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# Effect of Ethanol Extract of Suruhan Leaves (*Peperomia Pellucida L. Kunth*) on Blood Sugar Levels and Macroscopic Wounds in Male White Rats of the Wistar Strain (*Rattus norvegicus*) Diabetic Ulcer Model

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## ABSTRACT

**Background:** High blood sugar levels can cause diabetes mellitus (DM), which currently means more than one in 10 adults live with diabetes, with the biggest risk factor being obesity. Wound healing in DM patients will be hampered and increase the incidence of diabetic ulcers in Indonesia by 12% and the risk of developing diabetic ulcers by 55.4%. Diabetic ulcers and gangrene cases in Indonesia are the most common cases found in hospitals. Mortality due to ulcers and gangrene ranges from 17-23%, while the amputation rate ranges from 15-30%. Therapeutic potential in the treatment of diabetic ulcers is possessed by suruhan leaves which have anti-inflammatory, antipyretic, antimicrobial and anticancer effects, as well as having analgesic effects.

**Subjects and Method:** A total of 30 male white rats of the Wistar strain (*Rattus norvegicus*) were divided equally into control groups, negative control (STZ induction 40mg/kgBW), positive control (STZ induction 40mg/kgBW with metformin 50mg/kgBW/day), treatment group I (STZ induction 40mg/kgBW with ethanol extract of shrike leaves 40mg/kgBW), and treatment group II (STZ induction 40mg/kgBW). kgBB with ethanol extract of 80 mg/kgBB leaves). Next, blood sugar levels (KGD) and macroscopic examination of diabetic ulcer wounds are carried out. Data were analyzed using the Anova test.

**Results:** The lowest blood sugar levels (Mean= 183.83; SD= 11.39), the lowest wound area (Mean= 6.89; SD= 0.86), and the highest percentage of excision wound healing (Mean= 89.67; SD= 1.37) were found in the positive control group. There was a significant relationship between groups of mean blood sugar levels, between groups of wound area, and between groups of healing percentage of excision area ($p<0.05$).

**Conclusion:** Administration of ethanol extract of suruhan leaves (*Peperomia pellucida L. Kunth*) had an effect on reducing blood glucose levels and healing diabetic ulcer wounds in STZ-induced diabetic ulcer model mice.

**Keywords:** *Peperomia pellucida*, antihiperglikemia, wound healing

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## BACKGROUND

Diabetes Mellitus (DM) is a chronic and progressive metabolic disorder characterized by increased blood glucose levels (hyper-glycemia) because the pancreas does not produce enough insulin or the body cannot use the insulin it produces effectively. According to the International Diabetes Federation (IDF) 2021, globally, more than one in 10 adults now lives with diabetes. It is estimated that 643 million people will suffer from diabetes by 2030 (11.3% of the population). Indonesia ranks sixth with 10.3 million diabetes sufferers and this is expected to increase to 16.7 million in 2045 (IDF, 2021).

One of the complaints that occurs in DM patients is the appearance of wounds that are difficult to heal or are called diabetic ulcers (Goyal & Jialal, 2022). High blood sugar levels in DM patients affect wound healing which will cause diabetic wounds to experience a phase of persistent inflamma-tion which is associated with obstacles in the formation of mature granulation tissue and a decrease in wound healing power. The healing phase in DM patients is hampered by multifactors, including specific metabolic deficiencies, physiological response dis-orders such as hypoxia due to glycation of hemoglobin and changes in red blood cell membranes as well as narrowing of blood vessels which are meolecularly disturbed by high blood sugar levels which causes conti-nous glycation of hemoglobin. Wounds that are difficult to heal will eventually become diabetic ulcers (American Diabetes Associa-tion, 2021; Patel et al., 2019). The incidence of diabetic ulcers in Indonesia is 12% and the risk of developing diabetic ulcers is 55.4%. Diabetic ulcers and gangrene cases in Indonesia are the most common cases found in hospitals. Mortality due to ulcers and gangrene ranges from 17-23%, while the amputation rate ranges from 15-30%. DM causes ischemia due to decreased tissue circulation in the legs, thereby inhibiting the wound healing process, this allows germs to enter the wound and infection occurs. Infections that are not treated properly due to decreased leukocyte infiltration can develop into ulcers that develop into gangrene and the risk of amputation becomes greater (Sitompul et al., 2014). Wound healing occurs through the inflam-matory phase, proliferation phase, and remodeling phase. Wound healing in DM sufferers takes longer when viewed from microscopic factors compared to non-diabetic sufferers because the inflammatory phase is prolonged so that macroscopic wound healing will take longer for wound closure to occur (Sinno and Prakash, 2013; Handayani, 2016). Ren et al conducted research on administering kirenol to arti-ficial wounds with subjects in the form of mice with observations showing that during the epithelialization period, the epithelializa-tion phase increased in the group of diabetic mice (Ren et al., 2020).

