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THERAPEUTIC POTENTIAL OF ETHANOL EXTRACT OF *ACACIA NILOTICA* (L.) DELILE AND *ANOGEISSUS LEIOCARPUS* (DC.) GUILL. & PERR IN DIABETIC WOUND HEALING: EVIDENCE FROM MALE WISTER RAT

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ABSTRACT

The use of plants in traditional medicinal systems has been practiced for thousands of years and continues to supply people with new remedies. The current study evaluated the wound healing effect of ethanol extracts of *Acacia nilotica* pod and *Anogeissus leiocarpus* stem bark on rat models. Fourty two (42) Streptozotocin (60 mg/kg) induced diabetic male Wistar rats were divided into seven (7) groups of six (6) rats each. A one-centimeter-diameter excision wound was created on the mid-dorsal area of the experimental diabetic rats. The treatment groups were treated daily with the plant extracts by oral administration at doses of 200 mg/kg and 400 mg/kg for 14 days. Blood glucose level, percentage of wound contraction of the experimental rat groups were observed for 21 days. Histopathological examination was also carried out at the end of the experiment. The findings indicated that both *A. leiocarpus* at doses of 200 mg/kg, 400 mg/kg and *A. nilotica* at 200 mg/kg enhanced wound contraction in the diabetic rats at day 14 compared to the standard drug (Metformin) which occurred at day 21. This showed a significant reduction in blood glucose level of the treated diabetic rats as well as wound healing effect by the tested plants extract.

Keywords: *Acacia nilotica*, *Anogeissus leiocarpus*, Anti-diabetic, Diabetic rat, Streptozotocin, Wound healing

INTRODUCTION

Diabetic wound healing presents several challenges that can complicate the management and delay the healing process. Some of the key challenges in diabetic wound healing include: impaired blood circulation, neuropathy, infection, chronic inflammation, poor glycemic control, delayed epithelization and high cost of management (Saini & Verma, 2019). Addressing these challenges requires a comprehensive approach that involves close monitoring of blood sugar levels, optimization of vascular health, infection control, offloading pressure and exploring novel therapeutic strategies (Oguntibeju, 2019).

The use of medicinal plants in the treatment of various human ailments is of immense importance and has been widely accepted especially in resource-poor countries where access to hospitals and modern drugs is a problem thereby making people to focus on alternative and complementary therapies for disease management. In Nigeria, people are resorting to herbal medicine due to economic drop of the country coupled with increased inflation and with the belief that they have fewer side effects or are more effective in curing.

Indeed, documentation of indigenous knowledge on the use of plants for the treatment of various human ailments in Nigeria has been carried out effectively (Aiyeloja & Bello, 2006; Lawal, *et al.*, 2010; Sani & Aliyu, 2011a; Salihu *et al.*, 2015; Ali *et al.*, 2017) including diabetes and diabetic foot ulcer (Abubakar *et al*., 2017; Negbenebor *et al*., 2017; Sani *et al*., 2019; Buhari *et al*., 2021). However, many of their pharmacological properties remain unverified. It has thus become crucial to provide the public with sufficient information based on scientific evidence to ensure their safety, effectiveness, and proper quality.

Hence the research is using streptozotocin induced diabetic rats in validating the wound healing effect of ethanol extracts of *Acacia nilotica* pod and *Anogeisus leiorcapus* stem bark.

Acacia nilotica, also known as the Babul or Gum Arabic tree, is a plant native to Africa, Indian subcontinent and parts of the Middle East. Various parts of the tree, including the bark, leaves, and gum, have been traditionally used in herbal medicine for their potential health benefits. *Acacia nilotica* has been reported to possess antibacterial (Sani & Aliyu, 2022), anti-inflammatory (Sene *et al*., 2023), and wound healing properties (Kankara *et al*., 2017), which could potentially make it beneficial for diabetic wound healing.

Anogeissus leiocarpus, commonly referred to as African birch or "Marke" in Northern Nigeria, is a tree species in the family Combretaceae found in the tropical regions of Africa. It has been traditionally used in African folk medicine for various purposes including wound healing. Some researches have emphasized the possible therapeutic benefits of *Anogeissus leiocarpus*, including its antioxidant (Eltayeb *et al*., 2016), antibacterial (Sani & Aliyu, 2022) and wound healing effects (Victor *et al*., 2013). These properties may contribute to its potential in supporting diabetic wound healing.

