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Research Article

Effect of Fibroblast Growth Factor Combination with Ethanol Extract of *Morinda citrifolia* L. on Blood Glucose levels

Dharma S[1,*], Rahmawati Y[2], Nessa[2], Dillasamolla S[1]

ABSTRACT

A research has been conducted on the effect of giving Fibroblast Growth Factor (FGF) with *Morinda citrifolia* L. ethanol extract. This study aims to determine whether the administration of a combination of FGF with ethanol extract of noni fruit can reduce blood glucose levels in diabetes mice induced by alloxan. FGF requires amino acids in regenerating pancreatic β cells, where the amino acids expected from noni fruit can provide a signal response in regenerating pancreatic β cells. In addition, the active substances contained in noni fruit namely xeronine and flavonoid alkaloids can function to reduce blood glucose levels. Test animals were divided into 6 groups, each group consisted of 10 male white mice. Group 1 is a normal control group is a group without any given. Group 2 was a negative control group given 150 mg/kg alloxan. Group 3, 4, and 5 are the treatment groups that are given *alloxan* and the combination of noni fruit ethanol extract with 3 variations of dose (125; 350; and 1000) mg / KgBW plus FGF dose of 800 mg / kgBW, group 6 is the comparison which is only given FGF alone at a dose of 800 mg / kgBW. The study was conducted for 21 days, observed every 7th, 14th, 21st day using the Easy Touch®GCU digital device. The results of this study showed that administration of noni fruit ethanol extract with FGF was able to reduce blood glucose levels by significance ($p < 0.05$) and based on the percentage calculation of blood glucose levels as much as 44.9% at a dose of 1000 mg / kgBW on the day observations 21st.

Key words: Diabetes mellitus, FGF, *Morinda citrifolia.*

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INTRODUCTION

Diabetes mellitus (DM) or commonly known as diabetes is a chronic disease. If the pancreas is unable to produce enough insulin, or when the body is unable to use the insulin produced effectively.[1] Diabetes mellitus is a big threat in human life, because seen from the prevalence of diabetes mellitus estimated at 2.8% worldwide (171 million people suffer from diabetes mellitus) and is predicted to increase to reach 4.4% (366 million suffer from diabetes mellitus) in 2030. Diabetes mellitus in Indonesia becomes one of the health problems for the community every year, in 2000 it was reported that in Indonesia there were 8.4 million people with diabetes. This number is predicted to reach 21.3 million and rank fourth in the world after India, China and the United States in 2030.[2]

Although diabetes can now be controlled clinically by using insulin injection, this treatment is not healing and gives discomfort during use and for a long time can cause a number of clinical complications. Treatment with oral insulin and antidiabetic injections does not provide the same degree of control as the function of controlling blood glucose levels by pancreatic β cells and cannot prevent adverse consequences as a result of diabetes.[3]

Long-term treatment in controlling blood glucose levels to reach normal conditions requires new methods to improve the function of pancreatic β cells as insulin-producing naturally, so as to reduce side effects, uncomfortable use, and diabetes patients' dependence on the use of drugs and insulin.

In repairing and reviving tissues and reconnecting neuronal neural networks in the brain, a substance that plays a role in carrying out this task is needed, namely Fibroblast Growth Factor (FGF). FGF is responsible for signal stimulation in the process of early cell development forming a network.[4]

FGF is a group of proteins that have a role to mediate metabolic regulation both autocrine and paracrine.[5] FGF also has a role that is responsible for signal stimulation in the process of early cell development such as pattern setting, proliferation, differentiation and migration, forming a network.[4]

FGF in regenerating pancreatic β cells cannot be alone, FGF requires amino acids, where amino acids expected from noni fruit can help activate signals from FGF which play a role in regenerating pancreatic β cells. In noni fruit contains amino acids namely glutamic acid, aspartic acid, isoleucine.[6] Noni fruit also contains *proxeronine,* where *proxeronine* is converted into *xeronin* in the body by enzymes, this substance can also regenerate damaged pancreatic β cells, so that pancreatic β cells can function properly again and produce enough insulin to control glucose levels in the blood.[7]

