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Effect of African Leaf Extract (*Vernonia amygdalina*) on Blood Sugar Levels and Wound Healing in Mice with Type 2 Diabetes Mellitus

Mazaya Sharfina[1]*, Nur Kuswanti[2], Firas Khaleyla[3]
Biology Study Program, Faculty of Mathematics and Natural Sciences, Surabaya State University
*Corresponding Author, e-mail: mazaya.sharfina07@gmail.com

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Abstract
Long-term uncontrolled hyperglycemia in diabetes mellitus can lead to chronic complications, one of which is diabetic ulcers. African leaves have metabolite compounds that act as antidiabetics and accelerate wound healing. This study aims to identify the best effect and dose of African leaf extract on blood sugar levels and wound healing in Type 2 DM (T2DM) mice. This study used 24 male DDY mice grouped into six groups, namely negative control (A), positive control (B), metformin (C), African leaf extract doses of 75 mg/kgBW (D), 100 mg/kgBW (E), and 125 mg/kgBW (F). The induction of T2DM was done orally with a high-fat diet (HFD) and alloxan intraperitoneally. Wounds were made on the dorsal part of the mice as long as 1 cm. Administration of the extract was done orally. Wound healings were measured macroscopically based on the rates of wound healing and microscopically based on the density of the collagen fibers and the number of fibroblast cells. The data on fasting blood sugar levels, wound healing rates, and ulcer histology were analyzed statistically. The results showed that African leaf extract had a significant effect ($p<0.05$) on fasting blood sugar levels and wound healing, both macroscopically and microscopically. The 125 mg/kgBW dose of African leaf extract had the best result for blood sugar and wound healing. Thus, the African leaf extract is potentially useful for diabetic drugs and diabetic wound/ulcer healing.

Keywords: african leaf; diabetes mellitus; diabetic ulcer; wound healing
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INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease characterized by high blood sugar levels due to impaired insulin secretion, insulin performance, or both (ADA, 2022). According to the International Diabetes Federation (IDF) in 2019, as many as 483 million people aged 20-79 years had diabetes (Kemenkes RI, 2020). The World Health Organization (WHO) states that Indonesia has the fourth highest number of diabetics in the world after India, China, and the United States, and is expected to reach 21.3 million diabetics in 2030 (Imelda, 2019).

Diabetes mellitus is classified into three types, namely type 1 DM, type 2 DM, and gestational DM. (IDF, 2021). Type 2 diabetes mellitus (T2DM) is one of the most common diseases worldwide, with a prevalence of 90% of all diabetes. The causes of T2DM are insulin resistance and pancreatic β-cell dysfunction (Murtiningsih *et al*., 2021). Patients with DM in Indonesia mostly suffer from T2DM due to insulin resistance, inhibiting insulin receptor activity on cells and disturbances in β-cell function that cause unfulfilled insulin production from the pancreas, resulting in relative insulin deficiency (Nufus *et al*., 2021).

Hyperglycemia is a condition in which blood sugar levels exceed normal limits. A person can be declared diabetic if they have a fasting blood sugar above 126 mg/dL or a random blood sugar above 200 mg/dL (Yisahak & Narayan, 2017). Uncontrolled blood glucose levels over a long time can lead to complications. One of the chronic complications of diabetes in Indonesia is diabetic ulcers, with a prevalence of around 15%, with amputation rates reaching 30% and mortality of 32% (Pujiati & Suherni, 2019).

Diabetic ulcers are skin lesions involving all skin layers, which can spread to the tissues beneath the epidermis, tendons, muscles, bones, and joints, especially in the foot or lower leg area. This condition occurs in people with DM and is caused by elevated blood sugar levels (Wijonarko, 2016). Complications in DM occur due to metabolic changes that cause changes in the structure and

function of macromolecules in the body. Some complications of DM include diabetic retinopathy, nephropathy, neuropathy, and cardiomyopathy, as well as macroangiopathic complications such as atherosclerosis (Prawitasari, 2019). The main factor leading to diabetic ulcers is neuropathy. Neuropathy refers to a peripheral nerve disorder that results in a reduced ability to sense touch and pressure (Hindrianingtyas & Kuswanti, 2023). It includes a variety of sensory, motor, and autonomic nerve disorders, most commonly in the peripheral parts of the body, known as Diabetic Peripheral Neuropathy (DPN). This condition causes muscle atrophy, impaired pressure distribution in the feet, foot deformities, calluses, and numbness, putting the patient at risk of unrecognized wounds (Mildawati *et al*., 2019).