MATERIALS AND METHODS

Collection and identification of the selected plant parts

Fresh pods of *Acacia nilotica* and stem bark of *Anogeissus leiocarpus* were gathered from their natural habitats and were verified by a botanist in the Department of Plant Biology at Bayero University Kano. The specimens were assigned voucher numbers BUKHAN 186 for *A. nilotica* and BUKHAN 29 for *A. leiocarpus*.

The collected plant parts were dried under shade for two weeks. The dried parts were then ground into coarse powder using electric grinder and then subjected to the extraction method. Fifty gram (50 g) of each powdered plant materials was macerated with 500 ml of ethanol kept on a rotary shaker at 150 rpm with constant agitation for 72hrs. Thereafter, it was filtered through 8 layers of muslin cloth and then re-filtered through Whatman No. 1filter paper. The filtrate was then concentrated in a rotary evaporator at 40˚C yielding corresponding extracts.

Experimental animal groups

The research was conducted at the pharmacology laboratory of the Department of Pharmaceutical Sciences Bayero University, Kano.

Forty two (42) healthy male Wistar albino rats (150 - 200g weight) were used for the experimentation. The animals were housed in polypropylene cages lined with husk under standard conditions (25 ± 2°C, 12-hour light and dark cycle) and were given pelleted food (Purina) and water ad libitum. They were divided into seven groups, each consisting of six rats. Group I: Non-diabetic rats with wounds, serving as the normal control. Group II: Diabetic rats with wounds treated with the standard drug Metformin at 5 mg/kg. Group III: Diabetic rats with wounds that received no treatment, serving as the disease control (untreated). Group IV: Diabetic rats with wounds treated with *Acacia nilotica* at 200 mg/kg. Group V: Diabetic rats with wounds treated with *Acacia nilotica* at 400 mg/kg. Group VI: Diabetic rats with wounds treated with *Anogeissus leiocarpus* at 200 mg/kg. Group VII: Diabetic rats with wounds treated with *Anogeissus leiocarpus* at 400 mg/kg.

Induction of diabetes

This was carried out using the procedure described by Santosh *et al*. (2017). Streptozotocin (STZ) was used to induce diabetes by a single dose administration of 60mg/kg intra-peritoneal after overnight fast. Immediately following STZ induction, all animals were given 5% glucose water for 6 hours to prevent first-phase hypoglycemia. On the 7th day after Streptozotocin injection, fasting blood glucose levels were measured using glucose oxidase reagent strips and a Glucometer (Accu-check®). Only animals with glucose levels exceeding 250 mg/dl were included in the study.

Diabetic wound model

Rats were anesthetized with thiopentone sodium at a dose of 40 mg/kg via intra-peritoneal injection. Each rat was shaved on the right side with a razor blade, and a one-centimeter diameter excision wound was created on the mid-dorsum of each rat. On the first day after wounding, ethanol extracts of the plants, reconstituted in distilled water, were administered orally using a syringe at doses of 200 mg/kg and 400 mg/kg for 14 days to the treatment groups. The control group received an equal amount of citrate buffer. The rate of wound contraction and plasma glucose levels were assessed on Days 1, 7, and 14 of treatment, and again on Day 21 after treatment. The rate of wound contraction was tracked on transparent paper with a millimeter scale by measuring the wound area. It was calculated as a percentage of the original wound area using the following formula:

% wound contraction = (A0 −At) / A0 × 100

Where 'A0' is the original wound area and 'At' is the area of the wound at a specific period after wounding.

