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WOUND-HEALING ACTIVITY OF *DIOSCOREA PRAEHENSILIS* IS ASSOCIATED WITH UPREGULATION OF VEGF GENE EXPRESSION IN A RAT MODEL

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ABSTRACT

A wound is a physical injury that compromises the integrity of the skin or underlying tissues. A significant cost is associated with the management of chronic wounds worldwide. Dioscorea praehensilis (DP) is used traditionally to treat inflammatory conditions, scorpion bites, dyspepsia, and ulcers. We evaluated the wound-healing properties of the crude methanol extract of Dioscorea praehensilis in rats. We investigated its effect on vascular endothelial growth factor (VEGF) gene expression to understand its mechanism. DP rhizomes were extracted by maceration in 80% methanol. Ointment formulation was done using the Simple Ointment BP formula at varying concentrations of DP (2.5%, 5%, and 10%). Excision wounds sized about 300 mm2 were made with the aid of surgical scissors. Treatment was done for fifteen days. Silver sulfadiazine and simple ointment BP were used as positive and negative controls, respectively. The rate of wound contraction was measured at a three-day interval. The mechanism of the wound-healing property was investigated by evaluating VEGF gene expression in rat aortic rings cultured in 75, 125, 250, 500, and 1000 µg/mL of DP. DP ointment exhibited an inverse dose-dependent wound-healing effect, i.e, activity decreasing as the concentration increased, with the lowest concentration (2.5%) yielding the highest activity. Furthermore, VEGF gene expression significantly increased in the aortic rings treated with 500 and 1000 µg/mL of DP compared to the negative control. In conclusion, the ability of DP to upregulate the expression of the VEGF gene may contribute to its wound-healing properties in rats.

Keywords: Wound healing, Angiogenesis, VEGF, Dioscorea praehensilis, Wound contraction assay

INTRODUCTION

The skin is the largest organ in the human body, and it plays a crucial role in protecting the internal organs (Mamun *et al*., 2024; Rodrigues *et al*., 2019). A wound is a physical injury that compromises the integrity of the skin or underlying tissues (Mamun *et al*., 2024; Tessema & Molla, 2021). There is a huge cost associated with the management of chronic wounds globally. In the United States alone, the estimated cost of wound care in 2019 was put at over US$126 billion (Queen & Harding, 2023). *In* rural and low-income communities of African countries, *wounds* are highly prevalent, but data on skin wounds are scarce, with an estimated wound care cost ranging between US$0.001-0.5 billion (Toppino *et al*., 2022; Queen & Harding, 2023).

The wound healing process is an important but delicate phenomenon that includes stages such as hemostasis, inflammation, angiogenesis, growth, re-epithelialization, and tissue remodeling. Several factors are known to influence these processes (Grubbs & Manna, 2023). The first response to a wound is constriction of the injured blood vessels and activation of platelets to form a fibrin clot, which stops the blood flow and provides a framework for incoming inflammatory cells (Rodrigues *et al*., 2019). As the inflammatory phase ends, angiogenesis begins. This involves endothelial cell proliferation, migration, and branching to form new blood vessels and plays a key role in tissue repair and wound healing (Liu *et al*., 2023). Vascular Endothelial Growth Factor (VEGF), a polypeptide growth factor, and its tyrosine kinase receptors are the main regulators of angiogenesis, promoting cell mitosis and vascular permeability (Liu *et al*., 2023). High VEGF expression has been shown to predict increased angiogenesis in vascular endothelial cells, which appears to be a promising strategy for treating patients who benefit from the proliferation of new blood vessels during wound healing (Cochain *et al*., 2013). This is because the new vessels help create granulation tissue and deliver nutrients and oxygen to growing tissues (Li et al., 2003).

