INTERNATIONAL CONFERENCE
ON LIFESTYLE DISEASES AND NATURAL MEDICINE (ICOLIFEMED)
Nomor ISSN: 3124-1115

Therapeutic Potential of Moringa oleifera-Based Cream on Burn Wound Healing: Inflammation Suppression and TGF-β1 Modulation in Mice

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ABSTRACT
Burns are tissue injuries that trigger complex inflammatory responses and require proper treatment to prevent further complications. Moringa oleifera L., or known as kelor, is a herbal plant containing bioactive compounds such as flavonoids, phenols, and tannins that have the potential as wound healing agents through anti-inflammatory mechanisms and stimulation of tissue regeneration. This study aims to evaluate the potential of M. oleifera leaf extract cream in reducing inflammation and increasing the expression of Transforming Growth Factor-β1 (TGF-β1) in mice (Mus musculus) with a second-degree burn model. The method used includes administering Moringa oleifera cream (MOC) with concentrations of 1.25%, 2.5%, and 5% on thermally induced burns. Evaluation of wound healing was carried out through histopathological observation with Hematoxylin-Eosin (HE) staining to determine the inflammation score, as well as immunohistochemistry (IHC) to measure TGF-β1 expression. The results showed that MOC was able to significantly reduced inflammation scores, and increased TGF-β1 expression compared to the negative control group. Cream with a concentration of 5% gave the most optimal effect in reducing inflammatory cell infiltration and increasing TGF-β1 expression. Thus, it can be concluded that M. oleifera leaf extract cream has the potential as a topical therapeutic agent for healing second-degree burns. A concentration of 5% is the most effective dose in accelerating the healing process through the mechanism of reducing inflammation and increasing TGF-β1 expression.

Keywords: Anti-inflammatory, burn injury, *Moringa oleifera*, TGF-β1, wound healing

INTRODUCTION
Burns are a common type of skin injury and can cause serious physiological and psychological impacts. According to data from the World Health Organization (WHO), burns are a leading cause of morbidity and mortality in various countries, particularly developing ones (Yakupu et al., 2022). In 2012, the prevalence of burns caused approximately 195,000 deaths worldwide, primarily in low-income and developing countries. Women in the ASEAN region are at higher risk of burns than other regions, with 27% of cases contributing to the global death toll, and nearly 70% of burn deaths occurring in Southeast Asia (Karimi et al., 2017). In Indonesia alone, the prevalence of burns reached 2.2% (Putri et al., 2023).

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Untreated burns can lead to secondary infections, delayed healing, and excessive scar tissue (Shady & Mostafa, 2022). Standard therapies such as silver sulfadiazine are effective in preventing infection, but can cause leukopenia, bacterial resistance, and cytotoxicity (Sasor & Chung, 2019), while corticosteroids carry the risk of suppressing the local immune response (Maulana et al., 2025). These limitations have driven the development of safer, more affordable, and regeneration-supporting topical alternatives. One natural ingredient with potential in wound healing is the moringa leaf (Moringa oleifera L.). The various pharmacological benefits of moringa leaves have long been recognized, including anti-inflammatory, antioxidant, and wound-healing activities (Najihudin, 2023). Known for suppressing inflammatory reactions and increasing growth factor production, the phytochemical content of moringa leaves includes flavonoids, saponins, tannins, and growth factors such as Transforming Growth Factor Beta 1 (TGF-β1) (Biswas & Dey, 2020).

Previous studies have shown that this extract significantly reduces TGF-β1 gene expression by 58.63%, as well as suppressing major inflammatory pathways such as P38 MAPK and NF-κB, with reductions of 46.73% and 54.46%, respectively. The reduction in the activity of the P38 and NF-κB pathways, which are the main regulators of pro-inflammatory cytokine production, leads to a decrease in excessive inflammation that often exacerbates tissue damage in wounds. Additionally, the reduction in TGF-β1 expression helps prevent excessive fibrosis, supporting normal wound healing processes and accelerating tissue regeneration (Eltawila et al., 2024). Based on the pharmacological activity of moringa leaves, this active ingredient was formulated into a cream formulation as an alternative topical treatment to accelerate burn wound healing. Studies show that the use of moringa leaf extract cream can increase collagen density and accelerate burn wound reepithelization. Additionally, this cream can also soothe and cool the injured area (Andy et al., 2022).

