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Topical Effectiveness of Bitter Melon (*Momordica charantia L.*) Leaf Extract on Healing of Cut Wounds in Female Wistar Rats

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ABSTRACT

Momordica charantia L. (bitter melon leaves) has long been utilized in traditional medicine for its anti-inflammatory and antioxidant properties. This research investigates the wound-healing efficacy of ointments formulated with bitter melon leaf extract. The extract was incorporated into ointments at concentrations of 5%, 10%, and 15%, and the formulations were compared with a negative control (base ointment) and a positive control consisting of Betadine® ointment (povidone–iodine 10% w/w). All preparations were applied topically once daily at approximately 0.1 g per wound. Wound recovery was assessed macroscopically using the Redness, Edema, Ecchymosis, Discharge, and Approximation (REEDA) scale, along with histopathological examinations conducted on day 15. Findings indicated that the 10% extract formulation provided the most effective acceleration of wound closure, with a median healing time of 8 days and superior histopathological outcomes in terms of re-epithelialization, fibroblast proliferation, and tissue remodeling. Statistical analyses using the Kruskal–Wallis and Mann–Whitney tests confirmed significant differences among groups ($p < 0.05$), revealing a non-linear dose–response pattern. The 15% formulation demonstrated reduced effectiveness, potentially related to increased viscosity or concentration-related cytotoxic effects. Overall, the study supports the potential of *Momordica charantia* L. extract, at an optimal concentration, as a promising plant-derived topical agent for wound healing.

Keywords: Bitter Melon Leaves, Herbal Ointment, *Momordica charantia*, Rat, Wound Healing

Introduction

Wounds damage body tissue that various physical, chemical, or biological factors can cause.[1] Handling wounds, especially infected ones, requires the right strategy to prevent complications such as further infection, accelerate tissue regeneration, and reduce the risk of infection.[2] Various innovations have been developed, such as the use of antibacterial hydrogels, polymeric scaffolds, and nanotechnology-based therapies that are not only able to inhibit bacterial growth, but also accelerate tissue regeneration through stimulation of angiogenesis, cell proliferation, and improvement of the wound microenvironment.[3] This approach has been proven effective in accelerating wound closure, reducing inflammation, and increasing the formation of new tissue, reducing the risk of infection and complications.[4] The wound-healing process is a highly regulated and multifaceted biological event that progresses through a series of consecutive stages, including hemostasis, inflammation, proliferation, and finally maturation or tissue remodeling.[5] The success of this process is greatly influenced by the physiological conditions of the body, such as oxygenation status, age, nutritional status, hormones, stress, diseases such as diabetes and obesity, and the use of drugs, alcohol, and smoking habits.[6]

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Any imbalance or disturbance within one of these stages may impair tissue regeneration and elevate the likelihood of complications, including infection, prolonged healing, and the development of abnormal scar tissue.[7] Postpartum perineal wounds are one form of wound that has a high morbidity burden on mothers.[8] These wounds can occur spontaneously due to tears during childbirth or through episiotomy. Beyond causing pain that may disrupt a mother's daily activities, perineal wounds carry a substantial risk of infection due to the moist perineal environment and its abundant microbial flora, thereby heightening the likelihood of complications such as infection and wound dehiscence.[9] The risk of infection and impaired perineal wound healing increases in cases of childbirth with episiotomy, high-degree tears, obesity, and less than optimal wound care, so special attention is needed in the treatment and prevention of infection in postpartum perineal wounds.[10] According to a report by the World Health Organization (WHO) in 2020, approximately 85% of mothers who give birth experience perineal tears. In Asia, nearly 50% of vaginal deliveries are accompanied by perineal tears, and more than 10% of these require further treatment in health facilities due to secondary infections. In Indonesia, the prevalence of perineal tears reaches 75% of all vaginal births and is one of the leading causes of postpartum infections. Studies in Nigeria reported an incidence of perineal tears of 11.4% in vaginal deliveries, while in Tanzania the prevalence reached 53%.[11,12] Meanwhile, in Brazil, approximately 88% of mothers experience first- or second-degree perineal tears after vaginal delivery.[13] Evidence from Mexico indicates that third- and fourth-degree perineal lacerations occur in about 2% of the overall population, with the incidence being higher among adolescent mothers.[14]
Conventional treatment of perineal wounds generally involves using antiseptics, analgesics, and antibiotics. However, these drugs often cause side effects such as irritation, antimicrobial resistance, and allergic reactions. Consequently, complementary and alternative medicine (CAM) utilizing medicinal plants is becoming increasingly

integrated into midwifery and community nursing practices in numerous countries. In Indonesia, plants such as betel leaf, binahong, and aloe vera have been proven effective in accelerating perineal wound healing and reducing the risk of infection.[15] Meanwhile, in China, traditional medicines such as Traditional Chinese Medicine (TCM) are also widely used to accelerate wound healing, including perineal wounds. Their mechanisms of action involve regulating the immune response and the skin microbiome.[16] According to the WHO, nearly 80% of people living in developing nations depend on traditional therapies—particularly medicinal plants—as a component of their primary health-care practices.[17]