The use of medicinal plants has gained widespread acceptance, particularly in resource-limited countries where access to hospitals and modern pharmaceuticals is limited (Buhari & Aliyu, 2024). *Dioscorea praehensilis,* commonly known as "bush yam", belongs to the *Dioscoreaceae* family, and it is one of the approximately 600 species of *Dioscorea*. In recent years, increasing attention has been paid to the phytochemicals of *Dioscorea*, such as steroidal saponins, polyphenols, allantoin, and, in particular, polysaccharides and diosgenin. These bioactive compounds possess anti-inflammatory activity and are protective against a variety of inflammatory diseases (Wang *et al*., 2023). Although the scientific literature is laden with reports of the pharmacological and medicinal importance of several species of the genus *Dioscorea*, there is a dearth of knowledge on the medicinal and therapeutic capabilities of *Dioscorea praehensilis* and its potential as a source of bioactive substances for the prevention and treatment of many diseases. Traditional healers use the tubers of *Dioscorea praehensilis* to treat various diseases, including inflammatory conditions and scorpion bites, stomach aches, diarrhea, dyspepsia, and ulcers (Adebisi *et al*., 2018; Ngelinkoto *et al*., 2021). A previous study has shown that *Dioscorea praehensilis* possesses an ameliorative effect on both indomethacin and ethanol-induced gastric ulceration in rats (Adebisi *et al*., 2022). This study aims to evaluate the wound-healing properties of the crude methanol extract of *Dioscorea praehensilis* in rats and its ability to influence the expression

of the vascular endothelial growth factor using a rat aortic ring pro-angiogenic model

MATERIALS AND METHODS

Materials

Chemicals, Solvents, and Equipment

All solvents were of analytical grade. Methanol was obtained from Guangdong Guanghua Sci-Tech Co., Ltd., Guangdong, China; formalin and ethanol were purchased from Sigma-Aldrich; endothelial basal media-2 (EBM-2) from Lonza Australia; hard paraffin and white soft paraffin (Lodha Petro India); wool fat and cetostearyl alcohol (Muby Chemicals India), while shaving cream (Veet-Reckitt Benckiser) was obtained from a local pharmacy. Distilled water was prepared with a distiller machine (Bibby Scientific Limited, England, United Kingdom). QIAGEN's one-step qRT-PCR and total RNA extraction kit used were obtained from QIAGEN, Dusseldorf, Germany.

Animals

Male and female Sprague–Dawley rats aged 8-10 weeks, weighing between 120-143 g, were obtained from the animal house facility of the Department of Pharmacology, Ahmadu Bello University, Zaria. The animals were housed under controlled conditions of temperature (23±2 °C), humidity (55 ± 10%), and lighting (12-h light/dark cycle) and provided with food and water *ad libitum*. Animals were acclimated for 2 weeks after arrival. All experiments were conducted according to the institution's guidelines for the care and use of laboratory animals in research, with Ethics approval number PTAC/Dp/(Me)Iv/37-21.

Collection, Identification, and Preparation of Plant Extract

The rhizomes of *Dioscorea praehensilis* (DP) were collected from Talata local government in Zamfara state, Nigeria, and were identified and authenticated at the Herbarium unit of the Department of Pharmacognosy, Faculty of Pharmaceutical Sciences, where a herbarium specimen with voucher number (PCG/UDUS/Dios/0002) was deposited. The rhizomes of DP were shade-dried and powdered using a mortar and pestle. Seven hundred and fifty grams (750 g) of the powdered sample was cold macerated in 2.3 liters of 80% methanol at room temperature with intermittent agitation for three days and filtered with Whatman filter paper. The resulting extract was evaporated to dryness over a water bath controlled at 45 °C.

Ointment Formulation

The ointment was formulated using the Simple ointment BP formula (BP, 1988). The total formulation weight was adjusted to 30 g, and the ointment was prepared as follows: 1.5 g of hard paraffin was weighed into a beaker and placed in a hot water bath to melt at a temperature of 45 °C. 1.5 g each of wool fat and cetostearyl alcohol were then added to the melted hard paraffin and stirred until properly melted and maintained at 45 °C. The volume was made up to 30 g by adding 25.5 g of white soft paraffin. DP ointment was prepared by adding different quantities of the extract into the ointment base, which was stirred continuously with a glass rod during cooling until the extract was homogenously dispersed to obtain 2.5, 5, and 10% concentrations. The working formula is presented in Table 1.