This study evaluated the effects of topical M. oleifera cream (MOC) on inflammation and TGF-β1 expression in a second-degree burn model in mice. The parameters to be measured include TGF-β1 protein expression using immunohistochemistry (IHC) and tissue healing levels based on histopathological analysis. The histological scoring system refers to the Greenhalgh method, which includes granulation tissue maturation and acute and chronic inflammation levels. The novelty of this research lies in the use of multiple concentrations of MOC (1.25%, 2.5%, and 5%) formulated as creams—an approach not previously explored in burn wound models.

METHODS

Moringa oleifera cream preparation and formulation

Moringa leaves obtained from local farmers in West Java, Indonesia was rinsed and dried at dryer machine at temperature 60°C. The dried leaves then extracted by maceration method using 96% ethanol. *M. oleifera* extract was processed in PT. Jamu Borobudur (Batch number 255PV03.3) based on Good Manufacturing Practices. Cream formulations containing 1.25%, 2.5%, and 5% concentrations of *M. oleifera* extract were prepared, each with a total weight of 100 g, following the composition outlined in Table 1 (Utoyo et al., 2025).

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Table 1. Formulation of Moringa oleifera Cream (MOC)

Ingredients	MOC 1.25 % Formula (g)	MOC 2.5% Formula (g)	MOC 5% Formula (g)
M. oleifera extract	1.25	2.5	5
CMC-Na	1	1	1
Stearate acid	10	10	10
Paraffin oil	8	8	8
Petrolatum vaselin	6	6	6
Triethanolamin	1	1	1
Sorbitan monostearate	2	2	2
Nipagin	0.05%	0.05%	0.05%
Distilled water	Ad 100	Ad 100	Ad 100

Ethical approval

This study regarding burn wounds has received ethical clearance from the Ethical Committee of Prima Indonesia University, Medan, Indonesia (Approval No. 026/KEPK/UNPRI/IV/2025).

Animal model preparation

The study was conducted at Aretha Medika Utama, Biomolecular and Biomedical Research Center, Bandung, Indonesia, from March to June 2025. The study procedures comprised the preparation and administration of the cream, handling of laboratory mice, and subsequent analysis of TGF-β1 expression and inflammation in a second-degree burn mice model.

A total of 35 healthy male mice with normal body weight (20–30 g), active behavior, visually healthy appearance, and no anatomical abnormalities were randomly selected for the study. Each experimental group consisted of 5 mice, with one additional mouse included per group to account for potential dropout. All procedures were carried out in standard facilities, with maintenance using an individually ventilated cages system. The room temperature was maintained at 22 (±3°C) and the humidity ranged from 50-60%. Lighting was regulated with 12 hours of darkness and 12 hours of light, while food and drink were provided ad libitum. The animals were acclimatized for 7 days before being treated.

Second-Degree burn wound injection in mice

The injection of second-degree burns was carried out referring to research by Utoyo et al. (2025). Mice were anesthetized using Ketamine 90 mg/Kg BB and Xylazin 10 mg/Kg BB. After that, the hair on the body was shaved using a clipper shaver. The back area of the mice, 2 cm^2 in size, was cleaned and sterilized with alcohol. The iron metal was heated in a

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heat plate, then attached to the skin of the mouse's back for 5 seconds to produce second-degree burns. The area was then compressed with saline solution for 1 minute to prevent the burns from spreading.

Post-Induction Therapeutic Intervention

Following the induction of second-degree burn wounds, each mouse received a cream by applying it topically once a day. Wound size reduction was monitored on days 3, 6, 9, and 12 to evaluate the healing progress. After the 12-day treatment period, all animals were euthanized via cervical dislocation. Burn wound tissue samples were subsequently collected for histological analysis.

Tissue Preparation for Histology

The collected tissues were fixed with 10% BNF for 2 – 3 days. Furthermore, the collected samples were observed with Hematoxylin-Eosin (H.E.) staining for inflammation observation and immunohistochemistry to see the TGF-β1 protein levels, with the aim of evaluating the cellular and molecular effects of each treatment on the wound healing process.