Histopathological examination

At the end of experimental period of three weeks the experimental rats (3 from each group) were fasted overnight and sacrificed by cervical decapitation. Organs such as Liver and Pancreas were dissected out and were washed in saline, fixed immediately in 10% formalin, dehydrated through a series of ethanol solutions, and embedded in paraffin. Thin sections of 4-5-µm-thickness were cut with the help of rotary microtome and were stained with hematoxylin and eosin for photomicroscopic observation. All histopathological changes were examined by a pathologist

Ethical approval

The animal utilization protocol of this study was approved by the unit of Animal Care and Use Research Ethics Committee (ACUREC), Directorate of Research, Innovation and Partnership, Bayero University, Kano with Animal use protocol (AUP) number: BUK/ACUREC/21/09/0005

Data analysis

The data was analyzed using one-way analysis of variance (ANOVA) and Turkey test was carried out to determine significant group differences ($p < 0.01$) between means by using SPSS statistical software package (SPSS, version 20.0)

RESULTS AND DISCUSSION

Anti-diabetic activity

Table 1.0 showed progress of blood glucose level of different groups of the experimental rats during the study period. It was observed that there was significant ($P<0.01$) decrease in blood glucose level of the experimental rats between day 14 and day 21 in standard Metformin group and in all the doses of the plants extract treatment groups as compared to the diseased control (untreated) group where there was no significant (($P<0.01$) reduction in blood glucose level during the experimental period.

Wound healing activity

Table 2.0 showed percentage wound contraction from day 7 to day 21 after treatment of the different treatment groups. Hundred percent (100%) wound contraction at day 14 was observed in normal control group, *A. leiocarpus* 200 mg/kg, *A. leiocarpus* 400 mg/kg and *A. nilotica* 200 mg/kg group. In addition, at day 21, 100% wound contraction was observed in standard Metformin group and *A.nilotica* 400 mg/kg group respectively. For the diseased control group, there was no 100% wound contraction even at day 21.

Histopathological examination

This was carried out to see whether the extracts could improve the histological appearance of the Liver and Pancreas of STZ induced diabetic rats. In this study, Plate 1 showed moderate hepatic necrosis (HN) in the diabetic untreated group and Metformin standard group. Normal hepatocytes (H) where observed in *A. nilotica* 400 mg/kg and *A. leiocarpus* 200 mg/kg rat groups. Vascular congestion (VC) was observed in *A. nilotica* 200 mg/kg and *A. leiocapus* 400 mg/kg rat group. For the pancreas as shown in plate 2, the untreated group showed intense islet necrosis (IIN), Metformin standard group showed moderate islet atrophy (IA), *A. nilotica* 400 mg/kg and *A. leiocarpus* 200 mg/kg showed slight islet cells necrosis (IN), *A.leiocarpus* 400 mg/kg showed normal islet (I) and *A. nilotica* 200 mg/kg shows islet atrophy (IA).

Table 1: Fasting blood glucose level (mg/dl) of diabetic wound model of rats treated with *A. nilotica* and *A. leiocarpus* ethanol extracts

Treatment Days	Normal control	Metformin	Untreated diabetic rats	*A. leiocarpus* 200 mg/ kg	*A. leiocarpus* 400 mg/ kg	*A. nilotica* 200 mg/ kg	*A. nilotica* 400 mg/ kg
Day 1	99.50±90.09^{c}	288.50±134.50^{a}	394.66±134.04^{d}	364.83±66.01^{b}	343.83±177.56^{b}	296.33±159.2^{b}	328.83±94.05^{b}
Day 7	103.50±9.48^{b}	139.80±15.97^{d}	506.25±3.40^{c}	450.00±163.56^{a}	371.75±87.34^{a}	326.20±189.61^{a}	335.83±116.48^{a}
Day 14	98.50±17.41^{d}	235.60±120.48^{b}	515.75±57.38^{b}	296.00±244.65^{c}	260.00±91.92^{c}	204.00±141.47^{c}	267.60±95.10^{d}
Day 21	123.50±10.41^{a}	219.25±82.89^{c}	525.25±47.26^{a}	220.50±146.37^{d}	247.00±141.42^{d}	131.00±14.14^{d}	282.00±0.00^{c}

*All values are Mean ± Standard deviation of six (6) replicates.
* Different superscript in the same column indicated significant difference within the groups at 1% (P<0.01) level of freedom.

