

Antidiabetic Activity of Noni (*Morinda citrifolia*) Extract on Swiss Webster Male Glucagon-Induced Mice

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Abstract: The antidiabetic activity of noni (*Morinda citrifolia*) extract on the blood glucose level of Swiss Webster male mice (*Mus musculus*) has been examined. This research aims to study the antidiabetic activity of noni fruit extract on blood glucose level by either induced or not induced with glucagon. Twenty-eight Webster male mice were divided into two main treatment groups. The first treatment group was further divided into four treatment sub-groups. These are (i) blank control (without any treatment), (ii) given distilled water only, (iii) given the extract in a dosage of 1,5 g/kg body weight (bw), and (iv) given the extract in a dosage of 3 g/kg bw. The second treated group was divided into three other treatment group. These are: (i) glucagon+ distilled water, (ii) glucagon+the extract in a dosage of 1,5 g/kg bw, and (iii) glucagon+the extract in a dosage of 3 g/kg bw. The experiment was done with four replicates to each sub-group. The volume of distilled water and the extract were given by gavage in a dosage of 10 ml/kg bw, whereas the glucagon was given through intramuscular injection in a dosage of 20 µg/kg bw. The treated sub-groups without glucagon were injected with distilled water and the extract once every two weeks for eight weeks (1th, 3th, 5th, 7th week) with per week interval for blood sampling (zero, 2nd, 4th, 6th, 8th week). The blood glucose levels (BGL) of this sub-group is fasting blood glucose level (BGLf) and two hours post-prandial (2-hrs pp) blood glucose level). The sub-groups with glucagon injection were given distilled water and the extract once a week for four weeks (1th-4th week) with three times per week blood sampling, namely before glucagon injection (BGLa), 10 minutes after the injection (BGLb) and 2 minutes after distilled water or the extract. The results of the statistic test showed (ANOVA $p < 0,05$) that BGL of noni fruit extract-treated mice (doses: 1,5 and 3 g/kg bw) without glucagon injection for eight weeks, tends to decrease. The distilled water feeding does not affect BGL. It can be seen that during 8 weeks of distilled water treatment, it appears that BGLf and BGLe of the distilled water group were not significantly different from the control group. Mice treated with noni fruit extract (doses: 1,5 and 3 g/kg bw) and glucagon injection for four weeks, showed constant BGL. The conclusion is that noni fruit extract helps to decrease blood glucose levels in both groups of mice either induced or not induced with glucagon. That can be seen from the result of statistical tests that shows BGLf and BGLe of the noni group, both at a dose of 1.5 g / kg bw and 3 g / kg bw, from week 2 to week 8 were significantly different from the control group. Meanwhile, in the mice treated with glucagon in the noni group with both doses, BGL decreased after administration of noni. That also shows the significant difference of BGLf and BGLe of the noni group with the control group.

Keywords: antidiabetic activity, blood glucose level, glucagon, *Morinda citrifolia*, noni fruit extract

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1. INTRODUCTION

In line with changes in lifestyle and the complexity of life today, various dangerous diseases have emerged and must be watched out for. One of them is diabetes mellitus or diabetes which causes complications of other diseases that can lead to death. The existence of various kinds of complex diseases is often treated with traditional medicine. One of them is the noni (*Morinda citrifolia* L.) from the Rubiaceae family. Noni in the world is found in tropical areas in Asia,

Africa, Australia, and island areas in the Pacific Ocean. Noni has various names in these areas such as: noni in Hawaii as a divine medicine that can help cure various diseases so it is often called magic plant, nonu or nono in Tahiti, cheese fruit in Australia (Bahalwan and Sjabana, 2002). Each part of *Morinda citrifolia* has its beneficial value for mankind especially the fruit of Noni has nutritional and healing Morales (Amareshwar *et al*, 2021). Noni is also used in industries as natural preservatives and chemical reagents (Reem *et.al*, 2017). Noni fruits are

