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Short Communication

The Effect of *Moringa oleifera* Leaf Extract on VEGF Gene and Wound Closure Rate in Wistar Rats

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ABSTRACT

Wound healing is a complex physiological process involving angiogenesis, collagen deposition, and the regulation of growth factors such as vascular endothelial growth factor (VEGF). *Moringa oleifera* Lam., widely cultivated in Indonesia, contains flavonoids, tannins, and saponins with antibacterial, antioxidant, and anti-inflammatory properties, making it a promising natural wound-healing agent. This true experimental randomized post-test-only control group study used 30 healthy male *Rattus norvegicus* (10–12 weeks; 250–300 g) divided into five groups: negative control (1% CMC), positive control (10% povidone-iodine), and *M. oleifera* extract at 5%, 10%, and 15%. The extract, obtained from a commercially available Indonesian Sidomuncul product, was diluted in 1% CMC. A standardized 1cm × 1mm dorsal thigh incision was created under ketamine anesthesia, with daily topical treatment for eight days. VEGF expression was quantified by qRT-PCR, and wound closure measured with a digital caliper. VEGF expression increased in the 5% (2.38 ± 0.34) and 10% (1.45 ± 0.15) extract groups but decreased at 15% (0.71 ± 0.18) compared to the negative control (1.00 ± 0.13), while povidone-iodine yielded the highest expression (12.85 ± 0.20); differences were not statistically significant (p=0.09). Wound closure was greatest in the 15% extract group (2.67 ± 0.71 mm), followed by 10% (2.81 ± 0.79mm) and povidone-iodine (2.82 ± 1.36mm), also without significance (p=0.88). Although *M. oleifera* exhibited dose-dependent trends in VEGF modulation and wound closure, the effects were not statistically significant, warranting further research with larger sample sizes and mechanistic analyses to identify its optimal therapeutic concentration.

Keywords: Wound healing, *Moringa oleifera*, VEGF gene, Angiogenesis, Wound closure.

Introduction

The skin is the body's largest organ and serves as the primary physical and immunological barrier, protecting internal structures from mechanical injury, chemical insults, and microbial invasion.[1,2] Disruption of this barrier, as in the case of wounds, can result from diverse causes including chemical exposure, temperature extremes, and trauma from blunt or sharp objects.[3,4] Global data, including reports from the 2018 and 2023 Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA), indicate that wounds caused by sharp objects account for over 20% of all wound cases, ranking third among the most prevalent wound types.[4,5] In Indonesia, the Ministry of Health (2022) reported that wound infections in hospitalized patients occur in 30–40% of cases, with the highest prevalence observed in burn and incised wounds.[6] Incised wounds are most frequently treated with povidone-iodine due to its broad-spectrum antimicrobial activity.[7] However, its use is not without drawbacks, as it may cause local inflammation, hypersensitivity, and, though rare, allergic reactions such as iododerma.[7,8] These limitations have driven increasing interest in developing safer, plant-based alternatives, particularly by harnessing Indonesia's rich botanical diversity.[9]

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One promising candidate is *Moringa oleifera* Lam., locally known as kelor, which is widely cultivated across Indonesia, particularly in tropical lowland and highland regions. The plant is rich in bioactive phytochemicals such as flavonoids, tannins, and saponins,[9-11] which possess antibacterial, antioxidant, and anti-inflammatory properties.[9,10,12] Experimental evidence suggests that *M. oleifera* enhances wound healing by stimulating angiogenesis, promoting collagen synthesis, and upregulating vascular endothelial growth factor (VEGF) expression.[12-15] Various topical formulations, particularly gels, have demonstrated accelerated wound closure and increased VEGF expression in animal models.[14,16,17] The aim of this study was to assess the efficacy of *M. oleifera* extract formulation in modulating VEGF expression and enhancing wound healing in Wistar rats, with the broader goal of identifying the optimal therapeutic concentration for future clinical translation.

Materials and Methods

Preparation of extract formulation

M. oleifera extract was sourced from a commercially available Indonesian Sido Muncul product. The extract was diluted with 1% carboxymethyl cellulose (CMC) to prepare topical formulations at concentrations of 5%, 10%, and 15%.[9,11]

Animals

A total of 30 healthy male Wistar rats (*Rattus norvegicus*), aged 10 - 12 weeks and weighing 250 - 300 g were obtained from Laboratory Animal Center, School of Life Sciences and Technology, Institut Teknologi Bandung (ITB), Indonesia. The animals were acclimatized for one week under controlled environmental conditions with adequate ventilation, a 12-hour light/dark cycle, and stable temperatures of 22 - 25°C, with access to food and water *ad libitum*.