Table 2: Percentage (%) Wound Contraction of the diabetic rat treated with *A. nilotica* and *A. leiocarpus* ethanol extract between day7 to day 21

S/N	Treatment Days	Normal control	Metformin	Untreated diabetic rats	*A.leiocarpus* 200 mg/ kg	*A.leiocarpus* 400 mg/ kg	*A. nilotica* 200 mg/ kg	*A. nilotica* 400 mg/ kg
1.	Day 7	95.82±8.86^{b}	93.12±9.44^{b}	85.92±8.03^{c}	84.84±11.83^{b}	66.62±15.13^{b}	90.84±12.00^{b}	82.91±10.56^{c}
2.	Day 14	100.00±0.00^{a}	99.50±1.11^{a}	91.05±9.66^{b}	100.00±0.00^{a}	100.00±0.00^{a}	100.00±0.00^{a}	96.40±4.36^{b}
3.	Day 21	100.00±0.00^{a}	100.00±0.00^{a}	94.25±7.32^{a}	100.00±0.00^{a}	100.00±0.00^{a}	100.00±0.00^{a}	100.00±0.00^{a}

*All values are Mean ± Standard deviation of six (6) replicates.
* Different superscript in the same column indicated significant difference within the groups at 1% (P<0.01) level of freedom

Histological examination of the Liver

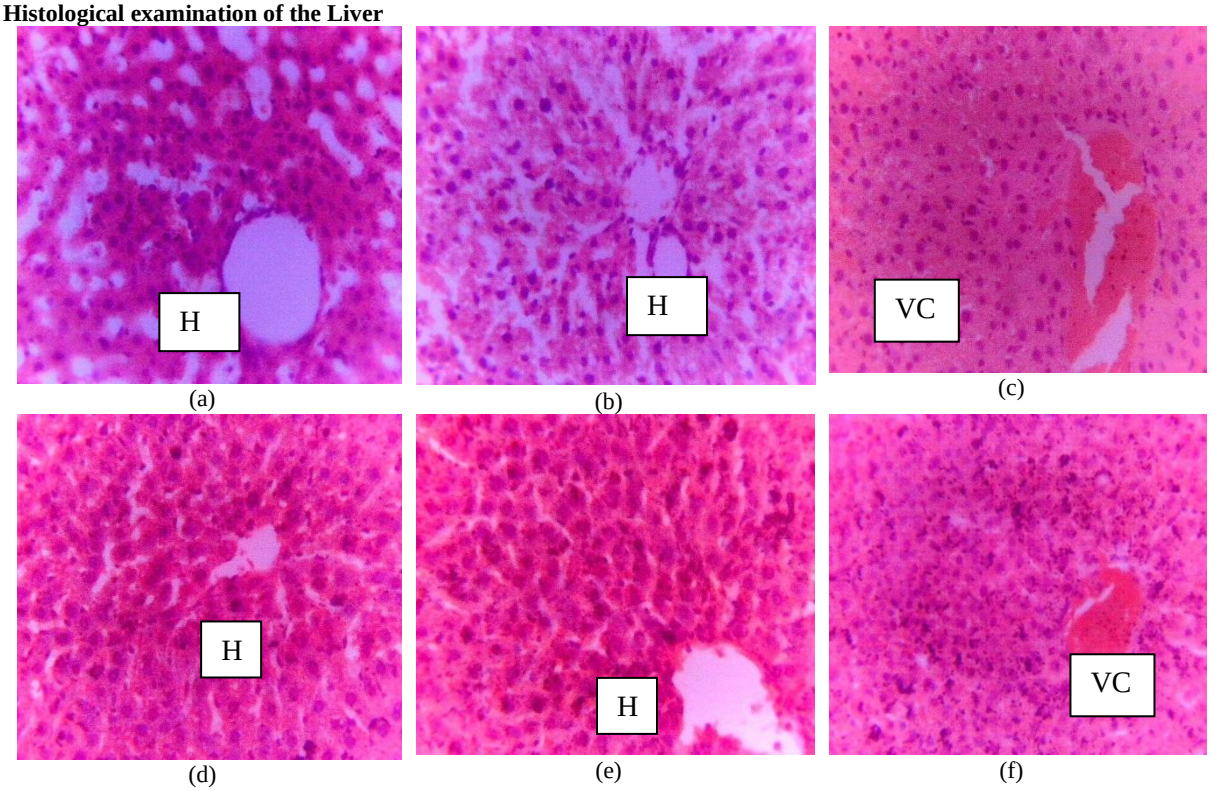
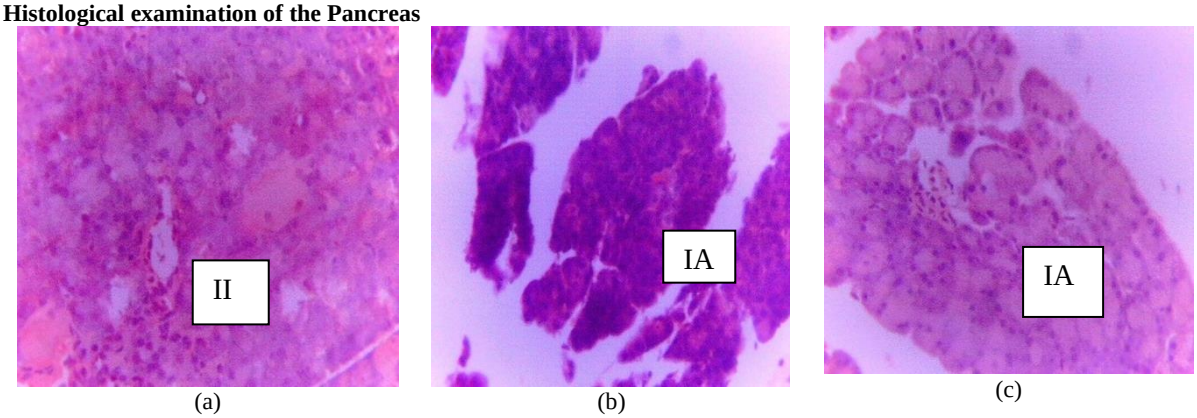
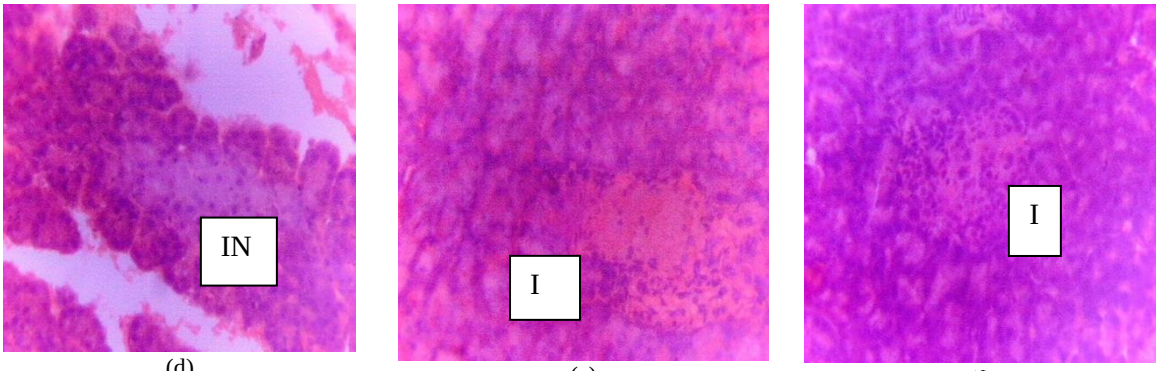


Plate 1: Photo micrograph of a section of the Liver tissue of rats; (a) Untreated diabetic rats with wound group showed moderate hepatic necrosis (HN), (b) diabetic rat with wound group after treatment with Metformin (5 mg/kg) showed moderate hepatic necrosis (HN), (c) diabetic rat with wound group after treatment with *A. nilotica* 200 mg/kg showed moderate vascular congestion (VC), (d) diabetic rat with wound group after treatment with *A. nilotica* 400 mg/kg showed normal hepatocytes (H), (e) diabetic rat with wound group after treatment with *A. leiocarpus* 200 mg/kg showed normal hepatocytes (H), (f) diabetic rat with wound group after treatment with *A. leiocarpus* showed intense vascular congestion (VC)