Bitter melon (*Momordica charantia L.*), a Cucurbitaceae species that grows abundantly in tropical areas including Indonesia and various parts of Asia, is one of the herbal plants frequently utilized to enhance wound repair. Both its leaves and fruit contain bioactive constituents—such as flavonoids, saponins, alkaloids, and tannins—that exhibit anti-inflammatory, antioxidant, and antimicrobial properties, thereby contributing significantly to the wound-healing process.[18] Research in Indonesia showed that ethanol extract of bitter melon fruit and leaves significantly accelerated wound healing in test animals, characterized by decreased wound length and improved skin histopathology.[19] Studies in Turkey also reported that topical dressings of bitter melon extract resulted in the highest percentage of wound healing (94.7%) compared to nitrofurazone or saline in a rat ischemic wound model [20]. This study evaluated the effectiveness of bitter melon leaf extract ointment in accelerating the healing of cuts.

Materials and Methods

Study Design

This research employed a laboratory-based experimental approach using a post-test–only control group design within a Completely Randomized Design (CRD). The test animals were assigned at random to five groups: a negative control receiving only the ointment base, a positive control treated with Betadine® ointment (povidone–iodine 10% w/w), and three treatment groups administered bitter melon (*Momordica charantia L.*) leaf extract ointment at concentrations of 5%, 10%, and 15%. Assessment of wound recovery was conducted through the REEDA scoring system and supported by histopathological examination of skin tissue.

Study Location and Duration

The research was conducted in the Phytochemistry, Pharmaceutics, Pharmacology, and Toxicology Laboratory of the Faculty of Pharmacy, Hasanuddin University, and the Anatomical Pathology Laboratory of Hasanuddin University Hospital, Makassar. The study was conducted from February to July 2025.

Animal Model and Sampling

The study involved 25 healthy adult female Wistar rats (*Rattus norvegicus*) aged 8–12 weeks and weighing 120–200 grams. The inclusion criteria required the animals to be healthy and active, with clean fur and no signs of infection or dermatological abnormalities. Rats exhibiting infection, severe stress, or reduced food and water intake during the intervention were excluded. Each experimental group comprised five rats, determined using the Federer formula with an additional adjustment to account for potential dropout. The samples were selected through a simple random sampling method.

Preparation of Extract and Ointments

Fresh leaves of *Momordica charantia* L. were thoroughly washed, dried at 40–50 °C, milled into a fine powder, and extracted by maceration in 70% ethanol for 3 × 24 hours using a solvent-to-sample ratio of 5:1 (v/w). The resulting filtrate was concentrated at 40 °C with a rotary evaporator to obtain a viscous extract. This extract was then incorporated into ointment formulations at concentrations of 5%, 10%, and 15% by adding 2.5 g, 5 g, and 7.5 g of extract, respectively, to a 50 g base. All formulations used the same ointment base, consisting of propylene glycol (5 g), sodium carboxymethyl cellulose (Na-CMC) (2.5 g), 1,3-dimethylol-5,5-dimethylhydantoin (DMDM hydantoin) (0.1 g), and distilled water adjusted to the remaining weight (39.9 g, 37.4 g, and 34.9 g for the 5%, 10%, and 15% preparations, respectively). The Na-CMC was first dispersed in distilled water, followed by the addition of propylene glycol and the preservative, after which the extract was gradually incorporated using geometric dilution before the final homogenization step. The basic ointment (negative control) contained no extract, while Betadine® ointment (povidone-iodine 10% w/w) served as the positive control.

Phytochemical Screening

A qualitative phytochemical screening of the bitter melon (*Momordica charantia L.*) leaf extract was conducted to identify secondary metabolites—including alkaloids, flavonoids, tannins, saponins, and triterpenoids—following the standard protocols of Harborne[21] and Evans[22] with minor adjustments. The identification process relied on observable color shifts or the formation of precipitates after the addition of specific reagents, such as Dragendorff's reagent for alkaloids, 1% w/v ferric chloride ($FeCl_3$, 1% w/v) for phenolic compounds and tannins, citroborate reagent for flavonoids, and a mixture of acetic anhydride and sulfuric acid for triterpenoids and steroids.

Ethical Approval

This research has received ethical approval from the Research Ethics Committee of the Faculty of Pharmacy, Hasanuddin University (Number: 1933/UN4.17/KP.06.05/2025). The research procedures used experimental animals to ensure animal welfare throughout the study, following the 3R principle (Replacement, Reduction, Refinement).

Wound Induction and Treatment Protocol

Before injury, the rats were acclimatized for 14 days and then anesthetized with 20 mg/kg intramuscular ketamine. A 2 cm long and 2 mm deep incision was made on the dorsal region using a sterile scalpel handle No. 3 fitted with a surgical blade No. 15, which is commonly used to achieve a precise and controlled linear incisions in small laboratory animals. Wound care began on the first day using an ointment appropriate for each group. The wounds were cleaned with 0.9% NaCl before ointment application and left open to facilitate daily observation. Treatment was performed daily at 8:00 a.m. for 14 days.