Treatment of diabetic ulcers includes empirical broad-spectrum antibiotics, with subsequent antibiotic selection based on the results of the specimen culture sensitivity test (Embil *et al*., 2018). Empirical antibiotics are used as the start of treatment to prevent infection. Prolonged use of antibiotics can cause side effects, namely antibiotic resistance. Therefore, there is a need for alternative treatments to cure DM accompanied by diabetic ulcers, among others, by utilizing natural extracts. African leaf (*Vernonia amygdalina*), also known as "Bitter Leaf", is one of the plant varieties used in herbal medicine. Chemical compounds contained in African leaves are alkaloids, saponins, tannins, and flavonoids (Febrianti *et al*., 2017). Alkaloids are antimicrobials that inhibit microbial growth. (Daturara *et al*., 2024). Flavonoids and tannins are compounds that can increase the number of fibroblasts in the wound healing process, so that wounds quickly improve. Saponins help collagen formation, increase the speed of epithelialization, and act as an antiseptic to help kill or prevent the growth of microorganisms (Senaen *et al*., 2021). Research by Eyo *et al*. (2014) compared other herbs; *Vernonia amygdalina* extract proved more effective in healing diabetic wounds, re-epithelialization, and collagen formation compared to therapy with *Zingiber officinalis* extract and *Ocimum gratissimum* extract or normal saline.

The wound healing process is characterized by wound surface closure, collagen contraction, accelerated epithelialization, and increased connective tissue density. Wound closure and collagen density are interrelated in diabetic ulcer healing, which is influenced by controlling blood sugar levels. (Azizah & Qomariyah, 2022). This study used mice instead of rats because mice are smaller, reproduce quickly, and have 99% genetic similarity to humans. This makes mice have physiological similarities with humans, so they are suitable as experimental animals (Stevani, 2016). The update of this study is to determine the effect of African leaf extract on the histology of ulcers observed from collagen density and the number of fibroblast cells to improve wound healing. Therefore, it is necessary to conduct further research on the potential of African leaf extract on wound healing (ulcers) of type II DM mice.

MATERIALS AND METHODS

This experimental study used a completely randomized design consisting of negative control treatment (without High-Fat Diet (HFD) + alloxan), positive control (HFD + alloxan), metformin (HFD + alloxan + metformin), and different doses of African leaf extract (75, 100, 125 mg/kgBB) with four replicates for each treatment. This research was carried out for three months, March - June 2024, in the Laboratory in the Biology Study Program, Faculty of Mathematics and Natural Sciences, The Surabaya State University.

African leaves used for extraction are green leaves and start from the third node at the base of the stem. Simplisia is made by cleaning the leaves and drying them in the oven for 3 days at a temperature of 60°C. After drying, the leaves were pulverized with a blender to produce powder. In the maceration stage, the simplisia powder was soaked with 96% ethanol solvent for 3×24 hours and then filtered to produce a filtrate. A filtrate was evaporated using a rotary evaporator at 60°C to obtain a 100% thick extract (Tuldjanah *et al*., 2020). Then it was diluted with 1% NaCMC into doses of 75, 100, and 125 mg/kgBW.

This study used male mice of the Deutschland Dunken Yoken (DDY) strain aged 2 months, weighing 25-30 g, a total of 24 animals, and acclimated for 7 days with CP 511 concentrate feed and drinking water ad libitum. After acclimation, all mice except the negative control group were fed a High Fat Diet (HFD) with a composition of 80% standard feed, 15% goat fat, and 5% duck egg yolk given ad libitum for 7 weeks until the mice experienced hypercholesterolemia (>130 mg/dL) (Tatto *et al*., 2017). Next, mice were induced with alloxan at a dose of 110 mg/kgBW via intraperitoneal injection. Six hours after induction, mice were given a 10% sucrose solution to drink within 2 days to avoid hypoglycemia. The fasting blood sugar of mice was measured after three days of alloxan

induction to ensure the mice were in a hyperglycemic condition (≥126 mg/dL) (Yisahak & Narayan, 2017).

Each fasting blood sugar measurement was carried out after the mice were fasted for 8-12 hours. Fasting blood sugar checks using the EasyTouch GCU brand glucometer. Blood was drawn using a lancet through the tail vein of the mice. The blood that comes out is dripped on the strip test that has been attached to the glucometer, and then the results are read on the screen. Fasting blood sugar measurements were taken on day 3 after alloxan induction (day 0 of treatment) and day 8 of treatment.