Table 1: Working Formula for Preparing *Dioscorea Praehensilis* Ointment

S/N	Excipients	Master Formula (Simple Ointment Bp) (g)	Working Formula (g)
1	Hard paraffin	50	1.5
2	Cetostearyl alcohol	50	1.5
3	Wool fat	50	1.5
4	White soft paraffin	850	25.5
	Total	1000	30

Wound Incision and Treatment

Animals were anesthetized using subcutaneous injection of ketamine (100 mg/kg). The wound area (the lower dorsal back) was prepared by cleaning with 70% alcohol, and the shaving cream was then applied and shaved using a blade. Methylene blue was used for marking a radius on the shaved part, and full-thickness excision circular wounds sized about 300 mm^2 were created along the markings using toothed forceps and scissors. Bleeding was stopped by blotting with cotton wool soaked in normal saline. The animals were then grouped into six groups of five per group as follows:

i. Group 1: 2.5% *Dioscorea praehensilis* ointment
ii. Group 2: 5% *Dioscorea praehensilis* ointment
iii. Group 3: 10% *Dioscorea praehensilis* ointment
iv. Group 4: Ointment-base i.e, vehicle-treated group (i.e., negative control)
v. Group 5: Positive control (1% Silver sulfadiazine)
vi. Group 6: Untreated group (normal control)

The treatment was done once daily topically in all the cases. The wounding day was considered day 0, and the treatment was done for fifteen days.

Measurement of Wound Contraction

The rate of wound contraction was measured every three days (days 3, 6, 9, 12, and 15) by measuring the diameter (in mm) using a Vernier caliper. On day fifteen, the final wound measurement was carried out, and the animals were sacrificed humanely. A skin biopsy was taken for histological analysis. Animals were properly fed, and their beddings were kept clean to avoid infections. Changes in wound diameter were evaluated, indicating the rate of wound contraction. The evaluated diameter was used to calculate the percentage of wound contraction, as follows:

$$\% \text{ Wound contraction} = \frac{Wound\ diameter\ on\ day\ 0 - Wound\ diameter\ on\ day\ (n) \quad X100}{\text{Wound area on day 0}}$$

where n is the number of days (3^{rd}, 6^{th}, etc.)

Histological Analysis

The skin biopsies were immediately fixed in a 10% neutral buffered formalin solution. All fixed tissues were dehydrated in ascending ethanol concentrations, cleared in xylene, and embedded in paraffin wax, melting at 60 °C. Serial sections (5 µm thick) were then mounted on 3-aminopropyl trisilane-coated slides and dried at 37 °C for 24 hours. Slide sections were deparaffinized, hydrated, stained with Mayer's hematoxylin and eosin dyes, and examined microscopically at 100× magnification.

Pro-Angiogenic Property and VEGF Gene Expression

Culture of rat aortic rings in the presence of the extract of Dioscorea praehensilis

The mechanism of the wound healing property of DP was investigated by evaluating the pro-angiogenic efficacy of the extract *in vitro* on rat aortic rings as described by Ernens *et al*. (2015). Thoracic aorta from male Sprague-Dawley rats, cross-sectioned into rings that are 1-2 mm in length, were cultured in cold serum-free Endothelial Basal Media-2 (EBM-2) media supplemented with 1% penicillin/streptomycin and 2.5 µg/ml amphotericin B with slight modification. Different concentrations (1000, 500, 250, 125, 75 µg/ml) of DP were added to the treatment groups, while recombinant VEGF (5 µg/ml) was included as a positive control, and the media was used as the negative control on day 1. The plate was then incubated at 37 ^{0}C, 5% CO_2 in a humidified incubator. On day 4, a fresh medium prepared as previously described was added, and the cultures were maintained until day 8.

RNA Extraction

On day 8, the total RNA was extracted using a Total RNA extraction kit (QIAGEN Dusseldorf, Germany), following the manufacturer's guidelines. The final total RNA quality was assessed by the spectrophotometric method (A_{260}/A_{280}). The RNA samples were then stored at -20^{o}C until used. For gene expression analysis, RNA samples with A_{260}/A_{280} readings of 1.8 to 2.0 were used.