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Ethical approval
Ethical approval was obtained from the Animal Ethics Committee of Universitas Kristen Maranatha under protocol number 077/KEP/VI/2024. All procedures followed the ethical principles of the 3Rs (Replacement, Reduction, Refinement) and the 5Fs (Freedom from hunger and thirst; discomfort; pain, injury, and disease; fear and distress; and freedom to express normal behavior).

Study design
This study employed a true experimental laboratory design with a randomized post-test-only control group approach, conducted at the Biomedical Laboratory, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia. The rats were randomly assigned into five groups of 6 animals each (n = 6).
A standardized incision wound (1 cm length × 1 mm depth) was created on the dorsal thigh of each rat under ketamine anesthesia (100 mg/kg body weight, intraperitoneally). The rats were thereafter treated as follows;
Group 1: Negative control – 0.1 mL of 1% carboxymethyl cellulose (CMC).
Group 2: Positive control – 0.1 mL of 10% povidone-iodine.
Group 3: Treatment 1 – 0.1 mL *Moringa oleifera* extract 5%.
Group 4: Treatment 2 – 0.1 mL *M. oleifera* extract 10%.
Group 5: Treatment 3 – 0.1 mL *M. oleifera* extract 15%.
Treatments were applied topically once daily for eight consecutive days. Wound dimensions were recorded daily using a digital caliper to calculate percentage wound closure. On day eight, wound tissues were harvested for vascular endothelial growth factor (VEGF) gene expression analysis using quantitative real-time polymerase chain reaction (qRT-PCR).[12,15]

Statistical analysis
Data were analyzed using SPSS version 22. Normality was assessed via the Shapiro–Wilk test and homogeneity via Levene's test. Differences in VEGF expression among groups were evaluated using the Kruskal–Wallis test, and wound closure rates was analyzed by one-way analysis of variance (ANOVA). A p-value < 0.05 was considered statistically significant.

Results and Discussion

Effect of Moringa oleifera on VEGF Gene Expression
The VEGF expression levels in each treatment group were evaluated and the results are presented in Figure 1. VEGF expression is crucial for angiogenesis in wound healing. The study results indicated variations in VEGF gene expression across treatment groups. The negative control group (CMC 1%) had a baseline value of 1.00 ± 0.13, whereas the povidone iodine 10% group exhibited the highest VEGF expression at 12.85 ± 0.20 times the baseline, highlighting its effectiveness in promoting blood vessel formation.[6] In contrast, *Moringa oleifera* extract formulation at 5% and 10% increased VEGF expression to 2.38 ± 0.34 and 1.45 ± 0.15, respectively, compared to the baseline, while the 15% concentration reduced VEGF expression to 0.71 ± 0.18, suggesting that higher doses may reduce VEGF effectiveness, potentially due to toxicity or flavonoid-mediated VEGF inhibition.[9,15]Lower doses of *Moringa oleifera* align with studies reporting optimal healing at high concentrations.[8,12] The presence of flavonoids and saponins in *Moringa oleifera* may stimulate VEGF through nitric oxide synthase activation, which promotes vasodilation and angiogenesis.[10,16] However, at higher concentrations, flavonoids may induce oxidative stress, impairing endothelial cells and inhibiting VEGF signaling.[13]
Additionally, tannins present in *Moringa oleifera* at high doses may act as inhibitors of VEGF pathways, limiting cell proliferation and new blood vessel formation.[13] These mechanisms explain why 15% extract concentration resulted in lower VEGF expression despite its effects on wound closure. The Kruskal-Wallis test (p = 0.09) confirmed no statistical significant differences among the groups, indicating that while *Moringa oleifera* influences VEGF expression, the changes were not statistically meaningful.[7]