Hematoxylin-Eosin examination (H.E)

Histopathological analysis was conducted using Hematoxylin and Eosin (H&E) staining. Skin tissue samples were fixed in 10% neutral buffered formalin for 2–3 days. Following fixation, the samples underwent dehydration using a graded series of ethanol concentrations for 2 hours, then cleared in graded xylene under continuous agitation. Subsequently, the tissues were embedded in liquid paraffin in stages, with the final embedding carried out at 100% paraffin at 60°C. The embedded tissues were allowed to solidify at room temperature to form paraffin blocks. These blocks were sectioned into 5 µm-thick slices using a rotary microtome (Leica RM 2135 BioCut). The sections were mounted on glass slides and stained with H&E. Histological analysis was performed using a light microscope, and ImageJ software was utilized to quantify inflammation scores (Widowati et al., 2024).

TGF-β1 protein expression by Immunohistochemistry (IHC)

Immunohistochemistry (IHC) was employed to detect antigen–antibody binding and visualize target protein expression in treated tissue sections. This technique is based on specific immunological interactions (antigen–antibody binding) coupled with enzymatic chemical reactions (enzyme–substrate interactions). In this study, antibodies were conjugated with peroxidase enzymes to facilitate visualization of antigen–antibody complexes. The IHC procedure included the following steps: sectioning of paraffin-embedded tissues, deparaffinization, rehydration through a graded ethanol series, antigen retrieval, and blocking of non-specific binding sites. Tissue sections were then incubated with a primary antibody targeting TGF-β1 (Anti- TGF-β1, Elabscience, E-AB-81493),

followed by incubation with a secondary antibody (Polyperoxidase-anti-Mouse/Rabbit IgG, Elabscience, E-IR-R217B). Detection was carried out using DAB (3,3'-diaminobenzidine) chromogen, producing a brown precipitate at the site of antigen expression. Slides were then counterstained with hematoxylin and eosin (H&E), dehydrated, cleared, and mounted for microscopic observation (Widowati et al., 2022).

Statistical Analysis

The data obtained were analyzed statistically using IBM SPSS 2.0 software. A descriptive test was performed to determine the mean, standard deviation, minimum, and maximum values from the research results. Next, normality and homogeneity tests were conducted. The Shapiro-Wilk test was used to assess the normality of the data. If the data were normally distributed ($P > 0.05$), the Levene test was used to evaluate homogeneity. When the data met both assumptions, a one-way ANOVA was conducted, followed by a Tukey HSD post-hoc test if significant differences were found ($P < 0.05$). However, if the data were not normally distributed, the Kruskal-Wallis test and Mann-Whitney post-hoc test were applied. A p-value of less than 0.05 was considered statistically significant (Widowati et al., 2022).

RESULTS

Burn Wound Reduction

Burn wound size reduction is expressed as the percentage decrease relative to the original wound size (Table 2). Treatment with MOC at concentrations of 1.25%, 2.5%, and 5% resulted in a significant reduction in burn wound area ($p < 0.05$), with the 5% MOC showing the greatest effect compared to the lower concentrations. Notably, the efficacy of the 5% MOC cream was comparable to that of silver sulfadiazine (SS) cream, as shown in Table 2. Statistical analysis confirmed that these reductions were significant, underscoring the effectiveness of the treatments in promoting wound healing.

Table 2. Average Percentage of Wound Healing

Group	Days of observation			
	Day 3	Day 6	Day 9	Day 12
I	100.00 ± 0.00^{dA}	100.00 ± 0.00^{eA}	100.00 ± 0.00^{dA}	100.00 ± 0.00^{eA}
II	1.60 ± 1.95^{aA}	8.90 ± 3.52^{aB}	24.90 ± 2.95^{aC}	38.90 ± 2.53^{aD}
III	2.20 ± 2.02^{abA}	5.20 ± 4.31^{aA}	18.90 ± 8.71^{aB}	37.40 ± 3.19^{aC}
IV	1.60 ± 2.22^{abA}	24.30 ± 3.33^{cB}	40.90 ± 7.24^{bcC}	53.30 ± 4.92^{bD}
V	4.25 ± 1.94^{bA}	14.15 ± 4.50^{bB}	40.00 ± 2.55^{bC}	61.40 ± 2.66^{cD}
VI	9.06 ± 4.55^{cA}	24.60 ± 3.88^{cB}	43.30 ± 7.11^{bC}	65.70 ± 4.09^{cD}
VII	13.93 ± 2.81^{cA}	34.40 ± 2.51^{dB}	45.90 ± 3.31^{cC}	71.10 ± 1.64^{dD}