Noni contains a large amount of *proxeronin* that can be formed into *xeronin.* Furthermore, it was stated that in the human intestine there is an enzyme *proxeronase* that can convert *proxeronin* to *xeronin.*

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The main function of *xeronin* in the body is to regulate the form and hardness (rigidity) of specific proteins in cells. If the function of proteins deviates, then the body will experience health problems.[8] *Proxeronine* is converted to *xeronin* alkaloids in the body by an enzyme called *proseroninase*[8] *Proxeronine* forms *xeronine* which can regenerate damaged pancreatic cells, so that pancreatic beta cells can function properly and produce enough insulin to control blood sugar levels.[9]

MATERIALS AND METHODS

Plant identification

Noni fruit plants were identified at Andalas University Herbarium.

Preparation of experimental animals

The experimental animals used in this experiment were male white mice weighing 20-30 g and aged 2-3 months. The number of mice used was 60 heads, divided into 6 groups. Each group consisted of 10 mice. One week before the research the mice were acclimatized.

Test animals fasted for 10 hours, before the test animals weighed BB. Checking the initial blood glucose level, 5 groups of test animals were induced with alloxan 150 mg / kg BW intra peritoneal, one group was normal control. Mice experiencing hyperglycemic after induction will show an increase in fasting blood glucose levels > 126 mg / dl

Test animals were divided into 6 groups, 5 groups were induced with alloxan and one group without alloxan (normal control).

Table 1 explain about groups of test animal. Group I normal controls: only fed, standardized mice and 0.5% Na CMC suspense orally every day during the study.

Group II negative control: given an alloxan 150 mg / kgBW induction intrapritoneally and CMC 0.5% orally.

Group III (Dose I): hyperglycemic white mice (alloxan-induced) which were given test preparations of FGF 800 mg / kg BW + noni fruit extract 125 mg / kg BW.

Group IV (Dose II): hyperglycemic white mice (alloxan-induced) given FGF test solution 800 mg / kg BW + noni fruit extract 350 mg / kg BW.

Group V (Dose III): hyperglycemic white mice (alloxan-induced) given FGF test solution 800 mg / kg BW + extract of noni fruit 1000 mg / kg BW.

Group VI administration of FGF only: hyperglycemic white mice (alloxan-induced) given 800 mg / kg BW of FGF solution.

Table 1: Group of animal test.

Group	Explanation
Group I (normal controls)	Only fed, standardized mice and 0.5% Na CMC suspense orally every day during the study.
Group II (negative control)	Given an alloxan 150 mg / kgBW induction intrapritoneally and CMC 0.5% orally.
Group III (dose I)	Hyperglycemic white mice (alloxan-induced) which were given test preparations of FGF 800 mg / kg BW + noni fruit extract 125 mg / kg BW.
Group IV (dose II)	Hyperglycemic white mice (alloxan-induced) given FGF test solution 800 mg / kg BW + noni fruit extract 350 mg / kg BW.
Group V (dose III)	Hyperglycemic white mice (alloxan-induced) given FGF test solution 800 mg / kg BW + extract of noni fruit 1000 mg / kg BW.
Group VI (administration of FGF only)	Hyperglycemic white mice (alloxan-induced) given 800 mg / kg BW of FGF solution.

Manufacture of noni fruit ethanol extract

First, the noni fruit that has been dried mashed with a blender and then soaked with 70% ethanol, soaked for 6 hours while occasionally stirring then allowed to stand for 24 hours. Then the extract is filtered and the pulp is soaked again with 70% ethanol and stirred once in a while for 6 hours and allowed to stand for 24 hours, do up to 3 repetitions. All maserat results are collected and then evaporated using an electric evaporator until a thick extract is obtained.[10]

Making FGF suspensions

The FGF content in egg white flour preparations is made by weighing the egg white flour containing FGF 800 mg / kg BW, weighing 50 mg Na.CMC and sprinkled into lumping containing 1 ml of distilled hot water, cover and leave for 15 minutes until a transparent mass is obtained, crushed then input the weighed extract was crushed until homogeneously diluted with distilled water up to 10 ml.[11]

Making suspensions of noni extract (*Morinda Citrifolia* L.)