Complementary DNA (cDNA) Synthesis and Reverse Transcription-Quantitative Polymerase Chain Reaction (RT- qPCR) Assay

Complementary DNA (cDNA) was synthesized using a QIAGEN one-step RT-PCR kit in a final volume of 20 µl according to the manufacturer's instructions. The following primers were used for VEGF-A: forward, 5′-CAGGCTGCTGTAACGATGAA-3′ and reverse, 5′-TTTCTTGCGCTTTCGTTTTT-3′; The template RNA, VEGF primer solution, dNTP Mix, 5x QIAGEN One-step RT-PCR buffer, and RNase-free water were thawed and placed on ice. The master mix containing RNase-free water, 5x QIAGEN One-step RT-PCR buffer, dNTP Mix, QIAGEN One-step RT-PCR enzyme mix, and RNasin (RNA inhibitor) was prepared, mixed thoroughly, and appropriate volumes were dispensed into PCR tubes. The template RNA (1µg/reaction) was then added to each PCR tube. The negative control had no RNA template. Actin-B was used as the housekeeping/ reference gene. The Thermal cycler was then programmed to have a PCR condition comprising reverse transcription at 50 °C for 30 minutes, an initial PCR activation step at 95 °C for 15 minutes, denaturation at 94 °C for 1 minute, annealing at 57 °C for 1 minute, extension at 72 °C for 1 minute, and final extension at 72 °C for 10 minutes. The total number of cycles was 35. Fluorescence was recorded at the end of the extension. To generate a standard curve, template RNA from untreated control aortic rings was used. Quantification of gene expression was calculated by the standard curve and cycle threshold of each sample. The results of gene expression were normalized to reference gene expression (actin-B), and the fold change was determined in comparison with untreated control using the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

Results were expressed as mean ± standard error of the mean. The difference between means was compared using One-way analysis of variance (ANOVA) followed by Tukey multiple comparisons post hoc. The results were analyzed using GraphPad Prism software version 8. The value of $p \leq 0.05$ was considered significant compared to the negative control.

RESULTS AND DISCUSSION

There was no significant difference in the percentage wound contraction on days 3 and 6 of treatment across all the treated groups compared to the negative control. On day 9, the percentage contraction of the wound in the group treated with 2.5% DP ointment and the positive control was significantly higher than the negative control. Furthermore, the percentage contraction obtained on this day in the 2.5% DP ointment was comparable to that of the positive control (i.e., $p>0.05$). On day 12, the percentage of wound contraction in the groups treated with 2.5%, 5% DP ointment and the positive control was significantly higher than the negative control. Similar to that obtained on day 9, there was no significant difference in the percentage wound contraction between the 2.5% DP ointment group and that of the positive control. On day 15, the percentage of wound contraction in all the treated groups (2.5%, 5%, 10%) and the positive control was significantly higher than the negative control. This is presented in Figure 1, while Figure 2 is a morphological representation of the wound healing across the groups. From the results of this study, the percentage wound contraction increased with decreasing concentration of DP extract incorporated in the ointment base, implying that a better activity was obtained with the ointment with the lowest concentration of the extract (i.e, 2.5%).

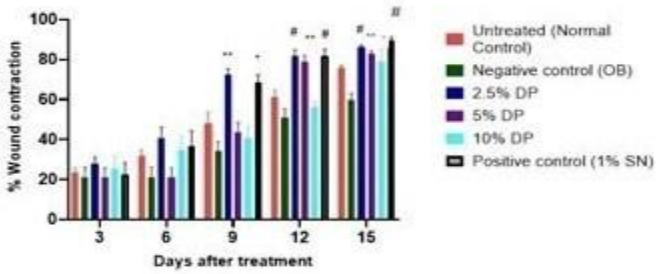

Figure 1: Effect of Crude Methanol Extract of *Dioscorea prehensilis* on Wound Contraction from day 3 to day 15 post-Treatment. Data are Presented as mean ±SEM.*=p≤0.01, **=p≤0.001, #= p<0.0001. OB= Ointment Base, DP=*Dioscorea prehensilis,* SN=Silver Sulfadiazine, N=5