The messenger plant (*Peperomia pellucida L. Kunth*) is one of the medicinal plants commonly used in Indonesia. This plant, which is included in the Piperaceae family, has many benefits and properties for body health, including being used empi-rically to treat fever, headaches and stomach aches (Kinho, 2011; Sutoyo, 2010). This plant can be used as an anti-bacterial, anti-inflammatory and analgesic. Several research results that have been conducted show that the suruhan plant has the potential to be anti-inflammatory, anti-pyretic, antimicrobial and anti-cancer, and has an analgesic effect (Khan et al., 2008; Wei et al., 2011; Mulyani & Laksana, 2011; Wijaya & Monica, 2004; Hembing, 2008).

Nwokocha et al. (2012) reported that this plant contains flavonoid compounds. Flavonoid compounds are antioxidant compounds and are thought to restore the sensitivity of insulin receptors in cells, this condition causes a decrease in blood glucose levels in mice (Nwokocha, 2012). The herb plant has antihyperglycemic activity. Research by Putri et al (2022) regarding suruhan leaf extract gel with a concentration of 50% had the greatest effect on healing burns. This shows that order leaves have the potential to heal second degree burns. So it can be hypothesized that the messenger plant can treat other open wounds such as diabetic ulcers along with its potential to be an antihyperglycemic drug (Jasmine, 2021; Putri & Puspitasari, 2022; Yufiradani et al., 2020). There is another research by Siahaan et al regarding the administration of ethanol extract from plants in T2 DM models with the result that chayote extract can be anti-hyperglycemia and anti-triglyceride (Siahaan et al., 2019, 2021). However, so far no information has been found regarding medicinal plants in varying doses as anti-inflammatory and wound healing processes, so it is necessary to carry out research regarding the use of suruhan leaves as an anti-diabetic. Therefore, this study aims to prove the effectiveness of suruhan leaves (*Peperomia pellucida L. Kunth*) on Blood Sugar Levels (KGD) and Macroscopic Diabetic Ulcer Wounds.

## SUBJECTS AND METHOD

### 1. Study Design

This was a randomized controlled trial using male white rats with a model of diabetic ulcers and excision wound treatment.

### 2. Population and Sample

The selection of mice as experimental animals was based on the consideration that genetically, mice are similar to humans and have the ability to adapt to the laboratory environment. The inclusion criteria in this study were age 2.5 – 3 months, body weight 150 – 200 grams, male gender, healthy condition (active and not disabled). blood sugar levels > 200 mg/dl (Type II DM), mice were made with excisional wounds with a diameter of 6 mm. Sample size estimation using Federer's formula. Each treatment group contained a minimum of 5 male mice. Researchers chose to use 6 male mice per group to prevent the death of experimental animals with a total of 5 treatment groups so that the total research sample was 30 mice. Samples were obtained using a simple random sampling method, while the order leaves were obtained using a purposive sampling method, taken from Pancur Batu Village, Deli Serdang, North Sumatra Province.

### 3. Study Variables

The dependent variable in this study is Blood Sugar Level (KGD), macroscopic (area and granulation of diabetic ulcer wounds). The independent variable was the dose of ethanol extract of suruh leaves, 40 mg/kg BW and 80 mg/kg BW.

### 4. Operational Definition of Variables

The Ethanol Extract of Suruhan Leaves (*Peperomia pellucida L. Kunth*) obtained was macerated using 96% ethanol solvent and filtered to obtain a filtrate. The filtrate obtained was then evaporated using a rotary evaporator to become a thick ethanol extract. The process of making and extracting simplicia is carried out in the integrated laboratory of the Faculty of Medicine, Methodist University of Indonesia. The extract is given orally using a dose of ethanol extract of leaves of 40 mg/kg BW and 80 mg/kg BW on days 3, 7, 14, 21 to 28.