Noni fruit ethanol extract weighed 125, 350, and 1000 mg / kg BW, respectively. Weighed 50 mg Na CMC sprinkled into mortars containing 1 ml of hot distilled water, cover and leave for 15 minutes until a transparent period was obtained, crushed then add the extract that had been weighed for a dose of 125, 350, and 1000 mg / kg BW , crush until homogeneous dilute with distilled water up to 10 ml.[11]

Monitoring blood glucose levels

Observation of the blood glucose levels of white mice after induction with *alloxan* was measured by measuring blood glucose levels (ACCU-Chek) for all groups.

Test preparations were given on day 1 for the next 21 days orally and an examination of blood glucose levels was carried out on days 7, 14, 21.

RESULTS

Noni obtained was identified at the Andalas University Herbarium. The results of the identification of the species *Morinda citrifolia* L. were included in the family Rubiaceae.[12]

Noni extract (*Morinda citrifolia* L.) can be known that the yield of noni extract is 26.68%, theoretically known in the Indonesian Herbal Pharmacopoeia edition 1-year 2008 extract yield not less than 10.9%, this shows the quality of ethanol extract of noni fruit is in good condition.

Phytochemical screening test of noni fruit ethanol extract containing flavonoids, steroids, phenolics and saponins. This phytochemical test is to provide information on the class of chemical content as a parameter of extract quality in relation to pharmacological effects.

The results of the ash content of the noni fruit extract was 0.81%, from the results of the ash content obtained in accordance with the standards stated in the Indonesian Pharmacopoeia edition 1 of 2008 no more than 0.8%.

Figure 1 is the results of average blood sugar levels (mg / dL) on the 7th, 14th, and 21st days, against the normal and negative control groups, groups III, IV, V, and VI.

Table 2 that is explain from the results of examination of blood glucose levels on day 7, obtained an average of glucose This shows that the induction of alloxan can increase the blood glucose levels of male white mice. Whereas in the normal

Control group which is a reference to normal blood glucose levels showed that blood glucose levels were stable in the normal range. After administering the test preparations in diabetic mice, the average blood

glucose levels for the group I dose, dose II, dose III, and FGF alone on the 7th day decreased.

At dose III, the greatest decrease in average blood glucose level of mice was seen, especially on the 21st day observation ($p < 0.05$). From the diagram above shows the ability of FGF and ethanol extract of noni can inhibit the rise in blood glucose levels of mice and can reduce blood glucose levels in diabetes mice.

At the dose of 350 mg / dl the decrease was 138.8 mg /dL, and observations on the 14th and 21st days also showed a decrease in blood glucose levels respectively 124.1 mg / dL and 104.4 mg / dL. If calculated as a percentage, there was a decrease of 34.51% and 44.9%, respectively. Group giving by FGF alone which was also a comparison saw decreases on days 7, 14 and 21 respectively 174; 167 and 163 mg / dL. And if it is calculated as a percentage on observation day 7; 14 and 21 results are obtained in a sequence of 9.61; 12.33 and 13.36%.

From Figure 2 the results of the average blood glucose level, the largest percentage reduction was at a dose of 1000 mg / kg BW on the 21st day observation of 44.90%. The percentage reduction in the group that was only given FGF 800 mg / kg BW on the 21st day observation indicated the smallest percentage compared to the dose group 125, 350, and 1000 mg / kg BW which was equal to 13.56%.

This is due to doses of 125, 350, and 1000 mg / kg BW of noni fruit is a dose combined with FGF 800 mg / kg BW. In noni fruit ethanol extract there are active compounds of amino acids (glutamic acid, aspartic acid, isoleucine), flavonoids, and xeronins that are able to work synergistically with FGF in reducing blood glucose levels, while the comparison group which is only given FGF works alone without any help from other compounds such as amino acids, flavonoids, *xeronin* in reducing blood glucose levels in diabetes mice.

Based on the above results, it shows that the higher dosage dosage given, gives the potential to decrease blood glucose levels which are higher at dose III and the longer the observation time also shows the higher potential on day 21.

The results of statistical tests conducted with one-way ANOVA on day 7, seen a significant difference between the 3 variations of the dose and comparison of the decrease in blood glucose levels of diabetes mice where $p<0.05$. On the 14th and 21st days which were tested statistically separately with one-way ANOVA, also gave significant results where $p<0.05$.