abundantly used in the preparation of juice for diabetics and also curing flu, cold, high blood pressure, fear and sadness (Amareshwar, *et al.*, 2021). All around the globe, it's been said that it has a wide variety of health advantages for cancer, infection and pain are all conditions that affect people (Whistler, 1992). The fruit of noni also has a long history of usage as a meal in tropical places all over the world (Amareshwar, *et al.*, 2021). In Indonesia, noni fruit has been known since ancient times as medicine because noni juice extract contains substances such as metal acetyl ester, moridon, soranjidol, turpentine (rejuvenates cells), acubin L, dammachantel, proxeronin, anthraquinone (anti-bacterial / anti-fungal), scopoletin, xeronin regulate the rigidity and form of specific and hypochemical proteins (Shin, 1995). Solomon (1999) conducted a survey of 40 specialist doctors. Eight thousand patients from the results of this survey showed a success rate of up to 78% for those who have used noni juice to treat various diseases such as high blood pressure, cholesterol, stroke, cancer, gout/rheumatism, diabetes, decreased stamina, depression, kidney disorder, stress, liver, colitis, sprains, bruises, diseases due to aging, indigestion, treating drug addiction, killing skin .fungi, parasites and at least seven kinds of harm. There have been no previous studies using glucagon as an inducer for diabetes. Most studies use alloxan and streptozotocin to lift BGL on the experimental animals. Therefore, we use glucagon as a hormone that is involved in controlling blood sugar (glucose) levels to rise BGL in the mice.

The noni extract in this study was given by gavage instead of intravenously injecting to know the effect of the extract on the BGL whereas there are not many studies done by gavage. In a study conducted by Bahalwan and Soedjarwo (2001), it was proven that giving noni fruit water extract can reduce blood sugar

levels of white rats (Wistar strain) induced by alloxan. in a study conducted by Sakinah (2018), RS3 (Resistant Starch Type 3) cassava starch proved to be able to blood sugar levels and increase GLP-1 levels in a rat model of type diabetes mellitus 2 during treatment for 4 weeks until RS3 Cassava starch is proven to be a modality new therapies in the treatment of disease type 2 diabetes mellitus. This study aims to determine the effect of noni fruit extract given by gavage on blood glucose levels of male mice that are induced or not induced with glucagon. This study needs to be done to know whether there is a significant difference in BGL of mice induced and not induced by glucagon when the mice are treated with noni extract.

2. MATERIAL AND METHODS

2.1. Experimental and rearing animals

The experimental animals used in this study were 28 male Swiss Webster mice (*Mus musculus L.*) aged 4 months with bw ranging from 35-40 grams. The experimental mice were kept in the animal pen on the 4th floor of the School of Life Sciences and Technology (SITH) ITB with room temperature conditions of 27 ± 1.5 °C with a humidity of $82 \pm 5\%$. Mice were fed with pellets produced by PT Charoen Pokphand Indonesia in excess (ad libitum). For drinking water, tap water is enough.

2.2. Experimental material

Noni fruit is obtained from the garden of a resident in the Cigadung area, Bandung, West Java. The specimen of noni fruit is made by drying 1000 grams of noni fruit that has been ripe in an oven at a temperature of 49 ± 1.5 °C for 5 hours and produces dried samples (I and II) with a dry weight of 480 gr. Before being given to the test animals, the thick extract of noni fruit that has been stable in weight

(total weight = 48 g) is dissolved in 100 ml of distilled water. The dosage used in the experiment is 1.5 grams and 3 grams of noni fruit extract per kilogram of bw. The stock solution was made in concentrations of 15% and 30% (w / v) by dissolving 15 g and 30 g of thick extract, which weighed stabilized into distilled water until it reached 100 ml solution, respectively.

2.3. Preliminary test

A preliminary test is performed to determine the dosage of glucagon and the timing of blood draws that are thought to increase glucose levels in the blood. The dosage of glucagon used has a range of 20-30 $\mu\text{g} / \text{kg bw}$. The time tested for blood collection was within 8-10 minutes after injection of glucagon. From this dosage range and the time of blood collection which increased blood glucose levels, it will be used in further tests.