*****The group designations were as follows: Group I served as the negative control (healthy rats), Group II as the positive control, Group III received the vehicle control (cream base), Group IV was treated with the comparative control (silver sulfadiazine cream), and Groups V, VI, and VII received MOC cream at concentrations of 1.25%, 2.5%, and 5%, respectively. Data are expressed as mean ± standard deviation. Lowercase superscript letters (a, b, c, d, and e) within the same column denote significant differences between treatment groups on the same observation day, while uppercase superscript letters (A, B, C, D, E) within the same row indicate significant differences across observation days within the same group.

Histological Evaluation of burn scar tissue

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Tissue observation was conducted directly using a light microscope, with visual evaluation in 5 fields of view for each mouse (replicates) to assess the level of infiltration and structural changes in the tissue. The results of the HE test in the negative control group (NC) showed normal skin tissue consisting of the epidermis, dermis, and hypodermis layers. The epidermis consists of the stratum corneum (SC), stratum spinosum (SS), and stratum basale (SB). The dermis layer begins with the dermal papillae (DP). In this layer, sebaceous glands (SG) and hair follicles (HF) can be found. The hypodermis contains adipose tissue (Figures 1).

The treatment groups of mice with burn injuries that received creams containing *Moringa oleifera* (MOC) at three different concentrations (1.25, 2.5, and 5%) exhibited similar histological findings, including the presence of neutrophil infiltration (NI) and fibrous granulation tissue (F), though with varying intensities. Collagen tissue (C) formation was also observed, indicating active tissue remodeling or maturation. This phase involves fibroblast proliferation, collagen deposition, angiogenesis, granulation tissue formation (comprising new connective tissue and microvasculature), and epithelialization (the regeneration of new epithelial layers) (Siu et al., 2025). Among the groups, the MOC5 group displayed lower levels of neutrophil infiltration and inflammation, suggesting a more advanced healing process compared to the other concentrations.