Blood sugar levels (KGD) were assessed as a result of blood testing on a familyDr glucometer stick and from the heart at the end of treatment measured using spectrophotometry. Observations and measurements of diabetic ulcer wounds were carried out every seven days by taking photos of the wounds and polypropylene sheets to measure the area of the wounds for 28 days as measured by IMAGE-J software. The granulation of diabetic ulcer wounds was assessed by looking at the formation of drying exudate in diabetic ulcer wounds macroscopically on days 0, 7, 14, 21, and 28. The percentage of wound healing was assessed on days 7, 14, 21, and 28. Calculation of the percentage of healing of excision wounds is carried out using the following formula L0-Ln/L0 x 100%; L0= Excision wound area on day 0, Ln= Excision wound on day-n.

**5. Study Instruments**

Wound healing examinations were carried out in the integrated laboratory of the Faculty of Medicine, Indonesian Methodist University, using the Blood Sugar Level (KGD) examination method and macroscopic assessment of the wound.

**6. Data analysis**

Blood Sugar Level (KGD) and macroscopic data (assessment of wound area and percentage of excision wound healing) are expressed as Mean, SD. Statistical analysis was performed using statistical software. Data normality and homogeneity tests were carried out. If the data is normally distributed and homogeneous then an ANOVA test is carried out, if the data is not normally distributed and homogeneous then the Kruskal-Wallis test is carried out. In this study, statistical test decisions were taken with a p value $<0.05$ which was considered significant. And the assessment of granulation after receiving ethanol extract of suruhan leaves (*Peperomia pellucida L.Kunth*) was analyzed descriptively.

**7. Research Ethics**

The use and handling of experimental animals in research laboratories is carried out in accordance with the ethical rules for animal research set out in the Helsinki declaration and ethical permit No. 43 /KEPK-FKUMI/EC/2023 obtained from the ethics committee of the UMI Medan Faculty of Medicine.

## RESULTS

Mean blood sugar levels were measured on days 0, 3, 7, 14, 21 and 28, after administering ethanol extract of suruhan leaves (*Peperomia pellucida L. Kunth*) and compared with the control group as shown in Table 1 and Table 2. Mean wound area and Table 4 percentage of excision wound healing, Note :

a. Group 1, normal controls (normal) were not given any treatment, like normal mice in general which were given excessive food and drink (ad libitum) in their cages.
b. Group 2, negative control was induced by Streptozotocin 40 mg/kgBW with an incision wound
c. Group 3, positive control, induced by Streptozotocin 40 mg/kgBW with incision wounds, with metformin 50 mg/kgBW, p.o
d. Group 4, the treatment group, was induced with Streptozotocin 40 mg/ kgBW with an incision wound, with ethanol extract of suruhan leaves 40 mg/kgBW, p.o.
e. Group 5, the treatment group, was induced with Streptozotocin 40 mg/kgBW with incision wounds, with ethanol

extract of suruhan leaves 80 mg/kgBW, p.o.

**1. Assessment of Blood Sugar Levels (BSL), Percentage of BSL Reduction and Calculation of the Percentage of effectiveness in reducing BSL in the test group compared with Metformin**

In Table 1 it is known that the highest mean blood sugar level in the treatment group on day 28 was in treatment group 5 (Mean=210; SD=26.94), while the lowest blood sugar level was in treatment group 3 (Mean=183.83; SD=11.39 ). There was a significant relationship between groups of mean blood sugar levels on days 3, 7, 14, 21, and 28 (P<0.05).

**Table 1. Average Blood Sugar Levels of Male Wistar White Rats (Rattus norvegicus).**

| Grup BSL | K1 | | K2 | | K3 | | K4 | | K5 | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | |
| BSL H-O | 99.83 | 8.35 | 103.67 | 12.85 | 107 | 6.29 | 104 | 9.59 | 107.33 | 4.63 | 0.765 |
| BSL H-3 | 102.72 | 8.65 | 294.83 | 43.17 | 280.17 | 37.29 | 278.5 | 84.77 | 346.17 | 57.6 | <0.001 |
| BSL H-7 | 109.5 | 7.42 | 288.83 | 18.38 | 202 | 13.11 | 243.17 | 58.99 | 254.67 | 47.36 | 0.001 |
| BSL H-14 | 102.5 | 9.61 | 249.17 | 40.27 | 187.5 | 8.41 | 202.33 | 12.50 | 203.5 | 14.3 | <0.001 |
| BSL H-21 | 100.67 | 10.05 | 243.33 | 35.62 | 177.83 | 13.80 | 199.17 | 6.73 | 200.33 | 13.26 | <0.001 |
| BSL H-28 | 109.83 | 8.66 | 237.17 | 14.43 | 183.83 | 11.39 | 207.83 | 17.11 | 210 | 26.94 | <0.001 |

