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Effect of Moringa Leaf Infusion (*Moringa oleifera*) on Reducing Blood Glucose and Total Cholesterol Levels in Mice (*Mus musculus*) with Diabetic Ulcers

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ABSTRACT

Background: Diabetes mellitus is a chronic disease in the form of metabolic disorders, which is characterized by blood glucose levels (KGD) that exceed normal limits and are accompanied by impaired metabolism of carbohydrates, lipids, and proteins, as a result of abnormalities in insulin secretion. This study aims to examine the effect of moringa leaf infusion on blood sugar levels, glucose tolerance, cholesterol levels, body weight, and wound healing duration.

Subjects and Method: This study is experimental using a posttest only controlled group design, using 25 male mice (*Mus musculus*) divided into 5 groups. The study was conducted at the Phytochemistry and Animal House Laboratory, Faculty of Medicine, Methodist University Indonesia from March to May 2022. The bound variables were body weight measured using a scale, current blood glucose levels and blood glucose levels with glucose loading measured with strips and glucometers, total cholesterol levels measured using strips and cholesterol measuring devices, and the length of mice wounds measured using a ruler. The data were analyzed using the Anova and Kruskal-Wallis tests.

Results: The administration of moringa leaf infusion had a significant effect on the reduction of the levels of each variable, namely a dose of 10% in body weight, a dose of 30% in KGD, 20% in KGD with glucose loading, 20% in cholesterol, and 20% in wound closure, which was proven based on the results of statistical tests.

Conclusion: Moringa leaf infusion can lower blood sugar levels, blood sugar levels by glucose depletion, cholesterol levels, body weight, and accelerate wound healing in sucrose-induced mice, and high fat diet.

Keywords: diabetes mellitus, moringa leaves, mice

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BACKGROUND

Lifestyle and socio-economic changes due to globalization and urbanization in society are one of the factors that increase the incidence of generative diseases. One of them is diabetes mellitus (DM) (Cho et al., 2018) DM is a chronic disease characterized by a state of higher than normal blood glucose levels (KGD). This state of increased KGD is also accompanied by disturbances in the metabolism of carbohydrates, lipids, and proteins. This occurs due to abnormalities in insulin secretion (Safitri, 2018)

According to the 10th edition of the Atlas Diabetes published by the International Diabetes Federation (IDF) in December 2021, it is reported that 1 in 10 adults worldwide is diagnosed with type 2 diabetes. It is also predicted that there will be an increase in the number of DM sufferers from 537 million people in 2021 to 786 million people in 2045. In Indonesia itself, the prevalence of DM reached 2% in 2018. This figure has increased by 0.5% from 2013. The prevalence of DM sufferers varies based on age group, gender, income level, and geographic region. In countries with high-income levels in the age group of 75-79 years, the prevalence of DM reaches 22%, then 19% in countries with middle-income levels in the age group of 60-74 years, and 8% in countries with low-income levels in the age group of 55-64 years. In comparison, the prevalence of people with DM among people aged 65 – 69 years in high-income countries is 3 times higher than in low-income countries (Cho et al., 2018)

DM can affect the quality of human resources, and also increase health costs considerably because the treatment is a lifelong treatment. Therefore, a program is needed to control this disease (Safitri, 2018) Utilizing plants as medicine is not new to the people of Indonesia. Knowledge of medicinal plants has become a culture that has been passed down from generation to generation. Some people believe that medicinal plants are safer to consume and only provide too few side effects when compared to patent drugs (Togubu et al., 2013) One of the plants that is quite well known among the Indonesian people as a KGD and cholesterol-lowering is the moringa plant. The flavonoid content in moringa is able to regenerate pancreatic beta cells so that it can reduce KGD. Flavonoids in moringa can also inhibit pancreatic cholesterol esterase activity, thereby reducing plasma cholesterol concentrations (Nisa Berawi et al., 2019; Togubu et al., 2013) Based on the description above, this study was conducted to determine the effect of moringa leaf infusion on the reduction of KGD, KGD with glucose, total cholesterol, body weight, and wound healing in male mice.