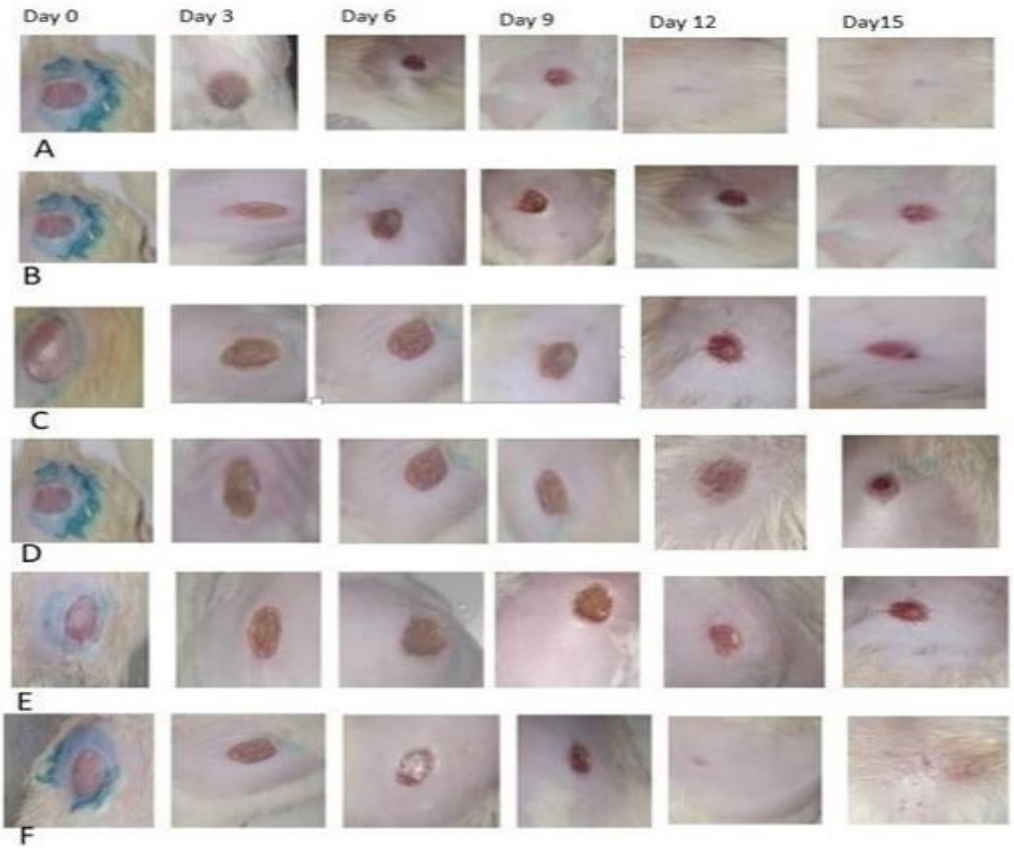

Figure 2: Morphological Presentation of the Wound Contraction Across the Groups on day 0, 3, 6, 9, 12, and 15. A, B, and C =2.5, 5.0, 10.0% DP Ointment; D, E, and F = Negative Control, Normal Control, and Positive Control (1% Silver Sulfadiazine), Respectively. N=5

The histological analysis of the skin biopsy shows sections of complete skin regeneration with bands of sub-epithelial collagen in the 2.5% DP ointment-treated group and complete skin regeneration in the positive control group. The histologic section in the 5% and 10% DP-treated groups shows skin ulceration with stromal edema and extensive granulation tissue, respectively. The negative control and the normal control groups show sections of skin ulceration, subepithelial fibroblast proliferation, and granulation tissue. The photomicrograph is shown in Figure 3.