BSL: Blood Sugar Levels
*Kruskal wallis Test
**Anova

**2. Macroscopic Wound Assessment (Wound Extent and granulation)**

In Table 2 it is known that the highest mean excision wound area in the treatment group on day 28 was in treatment group 4 (Mean= 9.19; SD=2.58), while the lowest excision wound area was in treatment group 3 (Mean=6.89; SD= 0.86). There was a significant relationship between groups of wound area on days 14, 21, and 28 (p <0.05).

**Table 2. Average Wound Area of Male Wistar White Rats (*Rattus norvegicus*)**

| Grup Wound Wide (WW) | K1 | | K2 | | K3 | | K4 | | K5 | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | |
| WW H-O | 69.54 | 5.20 | 68.92 | 3.51 | 66.7 | 4.93 | 69.27 | 4.16 | 70.55 | 8.11 | 0.798 |
| WW H-7 | 53.28 | 6.48 | 60.34 | 5.04 | 53.08 | 5.23 | 52.99 | 8.79 | 53.76 | 10.96 | 0.409 |
| WW H-14 | 36.29 | 6.07 | 49.65 | 5.47 | 32.95 | 8.99 | 36.41 | 8.05 | 38.00 | 7.13 | 0.006 |
| WW H-21 | 18.96 | 1.79 | 31.91 | 7.94 | 25.96 | 3.24 | 23.92 | 2.27 | 22.23 | 5.01 | 0.001 |
| WW H-28 | 9.23 | 1.39 | 17.50 | 4.83 | 6.89 | 0.86 | 9.19 | 2.58 | 8.19 | 1.86 | <0.001 |

WW : WIDE Wound excision
*Anova

In Figure 1, the results of the descriptive analysis of granulation in Figure A on Day-o treatment shows that granulation has not occurred.

Meanwhile, pictures B, C and D show that the excision wound has undergone granulation.

## Table 3. Description of wound healing granulation formation in male Wistar White Rats (*Rattus norvegicus*)

| **Group** | **Control negative** | | | | | **Control positive** | | | | | **STZ Induction Group 40 mg/Kg BW + Metformin 50mg/kg BW** | | | | | **STZ Induction Group 40 mg/Kg BW + Order Extract 40mg/kg BW** | | | | | **STZ Induction Group 40 mg/Kg BW + Order Extract 80mg/kg BW** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Repeat Day** | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 | 0 | 7 | 14 | 21 | 28 |
| 1 | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | **(+)** | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) |
| 2 | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) |
| 3 | (-) | (+) | (+) | **(+)** | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) |
| 4 | (-) | (+) | (+) | **(+)** | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | **(+)** | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) |
| 5 | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | **(+)** | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) |
| 6 | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) | (-) | (+) | (+) | (+) | (+) |

Table 3 Description of post-treatment wound healing granulation assessment
Information :
(+) : Granulation has formed
(-) : Granulation has not yet formed

