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Therapeutic Effect of Topical Ointment Ethanol Extract from *Patiwala* Leaves (*Lantana camara*) on Histological Profile of Incision Wounds in Diabetic Rat Models

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Abstract

Diabetic wounds are one of the neurovascular complications of diabetes. Hyperglycemia complicates the healing of diabetic wounds, which are susceptible to infection and chronic inflammation. Topical treatment using herbal extracts aims to reduce the side effects of surrounding tissue damage. A topical ointment made from ethanol extract of *Patiwala* (*Lantana camara*) leaves, which has been tested for product quality, has antibacterial and anti-inflammatory effects that has been proven to help accelerate the healing of diabetic wounds in rats through parameters such as reduced wound diameter, changes in the number of fibroblast cells, and collagen fiber formation seen in the histological profile during 21 days of therapy with a concentration of 15% ($p>0.05$) compared to the positive control of 10% betadine.

Keywords: Topical ointment; Lantana camara; Histological profile; Diabetic wounds; Fibroblast cells.

INTRODUCTION

Diabetes is a major cause of damage to various organs such as the heart, blood vessels, nerves, eyes, and kidneys (Harreiter & Roden, 2023; Cloete, 2022). One complication of diabetes related to blood vessel and nerve damage is diabetic wounds or diabetic neuropathy (Urso et al., 2021; McDermott et al., 2023). Sensory and motor neuropathy can cause various changes in the skin and muscles, which then lead to changes in pressure distribution in the peripheral area that triggers ulcers (Kurz, 2020; Akkus & Sert, 2022). The healing of diabetic ulcers or diabetic wounds is a serious concern for clinicians today. This is because the speed of diabetic wound healing is not the same as the healing of wounds in general. Diabetic wounds contain high blood glucose levels (hyperglycemia) which is known to be an energy source for pathogenic bacteria, making diabetic wounds very susceptible to infection and inflammation (Raja et al., 2023; Wang et al., 2025).

Topical treatment of diabetic wounds using chemical antibiotic ointments often causes side effects, including damage to the surrounding skin tissue. Therefore, various studies on herbal ointments are ongoing, with the hope that they can become an alternative treatment for diabetic wounds with minimal side effects. Herbal plant extracts intended to help accelerate diabetic wound healing must be able to inhibit pathogenic bacteria that trigger infection and inflammation in diabetic wounds in vitro (Ramachandran et al., 2023; Norman et al., 2021).

One of the local plants often used by the people of Southeast Sulawesi to treat wounds is the *Patiwala* leaf (*Lantana camara*). Several previous studies have reported the potential of *Lantana camara* in various preparations for incision wounds (Tamuntuan et al., 2021; Arifin et al., 2023; Saranani et al., 2023) but there has been no specific research on diabetic wounds. The ability of *Lantana camara* in treating wounds is influenced by its phytochemical compounds which functions as an antibacterial and anti-inflammatory (Sari et al., 2023; Hasnaeni et al., 2024). The results of phytochemical screening of *Lantana camara* vary quite a bit, depending on the geographical conditions of the place of growth as well as the analytical method used (Kapitan et al., 2024; Orji et al., 2024). The phytochemical compounds of ethanol extract of *Patiwala* leaves from Southeast Sulawesi has been reported in a study by Rosanty et al. (2025) with active compounds of alkaloids, flavonoids, tannins, saponins and terpenoids (Rosanty et al., 2025). Antibacterial activity test of the extract against several pathogenic bacteria causing diabetic ulcers in vitro including *Staphylococcus aureus*, *Staphylococcus epidermis*, *Proteus mirabilis*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Klebsiella* *pneumoniae* and *E.Coli* with ciprofloxacin as a positive control showed quite significant results. This study is a follow-up study of Rosanty (2025) which was conducted in vivo using a white rat model of the Wistar type with diabetic wounds to observe the histological profile after topical ointment therapy with ethanol extract of *Patiwala* leaves (*Lantana camara*).