Wounding was performed by first anesthetizing the mice using chloroform for ± 5 seconds. Next, the mice's hair on the dorsal part was removed and sterilized with 70% alcohol, then a wound was made along 1 cm with a depth of up to the subcutis using surgical scissors and sterile scalpels. Wound healing measurements were measured daily using a ruler. Wound length data was obtained, and then the speed of wound healing was calculated using the following formula.

$$\text{The rates of wound healing} = \frac{\text{The length of initial wound (cm)} - \text{The length of particular day's wound (cm)}}{\sum \text{days}}$$

Wound tissue was obtained by anesthetizing the mice using chloroform and then dissecting the dorsal skin that was injured ± 4 mm from the edge of the wound as a sample. Preparation of ulcer histology preparations begins with the fixation stage by placing the tissue into a 10% Neutral Buffered Formalin (NBF) solution for at least 24 hours. Tissue samples were processed by the paraffin method with a slice thickness of 4µm and Hematoxylin-Eosin staining (Khaleyla *et al*., 2021).

Observation of ulcer histology preparations was performed under a light microscope at 4 fields of view with 400x magnification. Observations of collagen density and fibroblast cell counts were performed with the scoring method, as presented in Table 1.

Table 1. Collagen density and fibroblast cell count assessment scores (Irwandi *et al*., 2022)

Score	Description
0	Collagen fibers are not visible, There are no fibroblast cells
1	The density of collagen fibers spreads thinly or slightly, There are <20 fibroblast cells
2	The density of collagen fibers is moderate and appears fused. There are 20-50 fibroblast cells
3	The density of collagen fibers is spread densely or many and are perfectly bound, There are >50 fibroblast cells.

Data on fasting blood sugar levels, wound healing speed, and ulcer histology scores were statistically analyzed by normality test using the Shapiro-Wilk test and homogeneity test using the Homogenity of Variances test. Fasting blood sugar data were normally distributed ($p>0.05$), then the One-Way ANOVA test ($p<0.05$) and Duncan's test were performed. Data on wound healing speed and ulcer histology score were not normally distributed, so nonparametric tests were carried out, namely the Kruskal-Wallis test ($p < 0.05$) and the Mann-Whitney test.

RESULTS

Based on the results of the research conducted, the results of fasting blood sugar levels were different for each treatment group. The data obtained included day 0 data after HFD + alloxan induction and day 8 after African leaf extract treatment with various doses and metformin administration, which can be seen in Table 2.

Based on the ANOVA test ($p<0.05$), it was found that there was an effect of African leaf extract on blood sugar levels. Based on Table 2, the Duncan test results show that the extract groups (D, E, F) are not significantly different from the negative control group (A) and metformin (C). The dose of 125 mg/kgBW of African leaf extract (F) is the best dose with a change in blood sugar reduction of 106, 75 mg/dL.

Table 2. Fasting blood sugar levels from all group

Treatment	Fasting Blood Sugar levels (mg/dL)		Changes (mg/dL)
	D-0	D-8	
A	106,5 ± 3,84[a]	116 ± 4,64[a]	↑ 9,5 ± 1,29[d]
B	151 ± 7,28[b]	141,5 ± 9,07[b]	↓ 9,5 ± 3,11[c]
C	145,75 ± 7,50[b]	119,5 ± 14,67[a]	↓ 26,25 ± 14,36[ab]
D	144,5 ± 7,70[b]	121,5 ± 3,64[a]	↓ 23 ± 7,87[b]
E	141 ± 7,58[b]	109,75 ± 6,10[a]	↓ 31, 25 ± 3,10[ab]
F	145 ± 9,00[b]	106,75 ± 10,64[a]	↓ 38,25 ± 11,81[a]

Notes: Different superscript notations indicate significant differences ($p<0.05$) in each measurement based on Duncan's test. A = negative control, B = positive control (HFD+alloxan), C = HFD+alloxan+metformin, D = HFD+alloxan+African leaf extract 75 mg/kgBW, E = HFD+alloxan+African leaf extract 100 mg/kgBW, F = HFD+alloxan+African leaf extract 125 mg/kgBW. ↑ indicating an increase, ↓ indicating a decrease in blood sugar levels. D-0 = day 0, D-8 = day 8.