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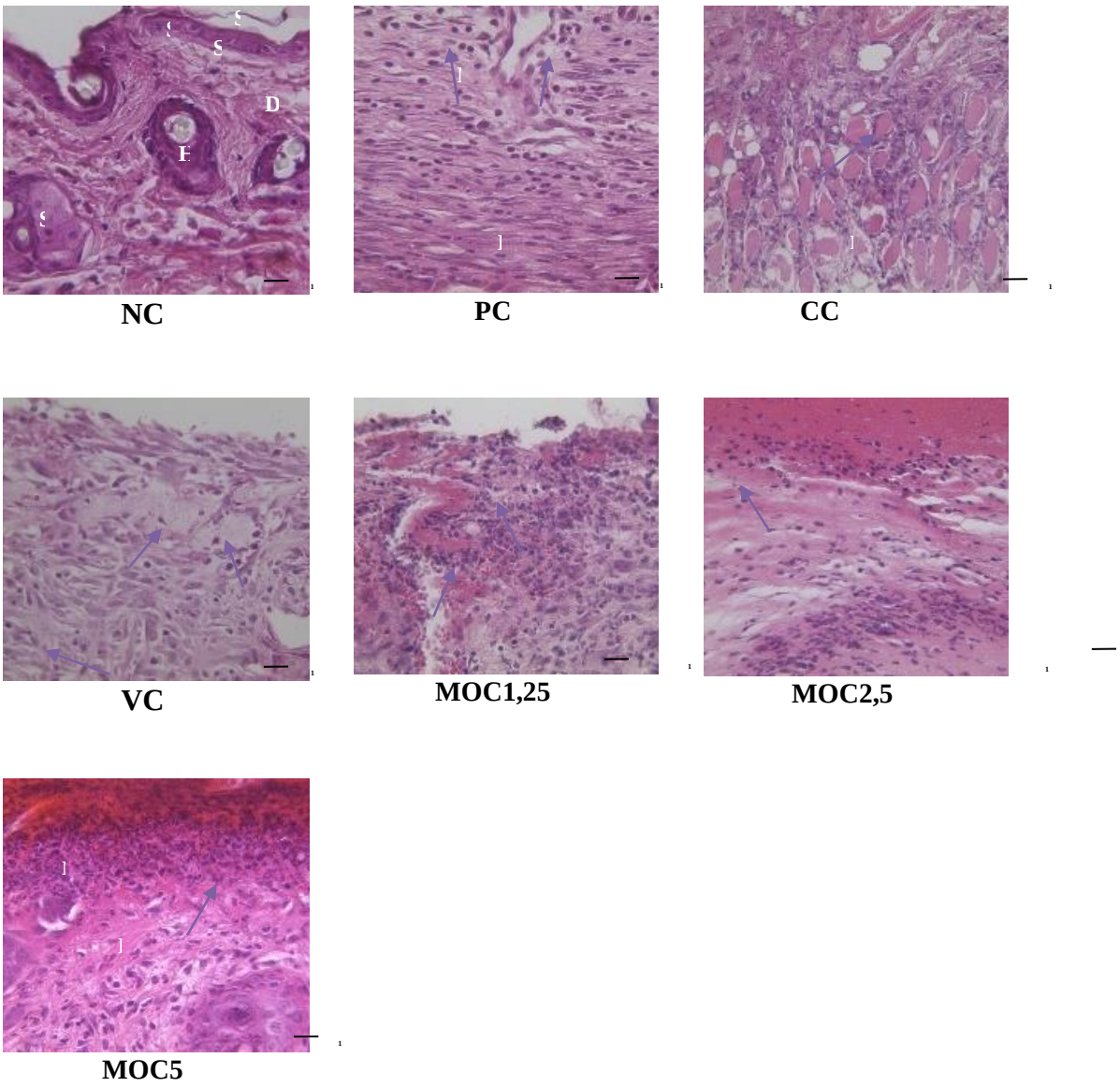

Figure 1. Histological of skin tissue

HF: Hair Follicle, F: Fibrous Granulation Tissue, D: Dermis, NI: Neutrophils Infiltration, SG: Sebaceous Gland
➔ Neutrophil

MOC Effect on Inflammation Score

The inflammation assessment results demonstrated that Group I (negative control) had the lowest inflammation score, with a mean of 0.00 ± 0.00, which was significantly different from all other groups ($P < 0.05$). This indicates the absence of inflammation in the skin tissue, making this group a valid reference for normal skin conditions. Groups II (positive control) and III (vehicle control) exhibited the highest inflammation scores among all treatment groups, with mean values of 2.600 ± 0.508 and 2.640 ± 0.288, respectively. These scores were significantly higher than those of the negative control group ($P < 0.05$), suggesting that the cream base lacking active ingredients did not offer therapeutic effects. Group IV (comparison group), which received topical silver sulfadiazine (SDS), showed a

considerably lower inflammation score (1.600 ± 0.565), significantly reduced compared to the positive control group ($P < 0.05$). Notably, Group VII, treated with 5% MOC, exhibited the lowest inflammation score among all groups, with a mean of 1.480 ± 0.623, significantly lower than the other groups ($P < 0.05$), including Group IV (SDS-treated), which is considered the gold standard for burn wound treatment. These findings indicate that the 5% *M. oleifera* cream formulation offers superior anti-inflammatory effects and may serve as a more effective alternative to SDS in burn wound management.