MATERIALS AND METHODS

Research Ethics and Design

This research was an experimental study involving 30 male Wistar rats. The research was conducted from June to December 2024 at the Biomedical Research Laboratory, Faculty of Medicine, Halu Oleo University. This study received ethical approval from the Health Research Ethics Committee, Tanjung Karang Ministry of Health Polytechnic, under No. 451/KEPK-TJK/VIII/2023.

Materials and equipment

The main material used in this study was a topical ointment of ethanol extract of *Patiwala* (*Lantana camara*) leaves formulated based on the results of in vitro extract effectiveness tests in the study by Rosanty (2025) with the following formula:

Materials	% ingredients in every 10 grams of formula			Function
	Formula			
	A	B	C	
Ethanol extract of Patiwala leaves (*Lantana camara)*	5	10	15	Active compound
Propil paraben	0.01	0.01	0.01	Preservative
Cera alba	2	2	2	Base
Vaselin album	Ad 100	Ad 100	Ad 100	Base

Other materials and equipment include measuring flasks, Erlenmeyer flasks, test tubes, stirring rods and dropper pipettes for making ointments, weighing rats using a MACS 1.5/W digital scale, scalpels for making incision wounds, calipers for measuring wound diameter. Making a diabetic rat models using an induction agent streptozotocin/STZ (Sigma-Aldrich) dissolved in 0.9% NaCl, measuring blood glucose levels in using a point of care testing (POCT) FORA 6 Plus (Switzerland). Histological observation of incision wounds using hematoxylin-eosin staining technique with natural buffered formalin 10% (Indopath-Paraform) for tissue fixation, ethanol 70%, 80% and 95% (Merck) for dehydration-rehydration, xylol (Bio-Analitika) for clearing, paraffin (Paraflakes) and basemold for embedding, microtome tool (Accu-Cut), object glass and deck glass for microtomy and preparation of preparations, hematoxylin (Biognost) and eosin (Indoreagen).

Treatment of experimental animals

The experimental animals used in this study were 30 white Wistar male rats with body weights ranging from 90-200 grams. The rats were divided into 3 groups with 10 rats each group consisting of K-7 for the intervention group for 7 days, K-14 for the intervention group for 14 days, and K-21 for the intervention group for 21 days. Then all rats were acclimatized in standard cages, fed standard food with a light/dark cycle for 2 weeks. Body weight (BW) and random blood glucose level measurements (RBG) were carried out on all rats before induction. Each group was then divided into 5 subgroups consisting of the 5% *Patiwala* ointment intervention group (K1), the 10% *Patiwala* ointment intervention group (K2), the 15% Patiwala ointment intervention group (K3), the 10% Betadine ointment positive control (KP) and the untreated negative control (KN), each subgroup consisting of 2 rats. STZ induction was performed on all rats with a single intraperitoneal dose of 50 mg/kgBW. After 5 days, BW and RBG levels were remeasured to confirm diabetes (RBG >200 mg/dL). A 5 cm incision wound was made in the low back of the diabetic rats. Treatment was administered twice daily to both the intervention and positive control groups. On the final day of the intervention, the rats were euthanasia using carbon monoxide. Skin fragments from the incision wounds were removed and fixed in 10% NBF for histological analysis. Intracardial blood was collected using gel separator tubes, other organs and tissues were also collected and stored in 10% NBF for further research.

Measurement of RBG levels

RBG levels were measured in each group two times: before STZ induction and 5 days after STZ induction. RBG levels were measured using the Fora 6 Plus device using the POCT method, which is based on the principle of enzymatic reactions. RBG levels are showed in milligrams per deciliter (mg/dL).

Measurement of wound diameters

Wound diameters were measured in each group two times: before STZ induction and 5 days after STZ induction. Wound diameter measurements using calipers, the results are showed in millimeters (mm).