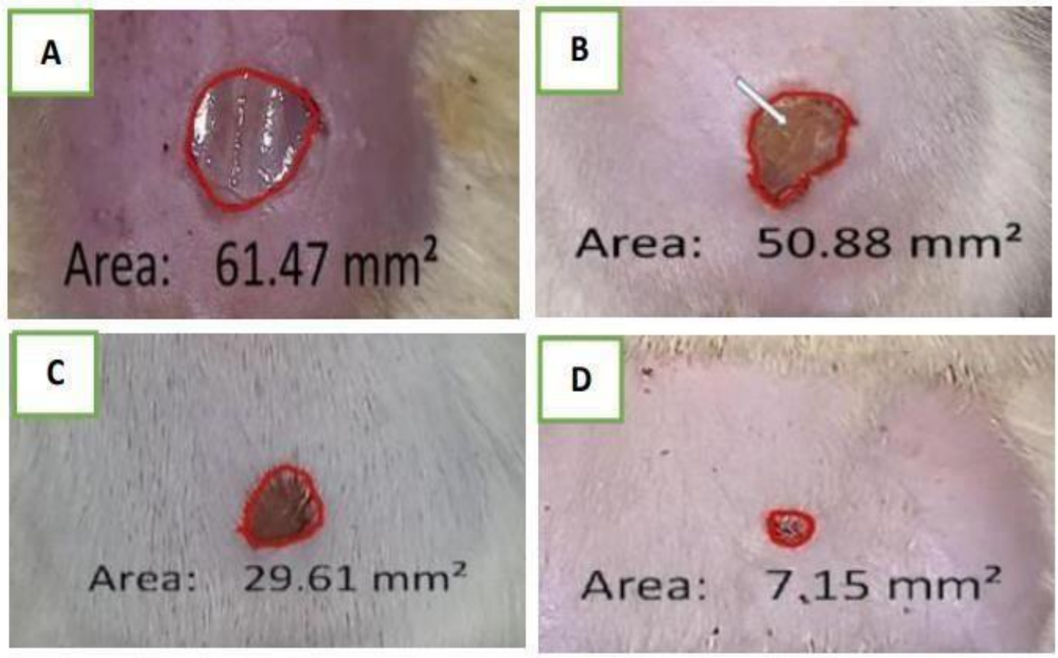


**Figure 1. Analysis of granulation analysis of excision wounds. A= Measurement of the area of the excision wound with image J (Wound Healing 0%), Week 0; B= Measurement of the excision wound area with image J (Wound Healing 17%), Week 1; C= Measurement of the area of the excision wound with image J (Wound Healing 52%), Week 3; D= Measurement of the area of the excision wound with image J (Wound Healing 88%), Week 4.**

In Table 3, it is known that the wound healing granulation picture of each treatment group on day 7 in all treatment groups had already formed granulation tissue.

In Table 4, it is known that the highest percentage of excision wound healing in the treatment group on the 28th day was in treatment group 3 (Mean= 89.67; SD=1.37), while the lowest percentage of excision wound healing was in treatment group 2 (Mean=74.5; SD=7.00). There was a significant relationship between groups in the percentage of excision wound healing on days 14, 21, and 28 (P<0.05).

**Table 4. Percentage of excision wound healing**

| Grup Excision Wide (EW) | K1 | | K2 | | K3 | | K4 | | K5 | | p |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | |
| EW H-7 | 23.33 | 8.89 | 12.33 | 5.43 | 19.83 | 10.49 | 23.83 | 10.28 | 23.67 | 12.06 | 0.189 |
| EW H-14 | 47.50 | 10.88 | 27.83 | 8.38 | 50.17 | 14.54 | 47.33 | 10.93 | 45.00 | 14.07 | 0.024 |
| EW H-21 | 72.67 | 2.73 | 53.5 | 12.18 | 61.00 | 5.62 | 65.5 | 2.66 | 68.00 | 9.14 | 0.002 |
| EW H-28 | 86.5 | 1.871 | 74.5 | 7.00 | 89.67 | 1.37 | 86.5 | 4.13 | 88.17 | 2.93 | 0.002 |

*Kruskal wallis Test
**Anova

## DISCUSSION

Type II DM is a metabolic disease characterized by hyperglycemia due to the body's failure to secrete insulin, ineffective insulin action, or both (Gunardi, 2020). Diabetes-related hyperglycemia is caused by an inability to regulate blood sugar levels, which is a key link between diabetes and its complications, including diabetic wounds. Diabetic wounds require a long healing time, are difficult to treat, and can last weeks, months, or even years. This is what makes it a special concern in healing diabetic wounds (Oguntibeju, 2019).

In the long term, type 2 DM can cause acute complications due to uncontrolled high blood sugar levels, including diabetic ulcers. Diabetic ulcers are a chronic complication of diabetes which is characterized by tissue death and open wounds on the skin surface (Safani et al., 2019).