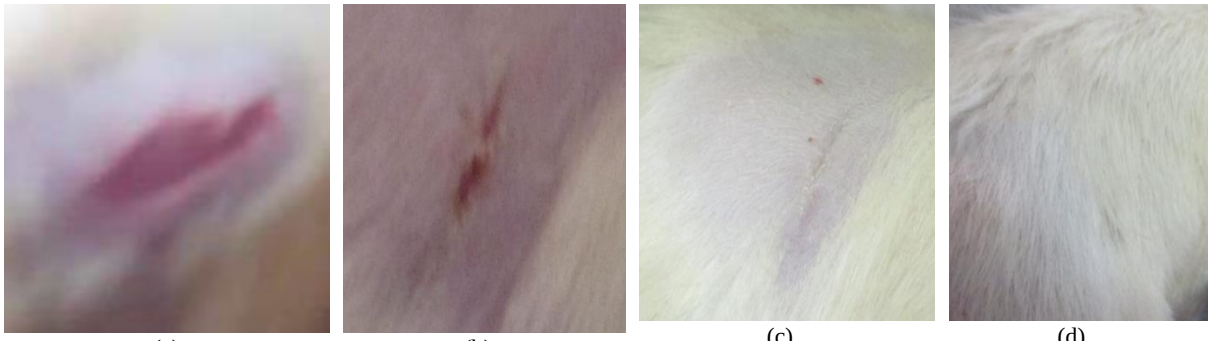
Histological examination of the Pancreas





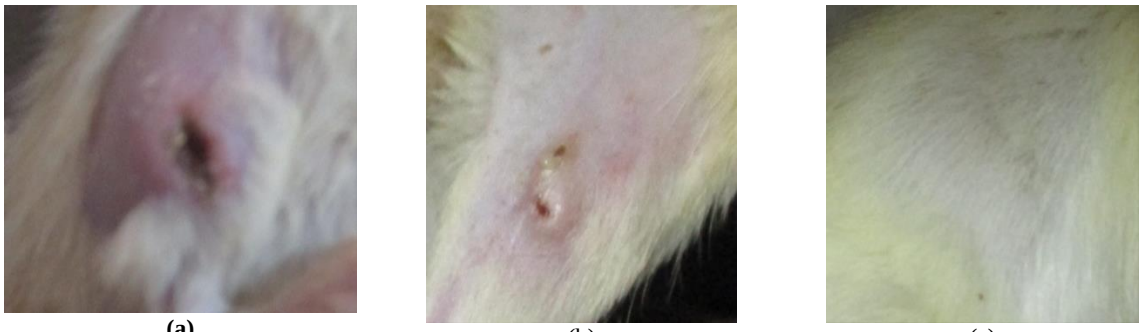
(d) (e) (f)

Plate 2: Photo micrograph of a section of the Pancreatic tissue of rats; (a) Untreated diabetic rats with wound group showed intense cell necrosis (IIN), (b) diabetic rat with wound group after treatment with Metformin (5 mg/kg)showed moderate Islet atrophy (IA), (c) diabetic rat with wound group after treatment with *A. nilotica* 200 mg/kg showed Islet atrophy (IA), (d) diabetic rat with wound group after treatment with *A. nilotica* 400 mg/kg showed slight islet cells necrosis (IN), (e) diabetic rat with wound group after treatment with *A. leiocarpus* 200 mg/kg showed slight islet cells necrosis (IN), (f) diabetic rat with wound group after treatment with *A. leiocarpus* 400 mg/kg showed normal isles (I).



