression in rats, in addition, flavonoid compounds can act as metal ion binders and prevent the formation of hydroxyl radicals (Slika et al., 2022). The results of this study are supported by research conducted by Souza et al. (2015) which looked at the ability of flavonoids to glutathione peroxidase levels in rat brains against aging and showed that flavonoids were able to prevent the activity of the enzyme

glutathione peroxidase (Souza et al., 2015). Prevention of this increase can be due to the ability of flavonoids to dampen free radicals (Maaliki et al., 2019).

Conclusion

Noni extract is a traditional plant that can be used as a healthy traditional plant if used. Giving noni ethanol extract as an antihyperglycemia drug in diabetic rats was able to lower blood glucose levels, reduce Malondialdehyde levels, and prevent increased activity of the enzyme glutathione peroxidase due to increased free radical response due to hyperglycemia conditions. Flavonoid compounds in noni ethanol extract can prevent an increase in blood glucose and reduce free radicals formed due to hyperglycemia conditions.

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The Author hereby declares that the work presented in this article is original and that any responsibility for claims relating to the content of this article will be borne by the Author.

Author Contributions

Conceptualization and methodology, I Putu Dedy Arjita (I.P.D.A), and I Putu Bayu Agus Saputra (P.B.A.S); formal analysis, Dhika Juliana Sukmana (D.J.S), I Putu Dedy Arjita (I.P.D.A), and I Putu Bayu Agus Saputra (P.B.A.S); investigation, I.P.D.A, P.B.A.S, and D.J.S; writing— original draft preparation, I.P.D.A, P.B.A.S, and D.J.S; writing— Review and editing, I.P.D.A, P.B.A.S, and D.J.S Visualization. P.B.A.S All authors have agreed to the published version of the manuscript.

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Conflicts of Interest

The authors state there is no conflict of interest.

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