Healing diabetic ulcers through high blood sugar levels causes diabetes sufferers to have a longer wound healing process. This is because the immune system response slows down so that the plasma is not controlled properly and causes prolonged inflammation (Azizah & Qomariyah, 2021; Jaiswal et al., 2017). Improper ulcer treatment will worsen the infection, causing amputation. Another alternative in treating type 2 DM is by utilizing the potential of plants such as Peperomia pellucida or known as the messenger plant (Olabanji et al., 2014; Pratiwi et al., 2021).

Table 1 shows that there were no significant differences between the groups at D-0 (before the study) because the mice in this study were healthy and homogeneous. On D-3 after STZ induction, the treatment group (K4 and K5) and the control group (K2 and K3) showed an increase in blood glucose levels (KGD >200 mg/dl), the mice had developed diabetes.

On D-7 &, 14, 21 there was a sharp decrease in blood glucose levels. This was thought to be caused by the presence of the enzymes hexokinase and glucokinase. Blood glucose levels are influenced by metabolic and hormonal processes. Hexokinase has a low Km for glucose, functions at a constant rate under normal conditions, but its activity can be inhibited by its product, namely glucose-6-phosphate. Glucokinase is an enzyme that plays a role in glycolysis in the liver and its reaction is not inhibited by its product, glucose-6-phosphate. This enzyme works at high glucose levels. However, this enzyme is reduced in diabetes mellitus (Sari et al., 2010). Glucose metabolism begins with the phosphorylation of glucose into glucose 6-phosphate through the transfer of a phosphate from ATP. Phosphorylation causes glucose to participate in metabolism in the cell because glucose 6-phosphate cannot be removed from the cell in physiological conditions. Hexokinase and glucokinase are enzymes that catalyze the reaction This and is a group of enzymes that are members of the isoenzyme family. Heksokinase and glucokinase catalyze the transfer of phosphate groups from ATP to glucose in the process of glucose phosphorylation by ATP to become glucose-6-phosphate. Hexokinase is an enzyme that works in muscle tissue, while glucokinase is an enzyme that works in the pancreas and liver. The work of hexokinase is inhibited by the product of this reaction, namely glucose-6-phosphate. When the concentration of glucose-6-phosphate reaches a high value, this product will act as a negative effector for hexokinase so that the activity of hexokinase is reduced or even lost. This is different from the enzyme glucokinase. This enzyme is not inhibited by the glucose-6-phosphate product but remains active while glucose is abundant. In the pancreas, this enzyme plays a role in glucose-stimulated insulin secretion, while in the liver, this enzyme is important in glucose uptake and conversion into glycogen. Mutations in this gene that alter the activity of the enzyme have been associated with several types of diabetes and hyperinsulinemic hypoglycemia (Aniket et al., 2015; Pearson et al., 2003).

However, on H-28 the KGD increased but still showed significance ($p<0.001$). This can be caused by the activity of the hexokinase enzyme having reached its maximum while the substrate, namely glucose, continues to increase so that the hexokinase enzyme cannot tolerate glucose levels in the blood.

The decrease in KGD in the K2 group without treatment probably occurred due to the body's self-healing mechanism through repair of pancreatic β cells and the gradual division of new cells (mitosis). The decrease in the number of pancreatic β cells in hyperglycemic animals began to appear on day 7 and continued to decrease until day 21 (Erwin et al., 2012). In general, the increase in glucose levels over time is caused by streptozotocin which damages pancreatic β cells so that insulin production decreases and causes blood glucose levels to increase (Szkudelski, 2001).

In the DM treatment of experimental mice, DM treatment was carried out experimentally by inducing STZ solution in the mice. STZ is a DM induction compound in experimental animals that is used to treat experimental diabetes. Based on the experimental results, it showed that after being induced by STZ, there were variations in the mice's blood glucose levels. This could be due to factors related to the different immune systems of each individual rat in responding to the STZ compound, thus causing differences in blood sugar levels that were not uniform at the start of treatment (Azizah & Qomariyah, 2021; Siahaan, 2017; Tangkumahat et al., 2017).