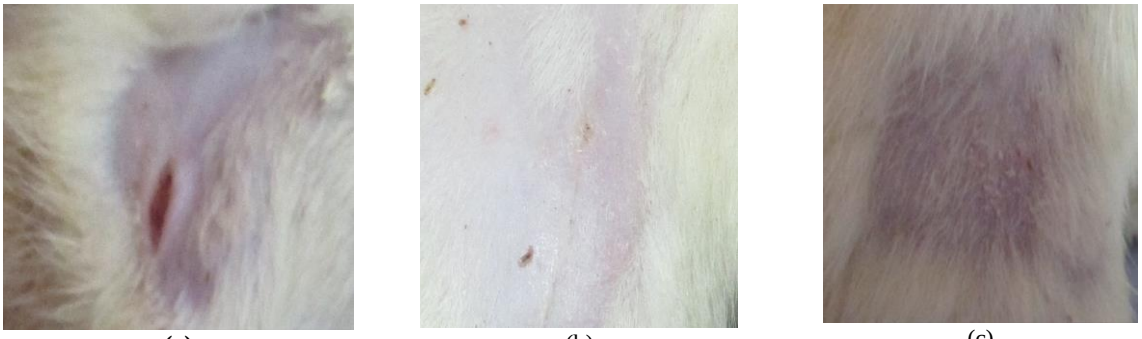
(a) (b) (c) (d)

Plate 3: Showed progress of wound healing in the experimental diabetic rats of the treated group with *A. nilotica* at a dose of 200 mg/kg (a) initial wound area (b) wound area at day 7 (c) wound area at day 14 (d) wound area at day 21



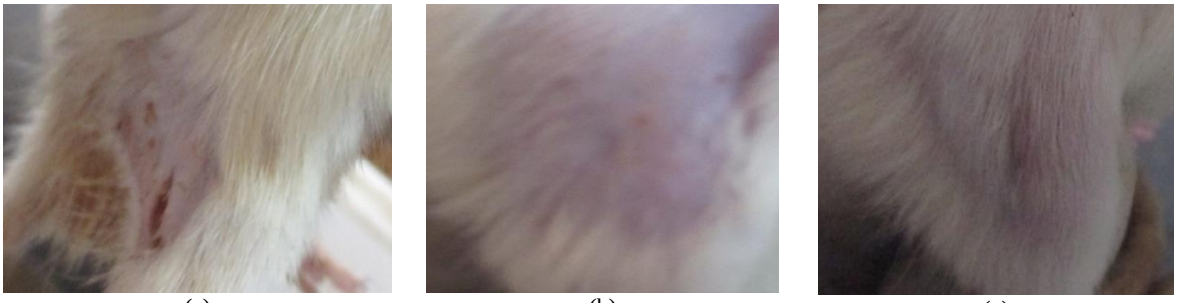
(a) (b) (c)

Plate 4: Showed progress of wound healing in the experimental diabetic rats of the treated group with *A. nilotica* at a dose of 400 mg/kg (a) wound area at day 7 (b) wound area at day 14 (c)wound area at day 21



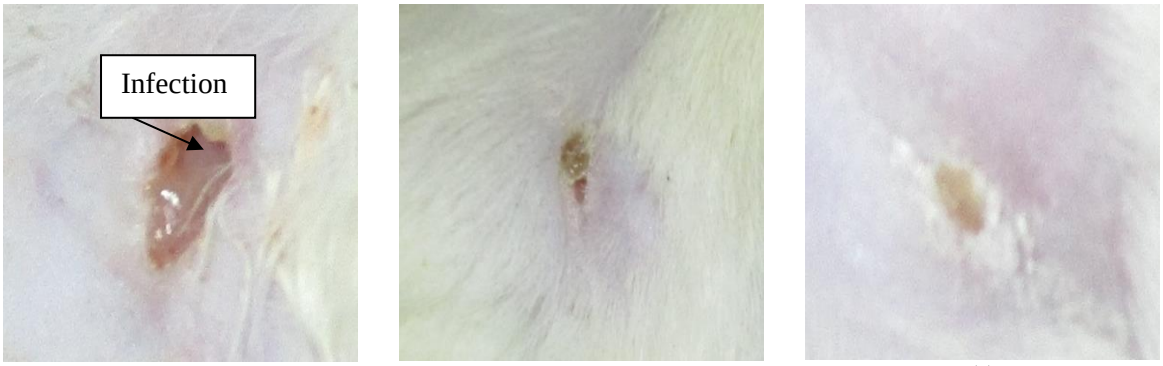
(a) (b) (c)

Plate 5: Showed progress of wound healing in the experimental diabetic rats of the treated group with *A. leiocarpus* at a dose of 400 mg/kg (a) wound area at day 7 (b) wound area at day 14 (c) wound area at day 21