SUBJECTS AND METHOD

1. Study Design

This was a randomized controlled trial. The study was conducted at the Animal House Laboratory, Faculty of Medicine, Methodist University Indonesia, in April – June 2022.

2. Population and Sample

The experimental animals used in this study were male mice with hyperglycemia and hypercholesterolemia. The selection of mice as experimental animals is based on the consideration that genetically mice have similarities with humans and have the ability to adapt to the laboratory environment. Sample allocation using inclusion and exclusion criteria. The inclusion criteria are male gender, healthy condition (active and not disabled), age 2-3 months, and weight 25-30 grams. The exclusion criteria were that male mice died during the study period. The sample size is calculated using the Federer formula. Based on the results for each group, a minimum of 5 male mice are included in each of the 5 treatment groups, resulting in a total study sample size of 25 mice.

3. Study Variable

The bound variables were weight, KGD, KGD with glucose loading, total cholesterol, and length of mice wounds.

The independent variable is the dose of moringa leaf infusion.

4. Variable Operational Definition

a. Body weight is a measure used to assess nutritional status.
b. KGD is a measure of the amount of glucose in the blood.
c. KGD with glucose loading is a measure of the amount of glucose in the blood which is measured 2 hours after glucose administration.
d. Total cholesterol is a measure of the total amount of cholesterol in the blood.
e. Wound length is a measure of the length of the wound on the body of a mouse measured using a ruler.

5. Study Instruments

Body weight measured using a scale, KGD measurement using a glucose stick and glucometer, cholesterol measurement using lidpidometer, and wound length measured using a ruler.

6. Data Analysis

The data obtained from the observation results are recorded and presented in the form of a standard deviation average. Data normality and homogeneity tests were carried out. If the data is normally distributed and homogeneous, an ANOVA test is carried out, followed by a post hoc test if it has an impact. If the data is not normally distributed and homogeneous, then the Kruskall-Wallis test is performed. In this study, the results of the statistical test were taken at a level of 5% ($p<0.05$) which was considered significant.

7. Study Ethics

The approval letter for the study ethics permit was obtained from the Study Ethics Commission of the Faculty of Medicine Universitas Methodist Indonesia, Medan.

RESULTS

The results of measuring the weight of mice for 3 weeks are presented in the Table 1. Based on the body weight measurements in Table 1, the lowest average body weight was found in the group of mice given 10% moringa leaf infusion (Mean = 17.94; SD= 0.7), while the highest average body weight was found in the positive control group of mice that were not given moringa leaf infusion (Mean = 30.86; SD= 1.29). The results of the ANOVA test showed a significant difference (p= 0.001), then followed by the Duncan Post-Hoc test, showing a significant difference between the 10% infusion group and the positive control group.

Table 1. Mean of body weight (gram)

Group	Mean	SD	p
Negative control	28.5	2.34^{c}	0.001
Positive control	30.86	1.29^{d}	
Infused 10%	17.94	0.7^{a}	
Infused 20%	24.2	8.34^{b}	
Infused 30%	19.78	4.83^{a}	

Description: The negative control of the mice was not given any treatment, only fed and drunk normally in their cages. Positive control of mice was induced by sucrose and high-fat feed. Infusion of 10% mice induced with sucrose, high-fat feed, and infusion of 10% moringa leaves. Infusion of 20% mice induced with sucrose, high-fat feed, and 20% moringa leaf infusion. Infusion of 30% mice induced with sucrose, high-fat feed, and infusion of 30% moringa leaves. Different notations show significant differences on Duncan's Post-Hoc test.

The results of the measurement of KGD of mice for 3 weeks are presented as mean and SD (Table 2).

Based on the measurement of blood glucose level in Table 2, the lowest average blood glucose was found in the negative control group (Mean= 91.6; SD= 2.07), while the highest average of blood glucose was found in the group of mice given 10% moringa leaf infusion (Mean= 173.6; SD= 76.97). The results of the ANOVA test found a significant difference (p= 0.035). Duncan Post-Hoc test showed a significant difference between the negative control group and the 10% infusion group.