Based on the results of observations, it showed that there was a decrease in blood glucose levels in each treatment group during the 14 days of observation (Table 1). On the final day (D-28) the K3 treatment group was already in a normal KGD condition (<200g/dl). Meanwhile, treatment K4 and K5 experienced a decrease in blood glucose levels compared to the negative treatment group, namely with a mean of 207.83 g/dl and 210 g/dl. This shows that there is antidiabetic activity in the ethanol extract of suruhan leaves. The results of the analysis of the reduction in blood glucose levels showed that administering the plant extract at a dose of 40 mg/kgBB provided the best (significant) reduction in blood glucose levels compared to a dose of 80 mg/kgBB. At a dose of 80 mg/kgBB, the effect actually decreased. This is because at this dose the body's ability to absorb the drug is maximal and at a larger dose of 80 mg/kgBB the effect of reducing blood glucose levels actually decreases. This is because the maximum ability to reduce blood glucose levels already works at a dose of 40 mg/kgBW, so that when the dose is increased it will not have too much of an effect on the body, it could even become toxic due to excessive doses (C. Saleh et al., 2012; Salma et al., 2013; Togubu et al., 2013).

Increasing the dose of the drug will increase the response proportionally to the increase in dose, but as the dose increases, the increase in response in this study actually decreases because it has reached a dose that can no longer increase the response. This often happens with natural medicines because the compounds contained in them are not single but consist of many different chemical compounds, where these ingredients work together to cause an effect. The results of the analysis showed that increasing the dose of the plant extract to a dose of 80 mg/kgBW did not increase hypoglycemic activity. This is because the binding receptors have been saturated and interactions have occurred with the chemical compounds contained in the messenger plant. If the receptors are saturated, then increasing the dose cannot achieve the maximum effect (Andranilla & Susilawati, 2018; Pasaribu et al., 2012).

Nwokocha et al. (2012) reported that messenger plants contain flavonoid compounds. Flavonoid compounds are antioxidant compounds and are thought to be able to restore the sensitivity of insulin receptors in cells (Nwokocha, 2012). This condition reduces blood sugar levels in mice (Saleh et al., 2012). Ganugapati et al. (2012) reported that flavonoids isolated from bananas have the ability to activate insulin receptors on cells and are an alternative treatment option for type II diabetes patients with insulin resistance (Ganugapati et al., 2012). This can increase insulin sensitivity due to the protective effect on pancreatic β cells. Flavonoid compounds are also able to inhibit alpha amylase and the glucosidase enzyme, as a result the breakdown of glucose fails so that it cannot be absorbed by the intestine and can result in decreased glucose absorption, glucose and fructose absorption from the intestine so that blood glucose levels fall (Eryuda & Soleha, 2016). The effect of suruhan leaf extract on hyperglycemic mice shows that this extract has the property of stimulating or regenerating insulin-secreting β cells and is very effective in controlling diabetes through various mechanisms due to the presence of hypoglycemic alkaloids, saponins and flavonoids (Pratiwi et al., 2021).

The results of examining the average area of excision wounds showed that there was a decrease in the size of the wound area in each treatment group during the 14 days of observation (Table 2). On the final day (D-28), the wound area in the K3 treatment group had decreased in size compared to the K4 and K5 treatment groups. However, the size of the wounds in the K4 and K5 treatment groups decreased compared to the K2 treatment group, this shows that there is wound healing activity in the ethanol extract of suruhan leaves.

Oguntibeju (2019) stated that diabetic wounds will take longer to heal. Delayed healing is due to metabolic disorders in DM sufferers as well as changes in the healing phase that are not as appropriate as they should be (Oguntibeju, 2019). This study showed the same results, in diabetic mice it took longer for the wound to close. Research conducted over 4 weeks showed that on average the wounds did not close completely, this proves that wounds in DM conditions cannot close completely as in normal conditions (without diabetes) which only takes 14 days to close (Figure 1). The size of the wound functions to determine the condition of the wound macroscopically, where the area of the wound shows changes in the wound, whether the ethanol extract of the suruhan leaves used makes a difference in the process of shrinking the wound.

Myofibroblasts are fibroblasts that have been differentiated, tasked with carrying out tissue contraction and assisting in remodeling (Amfotis et al., 2022; Sgonc & Gruber, 2013). At the beginning of the healing period, the ability of fibroblasts to contract or what are called myofibroblasts will pull the edges of the wound so that the two edges adhere or epithelium towards the center of the wound resulting in a reduction in the size of the wound (Muralidhar et al., 2013). Flavonoid compounds are able to stimulate the formation of epithelial cells and support the re-epithelialization process and increase myofibroblast activity. Saponin can increase fibronectin, then the fibrin clots that form will become the basis for re-epithelialization of the tissue (Amphotis et al., 2022). Therefore, if a fibrin clot forms quickly, fibroblasts will immediately proliferate into the wound area to immediately restore tissue (Indraswary, 2011).