Histological analysis

The skin tissue that had been fixed in 10% NBF solution for 1x24 hours was then dehydrated using ethanol in stages starting from 70%, 80%, and 95% for 2 hours each. Then, the dehydrated tissue was cleared using xylol solution for 2 cycles, each for 1 hour. Next, embedding was carried out in a basemold using liquid paraffin at a temperature of 40°C. After the tissue block was formed, tissue ribbons were cut on a microtome with a size of 5 µm. The tissue ribbons were placed on a glass object, fixed on a hotplate at a temperature of 40°C to remove residual paraffin, and then continued with hematoxylin and eosin staining. Histological observations were carried out under a microscope with a magnification of 40x (Orno, 2023). The number of fibroblast cells was counted in 15 fields of view on each slide and the results were presented as an average value.

Data analysis

The effects of STZ induction on rats BW and RBG levels were analyzed using the Wilcoxon test. Wound diameters and number of fibroblast cells after therapy in each subgroup within a group were analyzed using the One-Way ANOVA test and for comparison of wound diameter between groups using the Kruskal Wallis test. The histological results are presented in the form of micrographs followed by notes.

RESULTS AND DISCUSSION

Characteristics of topical ointment products

The topical ointment made from ethanol extract of *patiwala* leaves used in this study has been tested in vitro to have antibacterial effects against several bacteria that cause diabetic wounds. The table below is a description of the topical ointment product and the results of the quality test for the ointment preparation.

Table 1. Product quality report of Topical ointment of *Patiwala* leave ethanol extract.

Product	Product Quality Report					
	Organoleptic	**Homogenity**	**pH**	**Viscosity** (cP)	**Spreadability** (mm)	**Stickiness** (sec)
Topical ointment of Patiwala leave ethanol extract 	Lightly greenish brown color, distinctive odor, soft hydrocarbon ointment form, smooth without coarse particles, and easy to apply	Homogen	6.42	8.745	41	4

Ointment physical properties testing is conducted as part of efforts to ensure the quality and stability of the preparation and to ensure that the final product meets predetermined quality criteria. This evaluation is important because the physical characteristics of the ointment, such as visual appearance, texture, pH, and ability to spread and adhere to the skin surface, significantly influence the comfort of use and therapeutic effectiveness of topical preparations (Savitri et al., 2025; Wahyuni et al., 2025). The test results showed that the ointment could be applied to experimental rats and can be used as a reference for future formulation needs.

Effect of STZ induction on Body weight and Random blood glucose

This study used STZ as an induction agent in an animal model of diabetes mellitus. Table 2 explains the effect of STZ induction on increasing RBG levels with a mean level of 310.23 ± 59.12 (p<0.001) which is in line with the increase in BW of rats (p=0.013).

Table 2. Effect of STZ induction on Body weight and Random blood glucose.

Variables		**Mean ± SD**	**p value**
Body weight (g)	Pre-STZ	135.75 ± 49.39	0.013
	Post-STZ	144.22 ± 41.12	
Random blood glucose (mg/dL)	Pre-STZ	86.13 ± 17.74	<0.001*
	Post-STZ	310.23 ± 59.12	

**Wilcoxon test, the level of significance at p< 0.05*

Several studies have reported STZ is cytotoxic to pancreatic β-cells, and its effects are visible 72 hours after administration and are dose-dependent. The toxic effects of STZ begin with the uptake of STZ into cells via the low-affinity glucose transporter-2 (GLUT2) found in the plasma membrane of β-cells, hepatocytes, and renal tubular cells. This has been demonstrated by studies showing that insulin-producing cells that do not express GLUT2 are resistant to STZ induction (Al-Awar et al., 2016; Pandey & Dvorakova, 2020).