After a two-way ANOVA statistical test on the 7th day, 14, 21, a significant result ($p < 0.05$) was seen in the group and time, which means that there was an influence of the duration of observation and dosage variations during the administration of the test preparation ie fruit ethanol extract Noni and FGF to decrease blood glucose levels.

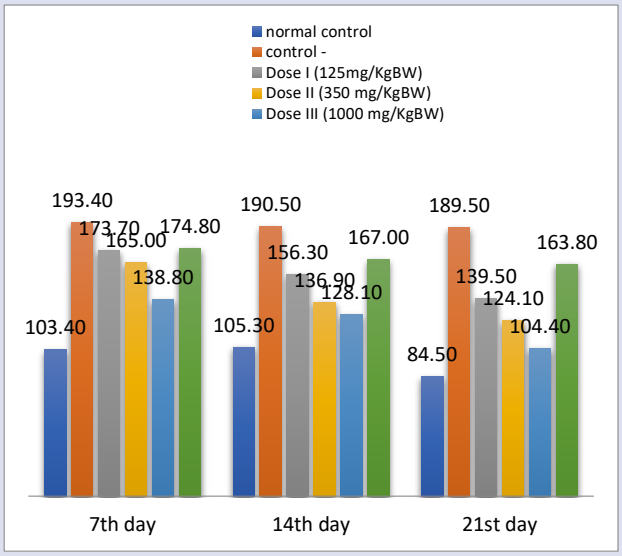

Figure 1: Diagram of the average blood glucose levels for 21 days of observation.

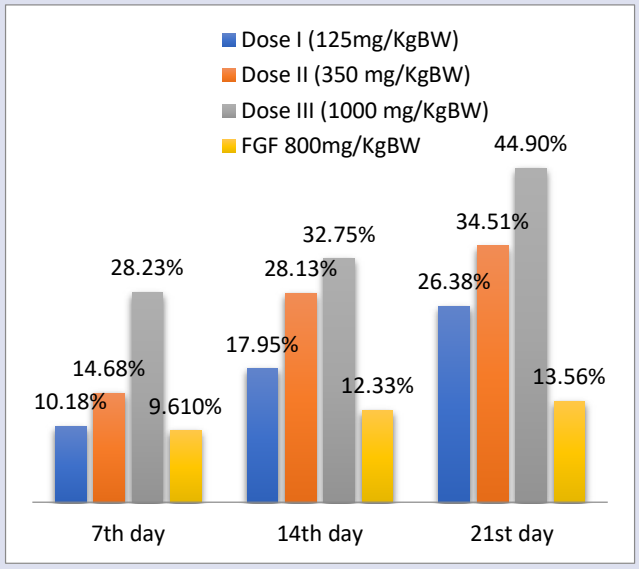

Figure 2: Diagram of percentage decrease in blood glucose level of the test preparation group.

Table 2: Average decrease in blood glucose (mg / dL) and percentage of decrease in blood glucose in contrast compared to negative controls at the same time.

Group / Dose	Average blood glucose levels (mg / dL) ± SD and percentage decrease in blood glucose (%) N= 10					
	7th day		14th day		21st day	
	Average	Percentage (%)	Average	Percentage (%)	Average	Percentage (%)
Normal control	103.40 ± 90		105.30 ± 90		106,10 ± 90	
Negative control	193.40 ± 50	-	190.50 ± 90	-	189.50 ± 90	-
125 mg/kg BW	173.70 ± 80	10.18 %	156.30 ± 80	17.95 %	139.50 ± 80	26.38 %
350 mg/kg BW	165.00 ± 50	14.68 %	136.90 ± 70	28.13 %	124.10 ± 50	34.51 %
1000 mg/kg BW	138.80 ± 40	28.23 %	128.10 ± 70	32.75 %	104.40 ± 90	44.90 %
FGF 800 mg/kg BW	174.80 ± 90	9.61 %	167.00 ± 50	12.33 %	163.80 ± 10	13.56 %

CONCLUSION

Based on the results of the study the effect of ethanol extract of *Morinda citrifolia* L. on the blood glucose levels of male white mice, the conclusion is: Giving FGF (800 mg / KgBB) with noni extract with 3 variations of doses (125, 350, 1000 mg / Kg BW)) can significantly reduce blood glucose levels in diabetic white male mice ($p<0.05$)

Giving dosage test dosages 1, 2 and 3 over the length of time of observation showed the percentage decrease in blood glucose levels seen at dose 3, with a percentage reduction of 44.90% on the 21st day.