2.4. Advanced test

The next stage is the implementation of further tests. In this follow-up test, 28 mice were used, 4 for each treatment. The mice were divided into 2 main groups, namely treatment group I (without injection of glucagon) and treatment II (by injection of glucagon). Group I was divided into 4 groups, namely (i) control blank (not given any substance), (ii) given distilled water, (iii) given noni extract at a dose of 1.5 g / kg bw and (iv) given noni extract at a dose of 3 g / kg bw. Each treatment group was given distilled water and noni fruit extract (dose 10 ml/kg bw) 2 weeks for 8 weeks (week 1,3,5,7) with an interval of 1 week for blood sampling (week -0,2,4,6,8). The glucose levels obtained in this group were fasting blood glucose levels (BGLf) and blood glucose levels 2 hours after the mice started feeding (BGLe). Group II was further divided into 3 groups, namely (i) glucagon +

distilled water, (ii) glucagon + noni extract at a dose of 1.5 g / kg bw and (iii) glucagon + noni extract at a dose of 3 g / kg bw. Glucagon is injected intramuscularly at a dose of 20 $\mu\text{g} / \text{kg bw}$. Each treatment group was given distilled water and noni fruit extract (dose 10 ml / kg bw) once a week for 4 weeks (week 1,2,3,4) with 3 blood samples, namely at the time before injection glucagon, 10 minutes after injection of glucagon and 2 minutes after giving distilled water or noni. Glucose levels in this group were BGL before injection of glucagon (BGLa), BGL after injection of glucagon (BGLb) and BGL after giving distilled water or noni (BGLc).

2.5. Blood sampling

Blood samples were collected once a week during the study in all treatment groups except for the treatment group with glucagon administration. Blood sampling for each mouse was carried out twice in each blood sampling, namely when the mice were fasting and 2 hours after the mice were fed. To obtain fasting blood glucose levels, mice were fasted first for 12 hours, in this case only fasting. eating while drinking is still given. After the blood was drawn, the mice were fed and the blood was drawn again 2 hours later. Blood was drawn from the blood vessels in the tail of the mice. Prior to blood collection, the tails were rinsed with 70% alcohol and then sliced to obtain blood using a bisturi knife. The blood is then collected in an ependorphous tube. The blood that was isolated was 0.1 ml using a 1 ml syringe which was divided into 10 scales. Then the blood sample was transferred into a test tube and added with $\text{Ba}(\text{OH})_2$ 0.3 N and ZnSO_4 5.0% each as much as 1.5 ml and shaken until well mixed then let stand for 3 minutes. Furthermore, the blood sample was centrifuged at a speed of 2500 rpm for 20 minutes. From the centrifugal results, two layers will be obtained, namely pellets containing protein and blood cells that settle at the bottom of the

tube, and supernatant in the form of a clear liquid at the top. This supernatant part is blood serum that has been separated from protein and blood cells, and this serum is hereinafter referred to as a blood sample, which will be measured its blood glucose content.

2.6. Determination of blood glucose levels

For the determination of blood glucose levels, a concentration of 100 mg/dl of blood glucose is needed, which is made by dissolving 100 mg of glucose in 100 ml of distilled water. Furthermore, standard blood and glucose samples were taken and placed into test tubes, 1 ml each and mixed with 1 ml of alkaline Cu solution. In addition, to measure blood glucose levels, a blank solution is required in the form of 1 ml alkaline Cu solution. Then all the mixture to be measured is heated in a water bath at 100°C for 20 minutes. After chilling, all mixtures were added with 1 ml of arsenomolybdate reagent and diluted with the addition of distilled water to have a final volume of 10 ml. Furthermore, the absorbance (A) of the sample was measured using a spectrophotometer at λ 630 nm.

2.7. Data analysis

The data obtained were then processed with Microsoft Excel 2013 and statistical analysis using the SPSS 10.00 for Windows program. The statistical tests used were ANOVA, Duncan's test and LD (Least Significant Difference) with a 95% confidence interval ($p < 0.05$).

3. RESULTS AND DISCUSSION

3.1. Preliminary test

Preliminary test results indicate that administration of glucagon at a dose of 20 $\mu\text{g} / \text{kg}$ bw can increase blood glucose levels in mice so that this dose

continues to be used in subsequent experiments. The time for blood sampling at 10-minute intervals after the injection of glucagon also showed an increase in blood glucose levels so that the blood sampling in the next experiment was carried out at this time interval after the injection of glucagon.