Table 3. Rate of wound healing, as well as collagen density and fibroblast cell count scores

Treatment	Wound Healing Rates (cm/day)	Collagen Density and Number of Fibroblast-Fibroblast Cells
A	0,122 ± 0,005[a]	2,88 ± 0,25[a]
B	0,053 ± 0,010[b]	1,44 ± 0,52[b]
C	0,059 ± 0,010[b]	2,31 ± 0,38[ac]
D	0,059 ± 0,010[b]	1,88 ± 0,25[bc]
E	0,069 ± 0,006[bc]	2,44 ± 0,43[a]
F	0,084 ± 0,010[c]	2,81 ± 0,24[a]

Notes: Different superscript notations indicate significant differences ($p<0,05$) in each measurement based on the Mann-Whitney test. A = negative control, B = positive control (HFD+alloxan), C = HFD+alloxan+metformin, D = HFD+alloxan+African leaf extract 75 mg/kgBW, E = HFD+alloxan+African leaf extract 100 mg/kgBW, F = HFD+alloxan+African leaf extract 125 mg/kgBW.

The result of the Kruskal-Wallis test ($p<0,05$) showed the effect of various treatments on wound healing rate, collagen density scores, and the number of fibroblast cells. Based on Table 3, it is known that the 125 mg/kgBW dose group (F) is significantly different from the other treatment groups on the average wound healing rate, while on the average collagen density score and the number of fibroblast cells, the 125 mg/kgBW dose group (F) is not significantly different from the negative control group (A), metformin (C), and the 100 mg/kgBW dose (E). Group F is the best treatment group in wound healing rate of 0,084 cm/day and collagen density scoreand number of fibroblast cells with a score of 2,81. The result of the observation of the histology of diabetic ulcers in diabetic mice can be seen in Figure 1.

Based on Figure 1, the results of observations of the histological picture of diabetic ulcers of type II DM mice in the negative control group (A) and 125 mg/kgBW dose of African leaf extract (F) showed high collagen density and fibroblast cell count. In the metformin group (C), 75 mg/kgBW dose of African leaf extract (D), and 100 mg/kgBW dose (E) showed moderate collagen density and fibroblast cell count. Meanwhile, in the positive control group (B), collagen density and the number of fibroblast cells were very low.

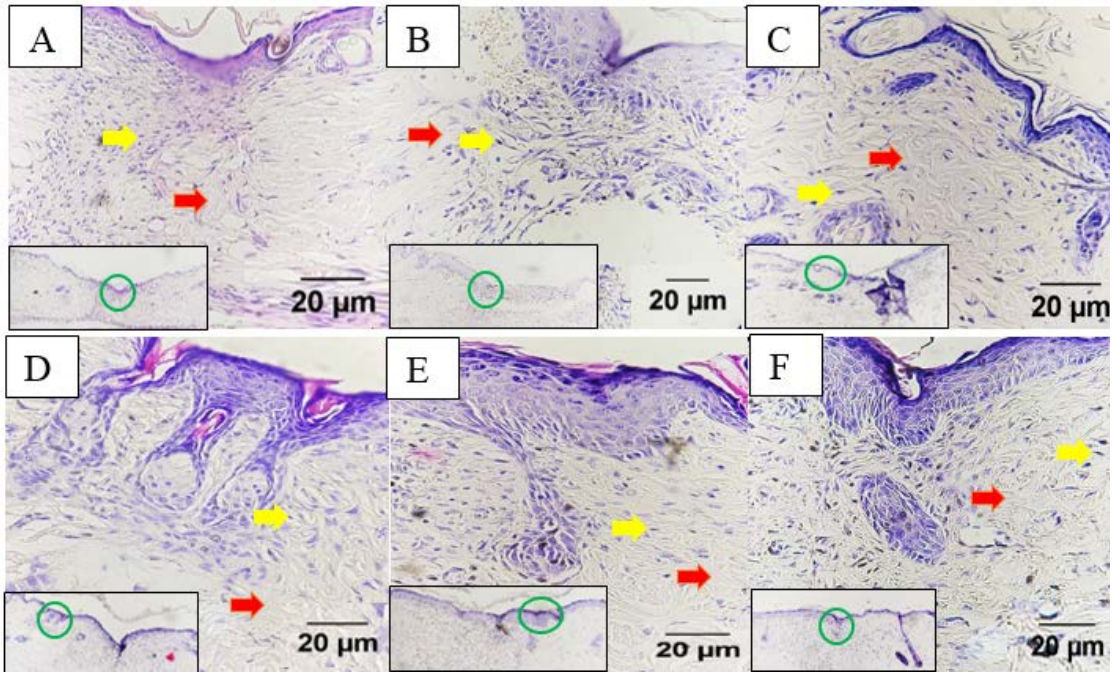

Figure 1. Observation of the histology of diabetic ulcers in type II DM mice. A = negative control, B = positive control (HFD+alloxan), C = HFD+alloxan+metformin, D = HFD+alloxan+African leaf extract 75 mg/kgBW, E = HFD+alloxan+African leaf extract 100 mg/kgBW, F = HFD+alloxan+African leaf extract 125 mg/kgBW. = collagen, = fibroblast cell.