Giving 3 variations of the combined dose with FGF compared to FGF alone, seen the potential for a decrease in glucose levels the smallest effect.

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THE ROLE OF THE WRITER

The writing of this journal was assisted by several writers, each of whom had the following tasks: Yulia Rahmawati helped complete the research, Nessa edited and compiled the article, Dwisari Dillasamolla and Yulia Rahmawati translated into English and Surya Dharma was responsible for setting the final completion of the article until it was published.

CONFLICTS OF INTEREST

There were no differences in opinion between authors during the preparation of this article.

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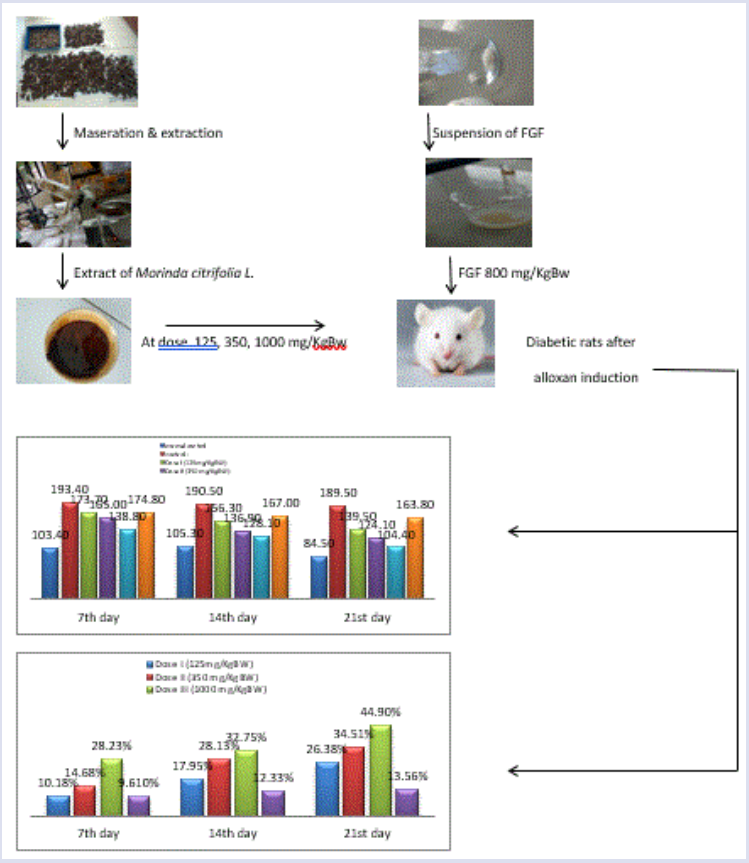
GRAPHICAL ABSTRACT



SUMMARY

Noni extract (*Morinda citrifolia* L.) can be known that the yield of noni extract is 26.68%. FGF requires amino acids in regenerating pancreatic β cells, where the amino acids expected from noni fruit can provide a signal response in regenerating pancreatic β cells. In addition, the active substances contained in noni fruit namely xeronine and flavonoid alkaloids can function to reduce blood glucose levels at diabetic rats after given 150 mg/kgBw alloxan. Giving FGF (800 mg / KgBB) with noni extract with 3 variations of doses (125, 350, 1000 mg / Kg BW) can significantly reduce blood glucose levels in diabetic white male mice ($p<0.05$). Giving dosage test dosages 1, 2 and 3 over the length of time of observation showed the percentage decrease in blood glucose levels seen at dose 3, with a percentage reduction of 44.90% on the 21st day. Giving 3 variations of the combined dose with FGF compared to FGF alone, seen the potential for a decrease in glucose levels the smallest effect.

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