The therapeutic effect of ointment on the diameter of rat wounds

Hyperglycemic conditions in diabetes reduce the healing rate of incision wounds in rats this is caused by several conditions such as impaired angiogenesis, neuropathy, chronic inflammatory responses and bacterial infections (Burgess et al., 2021). Changes in the diameter of the incision wound are a visual indicator of the healing effect of the ointment used, as presented in table 3.

Table 3. Comparison of wound diameter between groups and subgroups.

Groups/subgroups	K-7 (mm)	K-14 (mm)	K-21 (mm)	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
KP (betadine 10%	13.23 ± 0.01	1.23 ± 0.07	0.000 ± 0.00	0.095**
K1 (patiwala 5%)	18.90 ± 0.05	13.43 ± 0.07	4.85 ± 0.86	0.102**
K2 (patiwala 10%)	16.13 ± 0.15	9.54 ± 0.42	1.57 ± 0.07	0.102**
K3 (patiwala 15%)	15.91 ± 0.09	5.63 ± 0.07	0.00 ± 0.00	0.095**
p value	<0.001*	<0.001*	0.001*	

**One-way Anova test, **Kruskal Wallis test, the level of significance at p< 0.05*

The effectiveness of the ointment was estimated against 10% betadine as a positive control. The difference in wound diameter between subgroups in each group using the One-way ANOVA test showed a significant difference (p<0.001). In the 7-day therapy group (K7), the average KP wound diameter was 13.23 ± 0.01 mm, significantly different from the K1, K2, and K3 groups. The 14-day therapy group (K14) showed almost perfect wound closure in the KP (1.23 ± 0.07 mm), while the K3 therapy group showed quite good results with an average wound diameter of 5.63 ± 0.07 mm. A linear pattern was seen in the 21-day therapy group (K21) where the KP wound diameter was 0.000 ± 0.00 mm in line with K3, followed by K2 and K1. The results of the Kruskal-Wallis test between groups showed significant results (p>0.05) which proved that in all groups there was a significant change in wound diameter. Changes in wound diameter indicate the activity of the active compounds contained in the ointment. Several previous studies have examined the role of active ingredients in herbal extracts in in vivo diabetic wound healing (Nurwahita et al., 2024; Palupi et al., 2022; Wulandari et al., 2023) explains the role of active compounds such as alkaloids, flavonoids, tannins, saponins and terpenoids in accelerating the wound tissue regeneration process which is visible in changes in wound diameter. Physiological wound tissue regeneration involves muscle fiber repair, extracellular matrix remodeling, and collagen deposition. Theoretically, physiological wound closure occurs on days 10-14, but under hyperglycemic conditions, the remodeling process can take longer to compensate for the inflammation (Giha et al., 2022; Sun et al., 2024). *Patiwala* topical ointment, with its antibacterial and anti-inflammatory properties, helps prevent infection and chronic inflammation during the remodeling process.

The effect of ointment therapy on the number of fibroblast cells in rats

Unlike changes in wound diameter, which can be observed and measured visually, the number of fibroblast cells can only be observed and counted microscopically. The number of fibroblast cells is one indicator of successful wound healing, calculated in 15 large fields of view (HPF), as presented in table 4.

Table 4. Comparison of fibroblast cells between groups and subgroups.

Groups/subgroups	K-7 (cells/HPF)	K-14 (cells/HPF)	K-21 (cells/HPF)	p value
	Mean ± SD	Mean ± SD	Mean ± SD	
KP (betadine 10%)	178.50 ± 3.53	95.00 ± 4.24	108.00 ± 1.41	0.102**
K1 (patiwala 5%)	158.00 ± 4.24	110.00 ± 11.31	110.00 ± 9.89	0.180**
K2 (patiwala 10%)	167.50 ± 14.84	88.50 ± 4.94	75.00 ± 12.72	0.102**
K3 (patiwala 15%)	175.50 ± 12.02	156.50 ± 62.93	90.50 ± 16.42	0.180**
p value	0.303*	0.283*	0.036*	