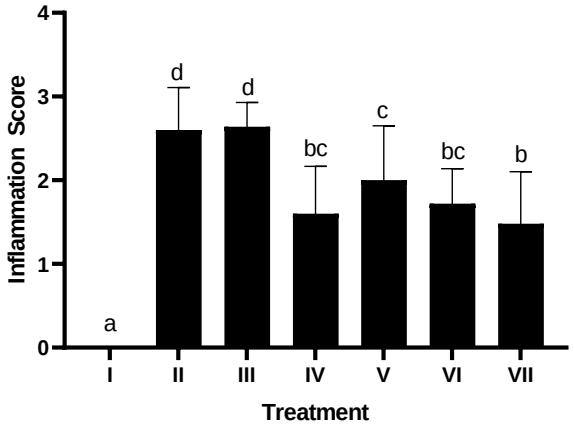

Figure 2. Effect of MOC on inflammation scores in a burn model of mice

(I: Negative Control (normal mice), II: Positive Control, III: Vehicle Control (Cream Base), IV: Comparison Control (SDS), V: M. oleifera Cream 1.25%, VI: M. oleifera Cream 2.5%, VII: M. oleifera Cream 5%). *Data are presented as mean ± standard deviation. Different superscript letters (a, b, c, d, e) indicate significant differences in each treatment based on the Mann-Whitney test ($p<0.05$).

MOC Effect on TGF-β1 Expression

Based on the research results, it appears that treatment with MOC increased TGF-β1 expression during the wound healing process (Figure 3). TGF-β1 expression is indicated by the appearance of a brown color after staining, as indicated by the black arrow. The observation that MOC upregulates TGF-β1 is beneficial for initiating and driving the necessary proliferative phase, as TGF-β1 is critical for promoting fibroblast activity, collagen deposition, angiogenesis, and granulation tissue formation (Pakyari et al., 2013). Group IV, consisting of burn-injured mice treated with silver sulfadiazine (SDS), exhibited the highest level of TGF-β1 expression among all groups ($P < 0.05$). Interestingly, Group VII, which received 5% MOC, showed no significant difference in TGF-β1 expression compared to Groups IV and VI, although the values in Group VII tended to closely approach those of Group IV. These results suggest that the application of 5% MOC may yield TGF-β1 expression levels nearly equivalent to SDS treatment, indicating its potential to promote wound healing. The increased TGF-β1 expression in this group reflects its likely involvement in stimulating the proliferative phase of tissue regeneration, an essential process in effective burn wound recovery.

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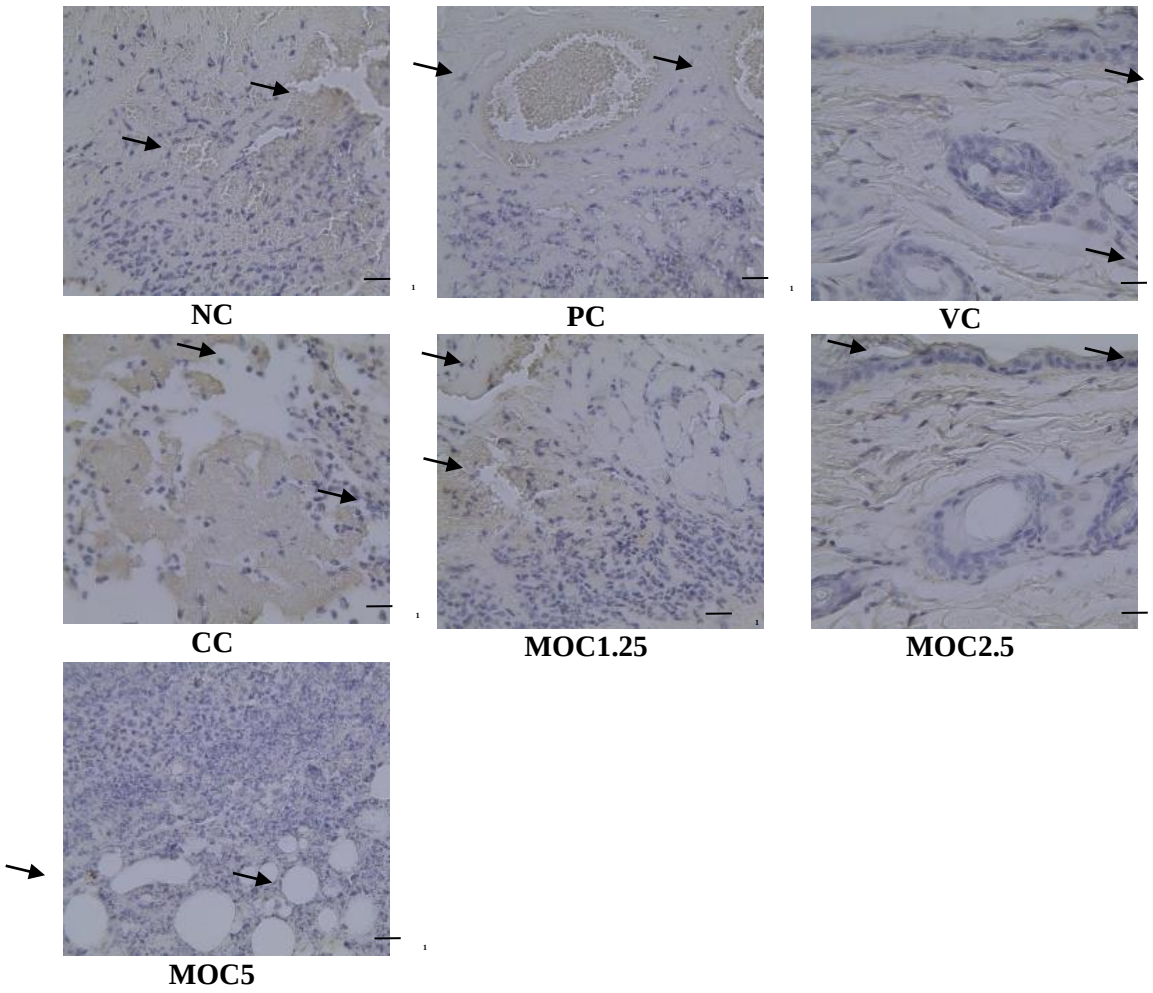