(a) (b) (c)

Plate 6: Showed progress of wound healing in the experimental diabetic rats of the treated group with *A. leiocarpus* at a dose of 200 mg/kg (a) wound area at day 7 (b) wound area at day 14 (c)wound area at day 21



(a) (b) (c)

Plate 7: Showed progress of wound healing in the experimental diabetic rats of the untreated group (a) wound area at day 7 (c) wound area at day 14 (d) wound area at day 21

Discussion

Diabetes can be triggered in animal models through pharmacological, surgical, or genetic methods (Frode & Medeiros, 2008). Among pharmacological agents, streptozotocin (STZ) and alloxan are commonly used to induce diabetes. STZ works by causing necrosis in β cells, leading to impaired insulin secretion or action, similar to the mechanisms observed in type 2 diabetes. In this study, the observed increase in blood glucose in diabetic rats may be attributed to the action of STZ. This was supported by the report of Nurdina *et al*. (2017) that a single dose of 60mg/kg STZ is capable to induced pancreatic β cells destruction in rats and subsequent reduction of insulin secretion there by elevating the fasting blood glucose level.

The decrease in blood glucose levels observed with the studied plants part could be due to the presence of certain bioactive compounds. Previous research has identified flavonoids, alkaloids, and saponins in these plants part (Alhassan *et al*., 2016; Jame, 2018; Hussain *et al*., 2022; Sani *et al*., 2024). Flavonoids have been shown to stimulate peripheral glucose uptake, regulate the activity and/or expression of the rate limiting enzymes, enhances lipogenesis, facilitate insulin release and conversion of proinsulin to insulin (Zheng *et al*., 2012). Saponins were found to have hypoglycemic activity in elderly diabetic patients by inhibition of α-amylase and α-glucosidase enzymes (Njogu *et al*., 2017). Alkaloids isolated from *Catharanthus roseus* enhanced glucose uptake in pancreatic and muscle cells by inhibiting the protein tyrosine phosphatase PTP-1B (Odoh and Ezugwu, 2012).

The results from the wound healing studies of ethanol extracts from *A. nilotica* and *A. leiocarpus* demonstrated that these plant extracts have wound healing potential in diabetic rats. This showed that *A. leiocarpus* 200mg/kg, 400mg/kg and *A. nilotica* 200mg/kg enhanced the wound contraction of diabetic rats faster than the standard Metformin. This finding is supported by Kankara *et al*. (2017), who investigated the wound healing potential of *A. nilotica* pod extract in non-diabetic Sprague-Dawley rats. Their study revealed that the topical application of *A. nilotica* pod extract significantly ($P<0.01$) improved the rate of wound healing compared to the control group. Additionally, Victor *et al*. (2013) confirmed the wound healing effectiveness of *A. leiocarpus* leaf extract in diabetic rats, showing increased wound contraction in the treated group compared to the control group. Moreover, it has been reported that diabetics are more prone to infections, which can delay the wound healing process (Sani *et al*., 2021). In this study, the untreated diabetic rats developed infections, which likely contributed to the delay in healing. However, ethanol extracts from *A. nilotica* pods and *A. leiocarpus* stems have been shown to have antibacterial activity against bacterial isolates associated with diabetic foot infections (Sani & Aliyu, 2022), which may help to promote wound healing.

Therefore, the fundamental mechanism behind their effects can be linked to their inherent characteristics, including antibacterial, antioxidant, wound-healing, and anti-inflammatory properties. Additionally, Sani *et al*. (2014) confirmed the antioxidant capability of the plants part studied, which might contribute to alleviating oxidative stress at the wound location.

The current study demonstrated histopathological alterations following STZ injection, characterized by damaged β cells. A similar finding was reported by Nurdina *et al*. (2017).

CONCLUSION

The ethanol extract from *A. nilotica* and *A. leiocarpus* demonstrated a notable reduction in blood sugar levels and improved wound healing in Wistar rats with streptozotocin-induced diabetes. However, toxicological studies of the investigated plants part are suggested to determine the

appropriate dosages for treating diabetic wounds. Continued research in this area may lead to the development of more effective treatments for diabetic wound healing

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