Based on the results of research on the effect of administering ethanol extract of suruhan leaves on the recovery of diabetic ulcer wounds, it was found that there was a decrease in the area of the wound and the formation of granulations in the wound tissue, shown in table 3 and figure 1. The increase in the formation of granulation tissue in the wound indicates a change in the wound by closing it further. diabetic ulcer scar skin. Based on the research results, it shows that the treatment groups (K2, K3, K4 and K5) had good wound recovery until the last day. Based on this, the percentage of wound area can be used as a measure or indicator related to the wound healing process due to the increasing growth of new tissue. long time to close the wound (Azizah et al., 2022).

The most optimal wound recovery occurred at a treatment dose of 40 mg/-KgBW (K4) with the administration of ethanol extract of suruhan leaves at a concentration of 40 mg/KgBW. This shows that there is a mutually influencing relationship between blood glucose levels and the recovery of diabetic ulcer wounds in diabetic rats. Blood glucose levels that are controlled or do not have high KGD, have good wound healing, however if blood glucose levels are high it can cause the wound healing ability to take longer. This is due to the decreased ability of blood vessels to vasoconstrict and vasodilate, resulting in poor tissue perfusion and high blood glucose levels supporting the proliferation of anaerobic pathogenic germs to reproduce (Veranita et al., 2016). Because the blood plasma around the wound has a high viscosity, it becomes a fertile environment for germs to grow. So the 40mg/KgBB (K4) dose treatment group showed excellent wound recovery compared to the 80mg/KgBW (K5) dose treatment group because it was supported by controlled blood glucose levels.

Based on table 4, the presentation of excision wound healing is obtained which is in accordance with table 2 where the best healing is in k3 but the ethanol extract of suruhan leaves also has the ability to heal excision wounds and statistically there is significance, which shows that k4 and k5 also have a wound healing effect but the healing process is K3 is faster than K4 and K5.

This plant can help the wound healing process because its leaves contain alkaloids, flavonoids, steroids, saponins, tannins and carbohydrates (Majumder & Kumar, 2011). Alkaloid compounds in the wound healing process are able to initiate fibroblasts towards the ulcer wound area so that the presence of an increasing number of fibroblasts can speed up wound healing. Then, flavonoid compounds also have antioxidant, antimicrobial and anti-inflammatory activity against diabetes mellitus wounds (Widayani et al., 2013). The ability of flavonoids as antioxidants is by inhibiting lipid peroxidation, protecting tissue from oxidative stress thereby increasing wound contraction. The tannin compounds contained in the extract also play a role in wound healing by neutralizing inflammatory proteins and inhibiting hypersecretion of mucosal fluid (Qomariah, 2014). Another secondary metabolite, namely saponin, also plays a role in wound healing by increasing tissue epithelialization and stimulating the formation of collagen fibers which play an important role in the wound closure process (Wijonarko et al., 2016).

Based on research results, administration of ethanol extract of suruhan leaves (*Peperomia pellucida L. Kunth*) had an effect on reducing blood glucose levels and healing diabetic ulcer wounds in STZ-induced diabetic ulcer model mice. This is proven by a decrease in KGD and a significant reduction in the size of diabetic ulcer wounds. The extract treatment group with a dose of 40 mg/kgBW was the most optimal dose in reducing blood glucose levels and healing diabetic ulcers towards wound closure. Administration of ethanol extract of ethanol extract of suruhan leaves (*Peperomia pellucida L. Kunth*) at a dose of 40 mg/kgBW provided the most optimal antidiabetic effect in reducing blood glucose levels and healing diabetic ulcers and wound closure in diabetes mellitus rats.

## AUTHOR CONTRIBUTION

Enggrek Pelita Hakim as a research member who carried out extraction, handling of experimental animals, induction and elisa examination. Jekson Martiar Siahaan as head researcher is responsible for selecting ideas, monitoring and evaluating research implementation, and data collection. Endy Juli Anto, Putri Chairani Eyanoer carried out data analysis and assisted in data interpretation.

## CONFLICT OF INTEREST

There is no conflict of interest in this research.

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