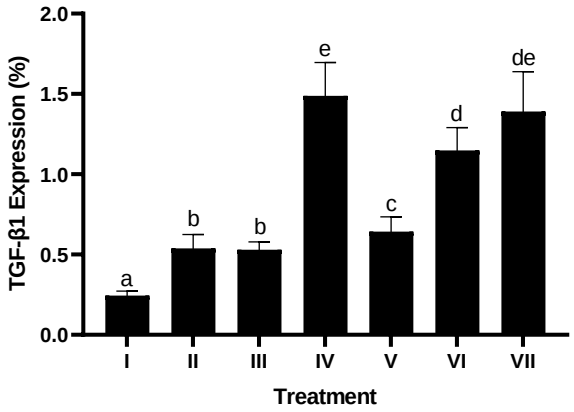

Figure 3. Effect of MOC on TGF-β1 expression in burn model mice

(I: Negative Control (normal mice), II: Positive Control, III: Vehicle Control (Cream Base), IV: Comparison Control (SDS), V: M. oleifera Cream 1.25%, VI: M. oleifera Cream 2.5%, VII: M. oleifera Cream 5%). *Data are presented as mean ± standard deviation. Different superscript letters (a, b, c, d, e) indicate significant differences in each treatment based on the Mann-Whitney test ($p<0.05$).

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DISCUSSION

Moringa oleifera L., a tropical plant widely recognized as a "superfood," is valued for its rich nutraceutical and pharmacological properties. It has long been utilized in traditional medicine due to its diverse bioactive components, including flavonoids (such as quercetin and kaempferol), polyphenols, tannins, and vitamin C, which act as natural antioxidants and anti-inflammatory agents. These compounds collectively contribute to its broad spectrum of biological activities, notably its wound healing potential (Jaya et al., 2023; Iqbal et al., 2023).

In the context of burn wound healing—particularly second-degree burns that involve damage to both the epidermis and part of the dermis—controlling inflammation and promoting tissue regeneration are critical. *M. oleifera* leaf extract has been shown to reduce inflammatory cell infiltration, suppress pro-inflammatory cytokines, and enhance fibroblast activity and collagen synthesis through the modulation of key molecular pathways, including Transforming Growth Factor Beta 1 (TGF-β1) (Shafie et al., 2022). In addition to its anti-inflammatory properties, the strong antioxidant content in *M. oleifera* leaves helps neutralize oxidative stress, which commonly accompanies burn injuries, thereby preventing further tissue damage and accelerating the proliferative phase of healing (Carballo-López et al., 2025).