DISCUSSION

The alloxan administration at a dose of 110 mg/kgBW is used to make mice in a state of type II diabetes mellitus (DM). Type II DM condition is characterized by fasting blood sugar levels ≥126 mg/dL (Yisahak & Narayan, 2017). In this study, the positive control group, the metformin group, and the extract group were induced by alloxan after 7 weeks of high-fat feeding. After 3 days of alloxan induction (D-0), fasting blood sugar levels were measured to ensure the mice were diabetic. Increase blood glucose levels in alloxan administration are caused by damage to the cell membrane permeability and the formation of free radicals (Irdalisa *et al*., 2021). The mechanism of alloxan-induced diabetes begins with the uptake of alloxan by pancreatic β-cells. Next, glutathione (GSH) reduces alloxan by binding to the -SH group, producing dialuric acid, which is then oxidized back to alloxan. This oxidation generates superoxide radicals and ROS, which produce hydrogen peroxide (H2O2). Alloxan can also increase Ca^{2+} ion levels in the cytosol by depolarizing pancreatic β-cells that open calcium channels. The increase in ROS and Ca^{2+} ions causes damage to pancreatic β-cells, leading to decreased insulin production (Yasaroh *et al*., 2021). Long-term uncontrolled blood glucose levels can lead to complications.

In this study, checking blood sugar levels in mice was carried out during fasting to avoid the impact of glucose on the food consumed by mice. The results of fasting blood sugar levels at D-8 showed significant differences compared to the initial conditions, especially after being treated with African leaf extract at various doses and metformin. When the D-8 results were compared with the negative control group, it was seen that the most optimal dose of African leaf extract was 125 mg/kgBW, because the blood sugar levels of this group experienced the highest blood sugar reduction changes and approached normal mice blood sugar levels. This means that good potential in reducing blood sugar levels is shown by the 125 mg/kgBW dose of African leaf extract, which confirms the effectiveness of the extract in helping the management of diabetes.

The results of research by Tandi *et al*. (2020) Showed that ethanol extract of African leaves at doses of 50 mg/kgBB and 100 mg/kgBB was effective in reducing blood sugar levels and stimulating pancreatic β-cell regeneration in male white rats induced by high-fat and STZ feed. In this case, the decrease in blood sugar levels is influenced by African leaf extract because of its properties, among others, as an antioxidant, antidiabetic, analgesic, and antimicrobial (Bestari, 2021). The properties of African leaves are due to the metabolite compounds contained in them. Flavonoid compounds found

in African leaves act as antioxidants by reducing Reactive Oxygen Species (ROS), thus protecting pancreatic β-cells from damage that can interfere with insulin production. Flavonoids can inhibit the absorption of carbohydrates by the α-glucosidase enzyme by breaking down carbohydrates into monosaccharides in the intestine. This will result in a decrease in blood sugar levels (Shi *et al*., 2019). Saponin compounds contained in African leaves play a role in regenerating the pancreas by increasing the number of β-cells in the islets of Langerhans. This will increase insulin secretion, which is useful for lowering blood sugar. There are also tannin compounds that help decrease blood sugar. Tannin compounds can inhibit free radicals, thus helping to reduce insulin resistance (Haryoto & Devi, 2018).

African leaf extract (*Vernonia amygdalina*) also affects wound healing in type II diabetes mellitus mice. Flavonoid compounds, tannins, alkaloids, and saponins contained in African leaves can accelerate the wound healing process. Flavonoid compounds have anti-inflammatory properties that can reduce inflammation in the skin and relieve redness in wounds that have stopped bleeding. In addition, flavonoids can minimize wounds due to oxidation reactions and prevent the formation of free radicals (Pebri *et al*., 2017). Meanwhile, tannins are astringent compounds that can precipitate cell surface proteins with low permeability. This results in hardening of the skin, light bleeding, closing of skin pores, and stopping of exudates (Pusparani *et al*., 2018). There are also saponin compounds found in African leaves that play a role in the wound healing process by helping collagen formation and increasing the speed of epithelialization (Calsum *et al*., 2018). This saponin compound also plays a role in killing and preventing the growth of microorganisms. This is what makes saponins cleansing and antiseptic. Alkaloid compounds also have properties such as saponins, namely as antimicrobials that inhibit microbial growth, and as analgesics and anti-inflammatories, such as flavonoids (Daturara *et al*., 2024). This is in line with the results of the study that the African leaf extract group doses of 75, 100, and 125 mg/kgBW (D, E, and F) showed better wound healing speed compared to the positive control and metformin. The 125 mg/kgBW dose of African leaf extract showed the fastest average wound healing rate among all treatments. This indicates the potential of African leaf extract to enhance the wound healing process, especially at higher doses (Table 3). This indicates that the higher the dose of African leaf extract given, the more effective the wound healing speed is characterized by the lengthening of wound healing so that the wound shrinks.