3.2. Advanced test

Treatment Group I (Without Glucagon Injection)

From the statistical test results (Table 1 & Table 2) it can be seen that at week 0 there was no significant difference between the BGL of all treated mice and control mice, both for BGLf and BGLe. The mice used in this study were mice with normal BGL or mice without diabetes. Insulin plays a major role in regulating BGL so that it is always at a normal value. The amount of insulin secreted is proportional to the level of glucose in the blood, to a certain extent, the amount of insulin secreted will remain (Murray, *et al.*, 1997). If the glucose in the blood is very high, and the insulin that is secreted is not proportional to the level of glucose in the blood, then the rate of decrease in BGL becomes rather slow (Murray *et al.*, 1997). Therefore, in the group of mice given glucagon, there was an increase in BGL. Although the BGL of the glucagon-treated mice group increased and was outside the normal BGL range, this group of mice did not develop diabetes. Giving glucagon and other hyperglycemic compounds such as diazoksid can increase the BGL of mice up to 200 mg/dl, at which point mice are said to have diabetes (Astriani, 1992; Fitri, 1998). A very high BGL causes the β cells of the pancreas to secrete additional insulin. Excessive insulin secretion results in damage to pancreatic β cells (Guyton, 1986) so that it can induce diabetes. High activity that requires a lot of energy can help accelerate the decrease in BGL because the use of glucose by muscle cells for energy

sources is greatly increased. According to Heinecke (1985), noni juice contains a lot of xeronine precursors, hereinafter referred to as proxeronine. Proxeronine synthesizes pure xeronine in the intestines with the help of a special enzyme which is also contained in noni juice. Based on the theory of Heinecke (1985), when synthesized, xeronine actually works at the molecular level to repair damaged cells. Heinecke (1985) also states that the main function of xeronine is to regulate the rigidity and shape of a particular protein. These proteins include insulin receptors on the surface of specific cells so that the receptors can work more effectively and efficiently. The activity of insulin receptors is related to the number of receptors present on target cells. The number of receptors can be reduced or increased depending on the condition and character of the cell (Murray, *et al.*, 1997).

Proxeronine when in the body, travel to the cytoplasm of specific cells and accumulates in the Golgi apparatus. Within the Golgi apparatus, proxeronine combines with other biochemical substances and forms a unit that is used by the body to help maintain cells function properly and efficiently. These biochemical ingredients include hormones, proteins, enzymes, serotonin, vitamins, minerals, antioxidants and others. The combination of proxeronine with these other compounds is specific and varies, depending on the needs of the cells of their destination. After being processed in the Golgi apparatus, proxeronine with the help of the enzyme proxeroninase is converted into xeronine. Then xeronine works together with other biochemical ingredients needed to form adaptogenic compounds for cells in need, thus enabling these cells to repair and restore themselves. It is in this process that the cells regain a state of homeostasis (balance) which in turn causes the body to be in a completely balanced state. The elevated blood glucose level following

glucagon administration is due to a physiological mechanism that is essentially opposite to insulin. Glucagon stimulates the synthesis and release of hepatic glucose through glycogenolytic mechanisms or through gluconeogenesis (Hadley, 1982). The glycogenolytic mechanism is very important in maintaining blood glucose levels in animals that have glycogen reserves in the liver. Physiologically, glucagon stimulates the conversion of amino acids into glucose in the liver. Glucagon also increases the conversion of amino acids and glycerol to glucose by influencing the enzymes in the glyconeogenic and glycolytic pathways in the liver. Glucagon also has a lipolytic mechanism in adipose tissue, free fatty acids and glycerol produced from fat cells are also used in hepatocytes in the process of gluconeogenesis (Guyton, 1986).