Table 2. Mean of blood glucose level (mg/dl)

Group	Mean	SD	p
Negative control	91.6	2.07[a]	0.035
Positive control	125	9.74[a]	
Infused 10%	173.6	76.97[b]	
Infused 20%	127.4	6.95[a]	
Infused 30%	116.2	29.49[a]	

Description: The negative control of the mice was not given any treatment, only fed and drunk normally in their cages. Positive control of mice was induced by sucrose and high-fat feed. Infusion of 10% mice induced with sucrose, high-fat feed, and infusion of 10% moringa leaves. Infusion of 20% mice induced with sucrose, high-fat feed, and 20% moringa leaf infusion. Infusion of 30% mice induced with sucrose, high-fat feed, and infusion of 30% moringa leaves. Different notations show significant differences on Duncan's Post-Hoc test.

The blood glucose levels in mice subjected to glucose loading for 3 weeks are presented in Table 3. Based on the measurement of KGD with glucose loading in Table 3, the lowest level was found in the group of mice given 20% moringa leaf infusion (Mean= 110.6; SD= 21.89), while the highest level was found in the group of mice given 10% moringa leaf infusion (Mean= 133.6; SD= 25.22). The results of the ANOVA test showed a significant difference (p<0.001). Post-Hoc Duncan test showed no significant difference between the groups.

Table 3. Mean of blood glucose level (mg/dl)

Group	Mean	SD	p
Positive control	111	5.78[b]	<0.001
Infused 10%	133.6	25.22[b]	
Infused 20%	110.6	21.89[b]	
Infused 30%	116.2	29.49[b]	

Description: Positive control of mice was induced by sucrose and high-fat feed. Infusion of 10% mice induced with sucrose, high-fat feed, and infusion of 10% moringa leaves. Infusion of 20% mice induced with sucrose, high-fat feed, and 20% moringa leaf infusion. Infusion of 30% mice induced with sucrose, high-fat feed, and infusion of 30% moringa leaves. Different notations show significant differences on Duncan's Post-Hoc test.

The results of the measurement of total cholesterol in mice for 3 weeks are presented in the table 4. Based on the measurement of total cholesterol in Table 4. the lowest mean was found in the negative control mouse group (Mean = 91.2; SD ± 1.78), while the highest mean was found in the positive control mouse group (Mean = 121; SD ± 8.71). The results of the ANOVA test showed a significant difference (p = 0.000), then continued with the Post-Hoc Duncan test, showing a significant difference between the negative control group and the other treatment groups.

Table 4. Mean of total cholesterol (mg/dl)

Group	Mean	SD	p
Negative control	91.2	1.78[a]	<0.001
Positive control	121	8.71[c]	
Infused 10%	112.4	4.77[b]	
Infused 20%	106	6.04[b]	
Infused 30%	106.6	4.45[b]	

Description: The negative control of the mice was not given any treatment, only fed and drunk normally in their cages. Positive control of mice was induced by sucrose and high-fat feed. Infusion of 10% mice induced with sucrose, high-fat feed, and infusion of 10% moringa leaves. Infusion of 20% mice induced with sucrose, high-fat feed, and 20% moringa leaf infusion. Infusion of 30% mice induced with sucrose, high-fat feed, and infusion of 30% moringa leaves. Different notations show significant differences on Duncan's Post-Hoc test.

The results of measuring the length of mice wounds for 3 weeks are presented in the table 5. Based on the Table 5, the shortest wound length was found in the group of mice given 20% moringa leaf infusion (Mean= 0.18 cm; SD= 0.14), while the longest wound length was found in the positive control mouse group (Mean= 0.64; SD= 0.11). The results of the ANOVA test showed a significant difference ($p<0.001$). Post-Hoc analysis using Duncan test showed a significant difference between the 20% infusion group and the positive control group.

Table 5. Mean of wound length (cm)

Group	Mean	SD	p
Positive control	0.64	0.11[d]	<0.001
Infused 10%	0.62	0.08[d]	
Infused 20%	0.18	0.14[b]	
Infused 30%	0.36	0.11[c]	

Description: Positive control of mice was induced by sucrose and high-fat feed. Infusion of 10% mice induced with sucrose, high-fat feed, and infusion of 10% moringa leaves. Infusion of 20% mice induced with sucrose, high-fat feed, and 20% moringa leaf infusion. Infusion of 30% mice induced with sucrose, high-fat feed, and infusion of 30% moringa leaves. Different notations show significant differences on Duncan's Post-Hoc test.