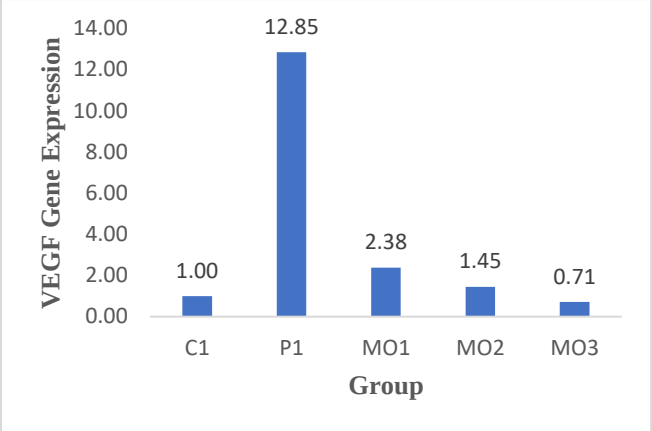

Figure 1: VEGF expression levels in each treatment group.
Note: C1 = Negative control (CMC 1%), P1 = Positive control (povidone-iodine 10%), MO1 = *Moringa oleifera* 5%, MO2 = *Moringa oleifera* 10%, MO3 = *Moringa oleifera* 15%

Effect of Moringa oleifera on wound closure rate
The rate of wound closure was assessed daily, and the results are illustrated in Figure 2. Analysis of wound length on day 8 showed that the *Moringa oleifera* extract groups had better wound closure rates compared to the negative control group. The wound closure rate analysis showed that *Moringa oleifera* extract at 10% and 15% concentrations resulted in faster healing, with wounds measuring 2.81 ± 0.79 mm and 2.67 ± 0.71 mm, respectively, compared to 3.26 ± 0.45 mm in the negative control group. Interestingly, these groups outperformed povidone iodine 10% (2.82 ± 1.36 mm), suggesting that *Moringa oleifera* has potential benefits in promoting wound healing, particularly at higher concentrations.[11]

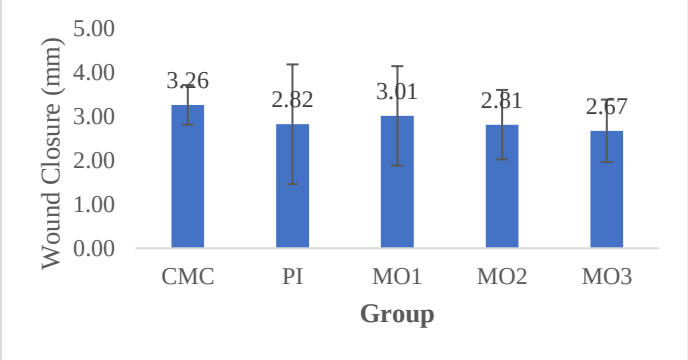

Figure 2: Wound closure progression over eight days
Note: C1 = Negative control (CMC 1%), P1 = Positive control (povidone-iodine 10%), MO1 = *Moringa oleifera* 5%, MO2 = *Moringa oleifera* 10%, MO3 = *Moringa oleifera* 15%

The discrepancy between VEGF expression and wound closure suggests that factors beyond VEGF activation influence wound healing.[14,17] Anti-inflammatory and antioxidant properties of *Moringa oleifera*, including flavonoids and alkaloids, may reduce oxidative stress and inflammation, facilitating faster tissue repair.[11] However, ANOVA results (p = 0.88) indicated no statistically significant differences among treatment groups, highlighting the need for further studies to validate these findings.
Several factors could have influenced these results, including biological variations among test subjects, behavioral factors such as scratching, and study limitations like sample size. Additionally, high doses of *Moringa oleifera* may trigger oxidative stress instead of promoting healing, as reported in prior research. These findings emphasize the need for controlled experiments to determine the optimal concentration for effective wound healing.

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Conclusion

This study demonstrates that *Moringa oleifera* extract does not significantly enhance VEGF gene expression or accelerate wound closure. While moderate increases in VEGF expression were observed at 5% and 10% concentrations, statistical analysis showed no significant differences compared to control groups. Similarly, wound closure was not meaningfully accelerated by *Moringa oleifera*, as no significant differences were found between treatment groups. Although *Moringa oleifera* has been suggested as a potential natural agent for wound healing, this study highlights the importance of further research to determine its optimal concentration and mechanism of action. Future studies should incorporate larger sample sizes and molecular analyses to understand better the biological effects of *Moringa oleifera* in wound healing.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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