**One-way Anova test, **Kruskal Wallis test, the level of significance at p< 0.05*

Table 4 shows that there was no significant difference in the number of fibroblast cells in K7 and K14 (p=0.303 & p=0.283). On the 7th day of therapy, all groups experienced a significant increase in the number of fibroblast cells, K3 was the group with the highest number of fibroblast cells (175.50 ± 12.02/HPF) approaching the number of KP fibroblast cells (178.50 ± 3.53/HPF). The pattern of changes in the number of fibroblast cells began to appear non-linear in K14 where KP showed a decrease in the number of fibroblast cells (95.00 ± 4.24/HPF) which was not in line with the decrease in the number of fibroblast cells in K3 and K1 which on average experienced a decrease but anomalous with K2. Although statistically there was no difference in the K14 group, K2 appeared to experience a very sharp decrease in the number of fibroblast cells (88.50 ± 4.94/HPF). Variations in fibroblast cell count patterns during wound healing are theoretically possible (Liu et al., 2021). In the initial phase of wound healing, fibroblasts are produced in large numbers to compensate for the inflammation (Guillamat-Prats, 2021; Liu et al., 2022). In the subsequent phase (10-14 days later), the number of fibroblasts decreases, and they are replaced by collagen fiber formation. In the 21-day therapy group (K21), there was a significant difference between treatment subgroups (p=0.036), this may be due to wound re-epithelialization and granulation tissue formation during the experimental period differing between animals. The distribution pattern of fibroblast cells and collagen fiber formation can be observed more clearly in the histological profile below.

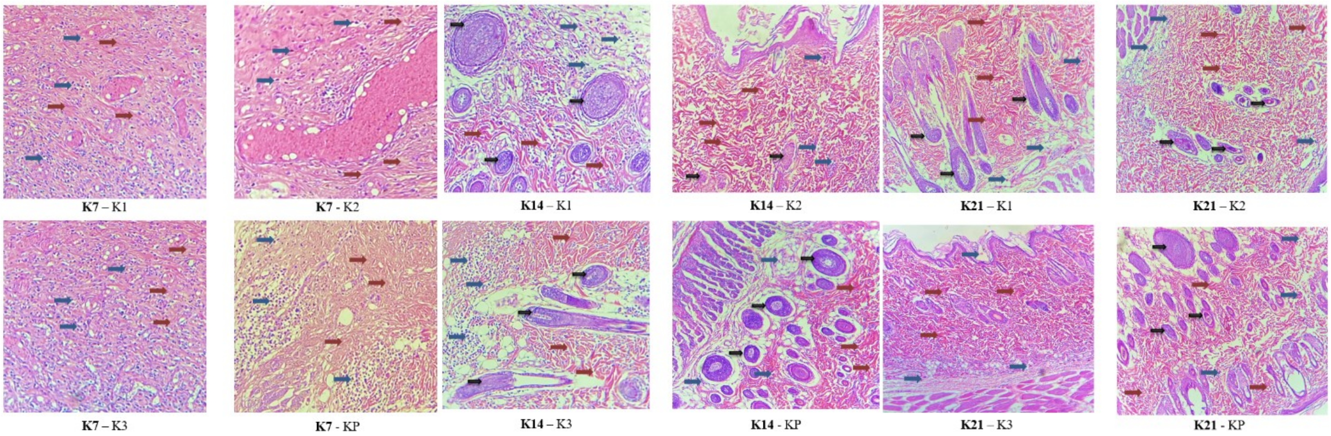

Figure 1. Changes in the number of fibroblast cells in mice after therapy with ethanol extract ointment of patiwala leaves at. K7 (7-day therapy group), K14 (14-day therapy group), K21 (21-day therapy group). K1 (5% patiwala ointment subgroup), K2 (10% patiwala ointment subgroup), K3 (15% patiwala ointment subgroup), KP (10% betadine positive control). Fibroblast cells ( ) collagen fibers ( ) dan hair follicles ( ).