There are several hormones that affect BGL, including growth hormone, cortisol, epinephrine and glucagon which all tend to increase BGL. Cortisol will be secreted in large quantities when a person or an animal, especially mice, is stressed. Increased cortisol can indirectly increase BGL. Furthermore, epinephrine will also be secreted if a person or an animal, especially mice, is stressed, where the epinephrine will stimulate the pancreatic α cells to secrete glucagon so that BGL increases (Guyton, 1986). From the experimental results, it appears that the application of solvent has no effect on BGL of mice, whether it is induced or not with glucagon. During 8 weeks of distilled water treatment, it appears that BGLf and BGLe of the distilled water group (Table 1 & Table 2) were not significantly different from the control group. From the results of statistical tests (Table 1 & Table 2) it can be seen that the BGLf and BGLe of the noni group, both at a dose of 1.5 g / kg bw and 3 g / kg bw, from week 2 to week 8 were significantly different from the control group. From the results of the total BGL statistical

test for 8 weeks (Table 1 & Table 2) and Figure 1, it appears that the BGLf of each treatment group I experienced an increase at 2 hours after the mice started feeding, but the BGLe of the control group and distilled water group were not within the normal BGL range. Meanwhile, both BGLf and BGLe in the noni group with both doses were under control but still in the normal BGL range.

Table 1. The results of BGLf statistical tests per 2 weeks for treatment group I

No	Treatment	BGLf \pm SD week to				
		0	2	4	6	8
1	Blank Control	69.0	80.73 \pm	117.79	59.57 \pm	84.70
		4 \pm 9.60a	9.60a	\pm 40.35 a	12.11a b	\pm 27,01 ab
2	Distilled water	68.1	80.48 \pm	87.87 \pm	54.47 \pm	74.07
		6 \pm 3. 89a	17.38a	36,41a b	24,41a b	\pm 66. 81bc
3	Noni 1,5	72,8	85,56 \pm	48,87 \pm	48,87 \pm	56.63
		1 \pm 9.83a	20.64b	4.86d	4.86d	\pm 25,07 cd
4	Noni 3	78,8	79,06 \pm	94,42 \pm	43,73 \pm	50.48
		1 \pm 8.71a	6,29bc	22.30c	18.21d	\pm 12,07 e

The scores followed by a different letter show significantly different at the 95% confidence interval. The dose of noni on the treatment column is in g / kg bw.

Table 2. The results of BGLe statistical tests per 2 weeks for treatment group I

No	Treatment	BGLe \pm SD week to				
		0	2	4	6	8
1	Blank Control	113.90 \pm	107.61	153.7	83,31	169,15
		16,67a	\pm 27,87 a	3 \pm 40, 18a	\pm 69,0 5ab	\pm 89,4 6ab
2	Distilled water	124,7 \pm 1	94,97 \pm	127.0	106.9	101,6
		5,57ab	11,78a b	6 \pm 42, 96ab	5 \pm 81, 83c	\pm 58,2 6c
3	Noni 1,5	100.94 \pm 4	91.18 \pm	115.6	82.79	99.94
		7,55c	4,36d	7 \pm 40, 40cd	\pm 9,64 ab	\pm 79,5 4e
4	Noni 3	99.98	91.19 \pm	126.4	61.11	104.26
		\pm 21.71c	16.89d	5 \pm 56, 09ab	\pm 6,73 d	\pm 86.1 6e

The scores followed by a different letter show significantly different at the 95% confidence interval. The dose of noni on the treatment column is in g / kg bw.

Treatment Group II (With Glucagon Injections)

In this group, mice were not fasted and obtained BGL immediately before administration of glucagon. After that, the mice were immediately given glucagon and obtained BGL 10 minutes after injection of glucagon because based on the preliminary test, glucagon had started to work at an interval of 10 minutes after

injection. To determine the effect of distilled water or noni extract on mouse BGL, mice were given distilled water or noni extract while the glucagon effect was still working. According to Carson and Koch (1998), glucagon has a working time of 12-27 minutes.

Table 3. Results of BGL statistical test per week for treatment group II

No	Treatment	Before injection with glucagon week to			
		1	2	3	4
5	Glucagon + distilled water	81.26 \pm	82.79	50.99 \pm	69.08 \pm 34
		17.00a	\pm 24.94a	21.26c	.88ab
6	Glucagon + Noni 1,5	95.43 \pm	65.11 \pm	71.18 \pm	68.09 \pm 42
		13.88a	11.86b	3,31d	.15ab
7	Glucagon + Noni 3	96.22 \pm	70.53 \pm	91.46 \pm	64.53 \pm 25
		7.6a	2.72b	14.35e	32ab