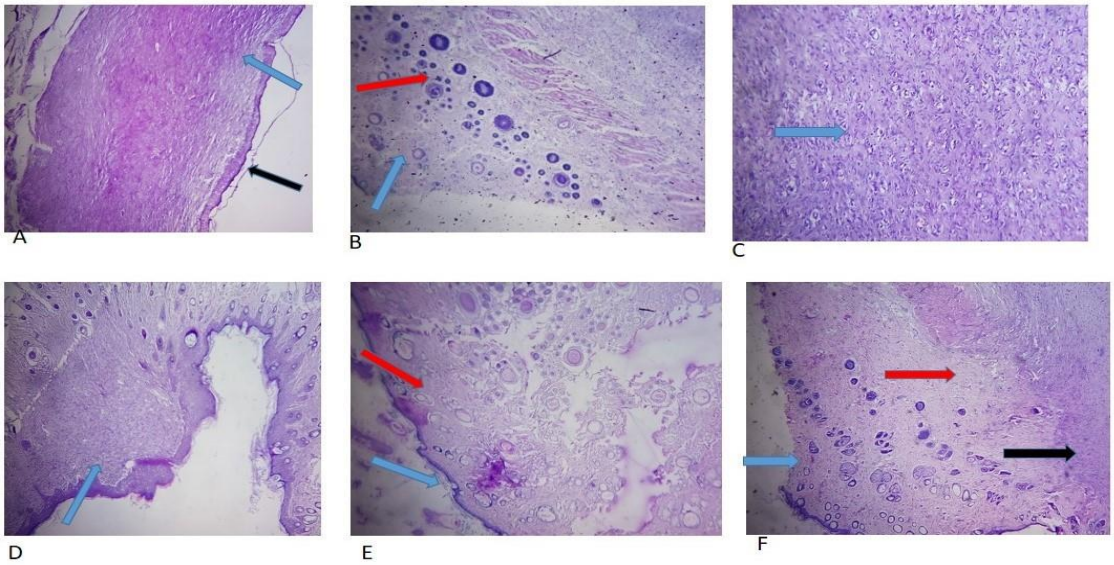

Figure 3: Histological analysis of the skin of the rats treated with 2.5, 5, and 10% of *Dioscorea praehensilis* ointment and the control groups.

A=Histologic section showing complete skin regeneration (Black arrow) with bands of sub-epithelial collagen (Blue arrow) in the 2.5% DP-treated group. H&EX100
B=Histologic section showing skin ulceration (Blue arrow) and stromal edema (Red arrow) in the 5% DP-treated group. H&Ex100
C=Histologic section showing extensive granulation tissue (Arrow) in the 10% DP-treated group. H&Ex100
D Histologic section showing subepithelial fibroblast proliferation (Blue arrow) in the ointment base (negative control) group. H&E100
E=Histologic section showing complete skin regeneration (Blue arrow) and fibrosis (Red arrow) in the positive control (1% Silver sulfadiazine) group. H&E100
F=Histologic section showing skin ulceration (Blue arrow), stromal myofibroblast (Red arrow), and granulation tissue (Black arrow) in the untreated group. H&Ex100

The possible mechanism of the wound-healing property of *Dioscorea praehensilis* was investigated in the rat aortic angiogenesis model by studying its effects on VEGF gene expression. The VEGF gene expression in the aortic rings treated with 500 and 1000 µg/mL of this extract was found to be significantly higher than that obtained with the untreated control. The VEGF gene expression in the aortic rings treated with 1000 µg/mL of DP extract was also found to be significantly higher than the standard (i.e., VEGF 5 µg/mL), as shown in Figure 4

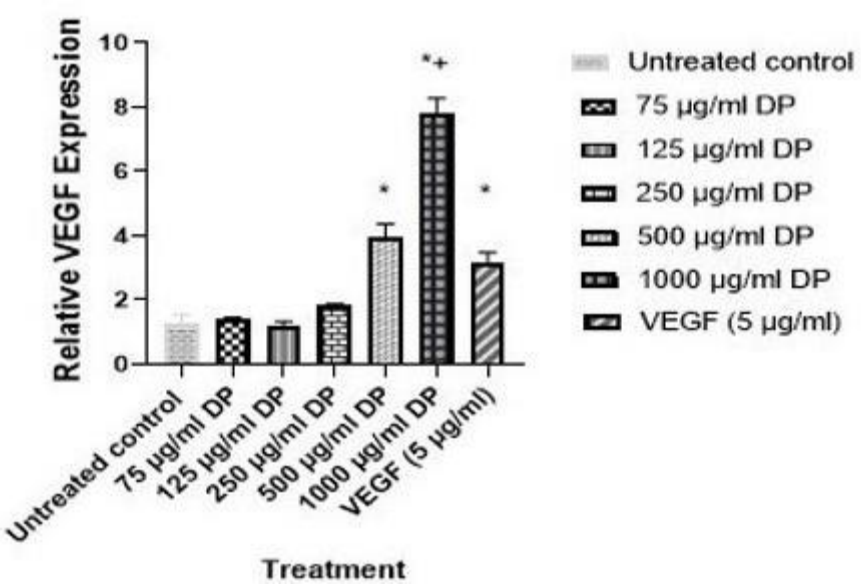

Figure 4: Relative expression level of VEGF in rat aortic ring treated with various concentrations of *Dioscorea praehensilis.* Data are shown as fold change of VEGF levels in aortic rings and presented as mean ± SEM. * $p<0.05$ compared to the untreated control. +$p<0.05$ compared to the positive control. VEGF=Vascular endothelial growth factor, DP= *Dioscorea praehensilis*, SEM = standard error of the mean, N=3