Proliferating fibroblasts accompany these vessels and begin to deposit collagen. During the proliferation phase, a special type of tissue that characterizes healing, called granulation tissue, appears. The term granulation tissue originates from its histological appearance, characterized by the proliferation of fibroblasts, smooth, thin-walled capillaries within a loose extracellular matrix. Granulation tissue then progressively accumulates a connective tissue matrix, ultimately producing dense fibrosis, which can undergo further remodeling over time (Kunkemoeller & Kyriakides, 2017). After injury, exposure of fibrillar collagen to the blood causes platelet aggregation and activation and releases chemotactic factors that initiate the wound healing process. Collagen fragments release leukocytic collagenase to attract fibroblasts to the wound area. Collagen then forms the foundation for a new extracellular matrix, thus accelerating the formation of granulation tissue. The saponin content in the ethanol extract ointment of patiwala leaves prevents wound infection (Chanu et al., 2023; Kunkemoeller & Kyriakides, 2017). According to Chanu (2023), the more connective tissue there is in a wound, the greater the contractile force of the wound so that the sides of the wound will be pulled and cause the wound to shrink. Fibroblast proliferation in the wound healing process is naturally stimulated by interleukin-Ib (IL-Ib), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). Fibroblast migration in the injured area is stimulated by transforming growth factor (TGF), a growth factor produced by granulation tissue formed during the inflammatory process (Gökşen et al., 2017). The wound healing process is greatly influenced by the role of fibroblast migration and proliferation in the injured area (Gökşen et al., 2017; Parmar et al., 2018). The content of the ethanol extract ointment of patiwala leaves applied to the wounds of test animals stimulates the synthesis of growth factors including FGF thereby increasing the activity of fibroblast cells to produce collagen and form connective tissue so that the wound heals quickly.

Ethanol extract ointment from patiwala leaves contains many phytochemical compounds such as flavonoids, tannins, phenols, terpenoids, saponins, and other nutrients that significantly affect health, including healing cuts in test animals. Research conducted by Saranani (2023) and Arifin (2023) found that flavonoids and tannins are among the components of *Lantana camara* that influence wound healing, particularly wound moisture. Flavonoids can stop bleeding in wounds and act as anti-inflammatories, influencing the production of inflammatory cells during the wound healing phase. The presence of flavonoids in the cream can help change the condition of wet wounds to become moister more quickly. The flavonoid content of *Lantana camara* is believed to play a significant role in the wound healing process. In addition to flavonoids, tannins act as astringents, reducing mucosal permeability and strengthening inter-mucosal bonds, thus preventing irritation. Therefore, tannins indirectly influence changes in moisture levels. In addition to affecting mucosal permeability, tannins can also affect the permeability of bacterial walls or membranes, causing bacteria (Zubair & Ahmad, 2019). These antibacterial properties can prevent wound infections. The saponins contained in *Lantana camara* can influence collagen production in the early stages of tissue repair and stimulate epithelial cell regeneration in the skin, thereby accelerating the wound healing process in test animals. Phenolic compounds play a role in preventing cell damage caused by free radicals, thus preventing inflammation (Kuan et al., 2025). In addition to saponins and phenolic compounds, *Lantana camara* also contains terpenoids, which are useful for reducing inflammatory activity (Zubair & Ahmad, 2019). The anti-inflammatory properties of *Lantana camara* can inhibit the inflammatory process in cuts in white Wistar rats, allowing the wound healing process to occur more quickly.

CONCLUSIONS

Based on the results of the research conducted, it was concluded that topical ointment of ethanol extract of *patiwala* leaves (*Lantana camara*) at a dose of 15% was able to accelerate the healing of incision wounds in diabetic rats as evidenced by changes in wound diameter, number of fibroblast cells and collagen fiber formation on the 21st day after therapy.

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