Table 4. Results of BGL statistical test per week for treatment group II

No	Treatment	After injection with glucagon week to			
		1	2	3	4
5	Glucagon + distilled water	112.30	113.90	62.19 \pm	81.14 \pm
		\pm	\pm	6.16c	57.37a
6	Glucagon + Noni 1,5	17.88a	16.67a	156.19 \pm	107.01
		123.87	85,56 \pm	59.29d	\pm 60.11
7	Glucagon + Noni 3	\pm 18.97 b	20.64b	91.46 \pm	98.65 \pm
		135.29	99.94 \pm	14.35e	88.60e
		\pm 20.19 b	79.50c		

The scores followed by a different letter show significantly different at the 95% confidence interval. The dose of noni on the treatment column is in g / kg bw.

From the results of the BGL statistical test for treatment group II (Tables 3 and 4) it can be seen that BGL before glucagon administration (BGLa) between each group at week 1 to week 3 is not significantly different and only significantly different at week 4. Meanwhile, BGL after administration of glucagon (BGLb) and after giving distilled water or noni extract (BGLc) between each group was significantly different from week 1 to week 4. From the results of the statistical test for treatment group II for 4 weeks (Table 6), it appears that BGLa between each group is not significantly different. However, it was only significantly different after giving glucagon. After administration of glucagon, it appeared that the BGL of the noni group with both doses was no longer in the normal range but also did not make the mice suffer from diabetes. After giving distilled water, the

BGL of mice appeared to be slightly increased. This is because the effect of glucagon is still working and distilled water is not able to reduce BGL in mice. Meanwhile, in the noni group with both doses, BGL decreased after administration of noni.

Table 5. Total BGLf and BGLe for 8 weeks treatment group I

NO	Group	BGLf \pm SD	BGLe \pm SD
1	Blank Control	82,36 \pm 22,13	125,54 \pm 35,13
2	Distilled water	73,01 \pm 12,69	111,08 \pm 14,29
3	Noni 1,5	71,93 \pm 19,51	98,10 \pm 12,27
4	Noni 3	69,30 \pm 21,35	96,59 \pm 23,71

Table 6. Total BGL for 4 weeks treatment group II

No	Treatment	Before injection with glucagon BGL (a) \pm SD	After injection with glucagon BGL (b) \pm SD	After giving distilled water / noni BGL (c) \pm SD
5	Glucagon + Distilled water	71.03 \pm 14.70a	92.38 \pm 11.23a	99.34 \pm 13.34a
6	Glucagon + Noni 1,5	74.95 \pm 13.87a	118.15 \pm 29.81b	73.92 \pm 12.72b
7	Glucagon + Noni 3	80.68 \pm 15.50a	106.33 \pm 19.66b	73.95 \pm 16.16b

From Table 6 it can be seen that in the distilled water and noni groups with both doses, BGL of mice increased after glucagon administration. After giving distilled water, the BGL of mice increased. Meanwhile, in treatment group I, it has been proven that distilled water does not have an effect on BGL of mice. The increase in BGL of mice after giving distilled water may be due to the effect of glucagon which is still working. However, after giving noni, the BGL of mice decreased. From Table 5 and Table 6, it appears that giving noni extract at a dose of 1.5 g / kg bw with glucagon administration shows a higher reduction in BGL than other groups so it can be said that the noni extract is more effective when consumed when BGL is very high (hyperglycemia). Based on the ANOVA statistical test found in Tables 1, 2 and 3, several standard deviation values were

obtained that were quite high. This is because the average blood glucose levels obtained are not normally distributed, indicating that the BGL of mice obtained in this experiment has a wide range. This research was conducted only to determine the effect of noni extract on BGL and it is not yet known the optimum dose of noni extract which can be used to reduce BGL so that further research can be done to find out.

4. CONCLUSION

From the results of this study, several conclusions can be drawn, as follows: Noni extract can reduce blood glucose levels of male mice, both induced and not induced with glucagon. Giving noni both at a dose of 1.5 g / kg and 3 g / kg bw resulted in significantly different BGLf and BGLe than BGLf and BGLe in the control group and the group given distilled water . Noni extract is more effective given to mice that have a very high BGL (hyperglycemia) in this case which is induced by glucagon.

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