DISCUSSION

The results of the experiment showed that weight loss occurred in the group given moringa leaves, but in the positive control group and the negative control group, there was an increase in body weight. Significantly different results were obtained in 10% and 30% infusion administration compared to the two control groups (Table 1). This is related to the anti-lipidemia effect of moringa leaves. After eating fatty foods, the fat will be liposurged in the lumen of the small intestine into free fatty acids and 2-monoacyl glycerol (MAG) which are then taken up by enterocytes via passive diffusion and CD36-specific transporters. When it is already in enterocytes, cholesterol will be converted into cholesterol esters while free fatty acids and MAG will fuse into triglycerides again. Cholesterol esters and triglycerides will then be transported along with phosphorlipids and form kilomicrons.

The chilomites will then enter the lymphatic ducts and eventually reach the liver. Once it reaches the liver, it will synthesize a triglyceride-rich lipoprotein called VLDL. Kilomicrons and VLDLs will deliver free fatty acids to the heart, skeletal muscle, and fat tissue for energy use and storage. Lipolysis is necessary to release fatty acids from triglyceride-rich lipoproteins into the circulation. This release is mediated by the enzyme lipoprotein lipase (LPL) stimulated by insulin. Free fatty acids can then be taken up by adipose and resynthesized into triglycerides in the cytoplasm. Although there are fatty acids taken up by adiposity and myocytes, some of these fatty acids remain in the plasma where they will bind to albumin and be transported to the liver.

In addition to this mechanism, the liver can also synthesize HDL which promotes the uptake of cholesterol from peripheral tissues including the walls of the arteries, and returns cholesterol to the liver. Thus fat metabolism is dynamic and depends on a variety of factors including postprandial state, triglyceride-rich lipoprotein concentration, HDL levels, energy use, insulin levels, and adipocyte cell sensitivity and function. (Klop B et al., 2013)In the case of a high-fat diet, there is an excess energy supply from the breakdown of fat which causes the storage of especially the fat tissue to be more than it is used. This triggers weight gain. Intervention with moringa leaf infusion that affects fat metabolism pathways can cause weight loss.

The substantial content of moringa leaves includes flavonoids and alkaloids. The antioxidant activity of flavonoids and alkaloids can regenerate and protect pancreatic cells, as well as stimulate insulin release through the sympathetic neurostimulating effect of alkaloids. Flavonoids have hypoglycemic activity by inhibiting important enzymes that play a role in breaking down carbohydrates into monosaccharides that can be absorbed by the intestines, namely the enzymes α amylase and α glucosidase. Therefore, there has been a decrease in KGD. (Pitriya et al., 2017)

From the results of blood glucose with glucose loading, no significant difference was found between groups, and glucose levels did not appear to be much different compared to before loading. This test is used to look for glucose intolerance (prediabetes) and diabetes. The homeostatic response to ingested glucose bolus requires coordinated regulation of various body systems that stimulate tissue glucose removal, inhibit endogenous glucose production, and regulate intestinal glucose entry. Therefore, the handling of glucose during a glucose tolerance test depends on many integrated factors, of which insulin secretion, insulin action, and glucose effectiveness are essential. According to WHO standards, people with fasting glucose <6 mM and post-exposure oral glucose <7.8 mM have normal glucose tolerance. However, in mice, it turned out that a different response was found where oral glucose clearance occurred faster so no significant difference was seen in the glucose tolerance test.

There are 2 explanations why glucose clearance in mice is fast. First, based on the results of the experiment, it was found that a very short and slight insulin response (a 2-fold increase, < 45 minutes) was able to clear the exposed glucose. This is because the glucose bolus in mice cleans occurs with a process that does not depend on insulin. Even with normal insulin levels alone, induction of hyperglycemia (with oral glucose exposure) is already able to provide a predominant stimulus to increase oral glucose uptake, thereby facilitating whole-body glucose uptake and exogenous glucose clearance. This mechanism has to do with the rapid metabolism of small animals that it needs to maintain body temperature. The second mechanism is related to stress-induced catecholamine. Mice are animals that are easily stressed because it is related to the self-defense mechanism from predators. When stressed, catecholamines will be induced so that they affect glucose metabolism. Catecholamines can cause an increase in endogenous glycolysis, inhibit glucose uptake by the liver and muscles, and increase the metabolic rate and glucose transport in brown adipose cells and the heart. Brown adipose tissue in mice is known to be large, so when stressed glucose will be discharged into these cells. The heart's uptake of glucose also increases during stress. (Sha ZJ et al., 2021)