In the wound healing stage, fibroblasts and collagen have a very important role in hemostasis, increasing cellular components, mutual interaction between platelets and fibronectin, playing a role in epidermal proliferation, encouraging the process of fibroplasia, and increasing growth factors (Giri *et al*., 2021). African leaf extract contains flavonoid compounds that function in scavenging free radicals such as ROS, related to phenolic OH groups, and preventing inflammation. This can repair damaged tissue and inhibit the inflammatory process. Flavonoids are also used as antioxidants that are useful in reducing the effects of inflammation (Fuadah, 2016). Saponins in African leaves play an important role in stimulating fibronectin production from fibroblasts, a protein that is crucial in the formation of the extracellular matrix. The fibrin matrix formed from the conversion of fibrinogen to fibrin is facilitated by growth factors such as TGF-β and PDGF (Platelet-Derived Growth Factor), which are important elements in the inflammatory phase. TGF-β plays a role in attracting immune cells (such as monocytes and macrophages) to the wound site, that against infection and begins the healing process (Martin & Nunan, 2015). Tannins are useful in accelerating fibroblast proliferation and collagen formation, and reducing the risk of infection, which in turn supports cell regeneration and accelerates the wound healing process (Gandhi, 2019). Alkaloid compounds in African leaves play an important role in disrupting the permeability structure of the bacterial cell wall, which triggers death and inhibits bacterial cell growth (Sari *et al*., 2024). The presence of these active compounds in African leaf extract is what causes the collagen fiber density score and the number of fibroblast cells in the 75, 100, and 125 mg/kgBW doses of African leaf extract treatment groups (D, E, and F) to be higher than the positive control group. The 125 mg/kgBW dose has the highest mean score, which proves that African leaf extract has an effect on wound healing seen from the histology of diabetic ulcers of mice based on collagen density and the number of fibroblast cells.

Metformin is a commonly used drug to treat type II diabetes by reducing glucose production in the liver, increasing insulin sensitivity in the body's cells, and reducing glucose absorption from the gut. This process helps to lower overall blood sugar levels (Bhandari & Kumari, 2017). In this case, metformin can heal wounds by increasing FGF (Fibroblast Growth Factor) and decreasing free radical molecules so that fibroblast cells and collagen fibers can be synthesized properly (Tamayanti *et al*., 2015). On the other hand, African leaf extract (*Vernonia amygdalina*) has bioactive compounds such as

flavonoids and saponins that provide antihyperglycemic effects, stimulate insulin secretion, and have anti-inflammatory and antioxidant properties that can accelerate wound healing, important for diabetics. Although metformin and African leaf extract can both accelerate wound healing, metformin has gastrointestinal side effects (Adewole & Akinmoladun, 2019). African leaf extract offers a more comprehensive approach with added cell protection benefits and is safer and more accessible than metformin. The dose of 125 mg/kgBW was the best dose of African leaf extract that was close to the negative control group in improving wound healing and lowering blood sugar compared to the doses of 75 mg/kgBW and 100 mg/kgBW. In this case, African leaf extract is proven to improve wound healing and control blood sugar optimally, especially at higher doses. Therefore, further research on the use of African leaf extract as an alternative or adjunct in type II diabetes therapy is highly recommended to find a more natural and effective treatment solution.

CONCLUSION

African leaf extract affects blood sugar levels and wound healing, as seen from the rate of wound healing and histology of diabetic ulcers. Blood sugar levels and wound healing macroscopically and microscopically in type II DM mice are best influenced by a 125 mg/kgBB dose of African leaf extract. Thus, the African leaf extract is potentially useful for diabetic drugs and diabetic wound/ulcer healing.

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CONFLICT OF INTEREST

There is no conflict of interest.

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