Discussion

In this study, the potential wound-healing property of *Dioscorea praehensilis* and its possible mechanism in relation to vascular endothelial growth factor gene expression were investigated. Healing of full-thickness wounds in normal animals occurs by contraction (Bao *et al*., 2009), which plays an important role in the wound healing process as it increases the extracellular matrix needed for tissue repair and re-epithelialization (Mulisa *et al*., 2015). The topical administration of methanol extract of *Dioscorea praehensilis* results in an increase in the percentage wound contraction compared to the negative control, indicating wound healing and tissue regeneration. This is also evident in the histological sections that show complete skin regeneration with bands of sub-epithelial collagen in the 2.5% DP ointment-treated group, as against those of 5 and 10% DP ointment that were still at the subepithelial fibroblast proliferation and tissue granulation formation stage and the skin ulceration with stromal edema that characterized the negative control group.

The wound healing process is known to involve an ordered sequence of events which starts with hemostasis and acute inflammation, followed by cellular proliferation, extracellular matrix deposition, remodeling, and finally scar formation (Johnson & Wilgus, 2014). Angiogenesis, the proliferation of new blood vessels from preexisting capillaries, is an important feature in the proliferative phase of wound healing, and chronic wounds are characterized by impaired angiogenesis (Honnegowda *et al*., 2015). The rat aortic ring model is one of the most commonly used techniques to study angiogenesis and its mechanisms. Its popularity is due to the ease of preparation, reproducibility of results, and ability to evaluate molecular and cellular interactions during the angiogenic process (Aplin & Nicosia, 2015). VEGF, a polypeptide growth factor through its receptor (VEGF-receptor 2), is a fundamental regulator of angiogenesis, and it is known to be the most important pro-angiogenic mediator during wound healing (Koch *et al*., 2011; Nissen *et al*., 1996). Delayed wound healing closure and decreased granulation tissue formation have been observed in mice lacking VEGF in the keratinocytes and myeloid cells (Bao *et al*., 2009). The ability of *Dioscorea praehensilis* to upregulate the gene expression of VEGF may therefore be a possible mechanism for its wound-healing property.

Previous phytochemical analysis of *Dioscorea praehensilis* shows the presence of saponins, tannins, flavonoids, steroids, phenols, terpenoids, and alkaloids (Wang *et al*., 2023). Saponins and flavonoids have been reported to possess wound-healing properties (Jian & Bari, 2010). Terpenoids have also been reported to promote wound healing and increase the rate of wound contraction and epithelization due

to their antimicrobial and astringent properties (Scortichini & Rossi, 1991). Flavonoids and tannins, on the other hand, encourage the wound healing process by reducing lipid peroxidation, scavenging free radicals or reactive oxygen species, thereby reducing cell necrosis and improving vascularity, which leads to an increase in capillary vessels and fibroblast formation (Pawar &Toppo, 2012).
Furthermore, a conventional wound treatment remedy should exhibit a synergistic effect of anti-inflammatory, antipyretic, antimicrobial, and astringent properties (Umeh *et al*., 2014). *Dioscorea* species have been reported to contain bioactive compounds with anti-inflammatory, antipyretic, antibacterial, astringent, and antioxidant properties (Adomeniene &Venskutonis, 2022; Hazrin-Chong *et al*., 2018; Obidiegwu *et al*., 2020; Wang *et al*., 2023). These properties may also be responsible for the wound-healing properties of DP observed in this study.

CONCLUSION

Topical administration of the methanol extract of *Dioscorea praehensilis* increases the rate of wound contraction in rats in an inverse dose-dependent manner, with the lowest concentration (2.5%) showing the greatest activity. The histological analysis of the skin of the treated rats showed complete skin regeneration with bands of sub-epithelial collagen. Furthermore, the extract up-regulated the expression of the VEGF gene, suggesting that this may be responsible for the observed wound healing property.

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