It can be seen in Table 4. that the cholesterol value of the negative control group was the lowest, in the range of 90 mg/dL. The positive control group had the highest cholesterol value compared to the other group, which reached 121 mg/dL. The value of 30% intravenous cholesterol tends to decrease, namely 106.6 mg/dL. In the results of the experiment, it can be seen that the cholesterol levels of the negative control group are significantly different compared to other groups which shows that induction of high-fat feed and Propylthiouracil successfully triggers an increase in cholesterol levels. Until now, no standard hypercholesterolemia has been found for rodence. From the data, it was found that the cholesterol levels of mice given moringa leaf infusion were significantly lower than that of positive controls. However, the cholesterol level has not reached the negative control level. This shows that moringa leaves have an anti-hyperlipidemia effect. Based on the results of network pharmacology analysis by Sha et al. (2021), there are 219 potential targets of the active compound M. oleifera and 185 targets of water-soluble active components for the treatment of hyperlipidemia. Analysis of cluster signaling pathways showed that nonalcoholic fatty liver pathways, insulin resistance, AMPK signaling pathways, estrogen signaling pathways, and cell apoptosis, are pathways that can be affected by the active compounds of moringa leaves. In addition, the potent active component of M. oleifera leaves can also inhibit metabolic inflammation of hyperlipidemia by modulating complement cascade signaling pathways and coagulation (Sha et al., 2021).

One of the important targets of moringa leaves in fat metabolism is the AMPK pathway. If activated, AMPK will induce metabolic changes through phosphorylation of the substrate. The activated pathways include glycolysis, gluconeogenesis, lipid oxidation, and mitochondrial division to produce energy. Meanwhile, AMPK will inhibit the lipogenic pathway, sterol synthesis, and lipid synthesis. (Garcia and Shaw, 2017) Another target of moringa leaves is PI3K/Akt which pathway activates the mTOR protein. Activation of the mTOR protein will lead to an increase in lipid synthesis. Inhibition of this pathway will decrease lipid synthesis (Tinahones et al., 2013).

From Table 5. It can be seen that in the group that was given an infusion with a concentration of 30%, it gave the fastest wound closure (the smallest wound length). For 3 weeks all mice experienced wound healing, where there was a decrease in wound length. In this study, it was found that the administration of moringa leaf infusion caused an acceleration of wound healing as seen in the smaller wound length in the moringa leaf group. This is in accordance with a previous study from Vijay and Kumar (2012) where topical exposure of moringa leaf extract to wounds causes faster epithelialization and increased wound contraction (Lambole and Kumar, 2012) In this study, an oral route was used and the effect of faster wound healing was still visible. In-vitro it is known that moringa leaves have the effect of increasing the proliferation and migration of fibroblasts in the wound area (Bogachkov et al., 2020) Systemically, the possibility of how moringa leaves can induce the acceleration of wound healing is through increased inflammatory processes, angiogenesis, reepithelialization, and oxidative stress. (Carvalho et al., 2021)

From the results of the study, it can be concluded that moringa leaf infusion with a concentration of 10% is the most effective in reducing the weight of mice, moringa leaf infusion with a concentration of 20% is the most effective in reducing KGD by loading glucose, total cholesterol, and healing mice wounds, and moringa leaf infusion with a concentration of 30% is the most effective in reducing KGD in mice.

AUTHOR CONTRIBUTIONS

Helen: The main researcher as the chief researcher who conducts studies, collects and processes data, and writes manuscripts.

Jekson: Give study ideas, guide studies, write manuscripts, and review.

Batara: Guiding research and reviewing

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CONFLICTS OF INTEREST

There is no conflict of interest in this study.

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