Second-degree burns initiate acute inflammatory responses, characterized by the infiltration of neutrophils and macrophages (Mulder et al., 2022). In this study, both the positive control group (burn without treatment) and the vehicle control group (base cream without active compounds) showed the highest inflammation scores ($P < 0.05$), indicating persistent inflammation in the absence of effective therapeutic intervention. Conversely, M. oleifera extract cream significantly reduced inflammation compared to these groups, with the 5% formulation showing the lowest score—closely approaching the score observed in the SDS-treated group. These findings support the anti-inflammatory potential of *M. oleifera*'s bioactive compounds—such as flavonoids, phenolics, tannins, and vitamin C—which are known to inhibit the activity of pro-inflammatory mediators including TNF-α, IL-1β, and COX-2 (Muhammad et al., 2016). The reduction in inflammation observed in the treated groups suggests that *M. oleifera* extract effectively limits inflammatory cell infiltration and dampens the inflammatory response, thereby facilitating the transition from the inflammatory to the proliferative phase of wound healing.

Moreover, the present findings showed that TGF-β1 expression was significantly elevated in the positive control group compared to the negative control, indicating that day 13 post-injury corresponds to the proliferative phase in burn healing. TGF-β1 is a crucial cytokine involved in the proliferative phase of wound repair. It plays key roles in fibroblast activation, collagen production, and angiogenesis—processes essential for tissue regeneration (Shady et al., 2022; Wang et al., 2017). TGF-β1, as a pleiotropic cytokine, orchestrates a complex network of cellular responses including growth, differentiation, extracellular matrix (ECM) production, and immune regulation (Valluru et al., 2011; Ramirez et al., 2014). Interestingly, mice treated with *M. oleifera* cream—particularly at 2.5% and 5% concentrations—showed TGF-β1 expression levels that closely approximated those observed in the SDS-treated group. This upregulation suggests that M. oleifera cream can stimulate wound healing pathways via TGF-β1 activation. These results are consistent with prior studies demonstrating that *M. oleifera* extract can significantly enhance TGF-β1

expression, promote fibroblast activity, and support cell proliferation and migration to the wound site (Al-Ghanayem et al., 2022). Topical application of *M. oleifera* has also been associated with increased collagen deposition and granulation tissue formation. Its bioactive components, such as quercetin and kaempferol, are known to stimulate TGF-β1 expression while concurrently reducing oxidative stress, thus supporting both the anti-inflammatory and proliferative phases of healing (Shady et al., 2022; Al-Ghanayem et al., 2022).

Moreover, emerging evidence suggests that *M. oleifera* modulates TGF-β1 expression through intracellular signaling pathways. Activation of pathways such as Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) and Mitogen-Activated Protein Kinase (MAPK) has been linked to increased TGF-β1 expression following *M. oleifera* extract application. This indicates that the wound healing properties of *M. oleifera* are not solely due to direct cellular effects, but also involve the regulation of broader signaling cascades that influence overall tissue repair (Tan et al., 2015; Ningrum et al., 2023). TGF-β1 plays a dual role in tissue repair and scar formation. While reduced TGF-β1 levels are associated with impaired healing and hypertrophic scarring or keloids, increased TGF-β1 promotes connective tissue regeneration through enhanced collagen synthesis, thereby accelerating wound closure (Lee et al., 2022). The observed reduction in inflammatory scores, accompanied by increased TGF-β1 expression in *M. oleifera*-treated groups, highlights the dual function of the extract in modulating inflammation and promoting tissue regeneration.

CONCLUSION

In conclusion, this study demonstrates that topical *M. oleifera* extract cream, particularly at a 5% concentration, significantly reduces inflammation and enhances TGF-β1 expression in second-degree burn wounds. These findings support its potential use as a natural topical alternative for burn treatment, with the 5% formulation offering the most favorable therapeutic outcome. Before widespread clinical application, further studies on the toxicity and safety of topical *Moringa oleifera* leaf extract cream are necessary, including both short-term and long-term evaluations, along with the development of optimized formulations suitable for clinical use.

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Nomor ISSN: 3124-1115