Wound Assessment

Macroscopic evaluation of wound recovery was carried out using the REEDA scale, which measures five indicators: redness, edema, ecchymosis, exudate, and approximation of the wound edges. The total score ranges from 0 to 15, where lower values reflect a more advanced stage of healing. On day 15, histopathological examination was performed using hematoxylin-eosin (HE) staining to observe tissue regeneration processes such as re-epithelialization, fibroblasts, and inflammation, under a binocular light microscope (Olympus CX23, Olympus Corporation, Italy) at 10-40× magnification.

Statistical Analysis

The wound healing scores obtained from the REEDA assessment and the histopathological evaluations were processed using the Statistical Package for the Social Sciences (SPSS) version 24. Group comparisons were conducted with the Kruskal–Wallis test, followed by the Mann–Whitney U test as a post hoc analysis to identify specific pairwise differences. A p-value of <0.05 was considered statistically significant.

Results and Discussion

Wound Healing Time

The study showed variations in wound healing time between treatment groups. Rats receiving the 10% *Momordica charantia* L. leaf extract ointment—prepared according to the formulation and procedures described in the Methods section—experienced the fastest healing, with a median duration of 8 days (range 8–10 days). The group using Betadine ointment (povidone-iodine 10% w/w, applied topically at approximately 0.1 g per wound once daily) had a median healing time of 9 days (range 9-11 days). Meanwhile, the group with the 5% extract showed slower healing (median 11 days), and the group with the 15% extract and the base ointment had the longest healing time, each with a

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median of 14 days (range 14-15 days) (Table 1). The Kruskal–Wallis statistical test revealed a significant difference among all treatment groups, yielding a p-value of 0.000, which indicates statistical significance at the $p < 0.05$ level.

Table 1: Length of wound healing for each treatment group in female rats (n=25)

Groups	n	Median	Minimum	Maximum
Basic ointment	5	14	14	15
Betadine ointment	5	9	9	11
Bitter melon leaf extract ointment 5%	5	11	11	12
Bitter melon leaf extract ointment 10%	5	8	8	10
Bitter melon leaf extract ointment 15%	5	14	14	15

The evaluation results of the mean ranking indicated that the group receiving the 10% bitter melon extract ointment obtained the lowest mean ranking (4.00), which reflects the fastest wound healing process among the other groups. In contrast, the group given the basic ointment (21.00) and the 15% bitter melon extract (20.00) showed the highest mean ranking, indicating that these two groups experienced the slowest wound healing process (Table 2). The Mann–Whitney post hoc analysis further clarified the differences among the treatment groups, revealing significant distinctions between the base ointment and the Betadine ointment ($p = 0.007$), the 5% bitter melon extract ($p = 0.006$), and the 10% bitter melon extract ($p = 0.007$). In contrast, no significant difference was observed between the base ointment and the 15% extract formulation ($p = 0.513$).

Table 2: Length of wound healing in the treatment group of female rats (n=25)

Groups	n	Mean Healing (Days)	Time	p-value*
Basic ointment	5	21.00		
Betadine ointment	5	7.40		
Bitter melon leaf extract ointment 5%	5	12.60		0.000
Bitter melon leaf extract ointment 10%	5	4.00		
Bitter melon leaf extract ointment 15%	5	20.00		

* $p < 0.05$ based on the Kruskal–Wallis test for overall comparison among all groups.

These results suggest that increasing the concentration of bitter melon extract does not consistently correspond to faster wound healing (Table 3). These findings indicate a non-linear dose-response curve pattern in using bitter melon extract for wound healing, where a moderate concentration (10%) provides optimal healing effectiveness. Experimental studies on animals by Pazry and Astriyani [19,23] show that bitter melon extract can accelerate wound healing, but its effectiveness is greatly influenced by the dose used. Concentrations that are too high do not always increase the healing rate and can even decrease effectiveness, as seen in the group with the highest extract concentration, which showed no significant difference compared to the control. This phenomenon is in line with previous findings by Zulkefli *et al.* [24] This study stated that optimal concentrations of bioactive compounds, such as flavonoids in bitter melon extract, can stimulate fibroblast proliferation, angiogenesis, and epithelialization. In contrast, excessive concentrations can potentially cause cytotoxic effects or inhibit tissue regeneration due to oxidative stress.[24]

Pharmacologically, the content of flavonoids, saponins, and alkaloids in bitter melon leaves is known to play an important role in the wound healing process through anti-inflammatory and antioxidant activity, as well as accelerating the formation of collagen and tissue regeneration.[25,26] Flavonoids and saponins in bitter melon leaf extract can stimulate the proliferation of fibroblasts, angiogenesis, and accelerate the epithelialization phase, thereby accelerating the closure of the wound.[19] Saponin also plays a role in reducing bacterial colonization and supports the formation of healthy granulation tissue.[27] However, the use of extract concentrations that are too high can disrupt the integrity of cell membranes or increase the viscosity of topical preparations, potentially inhibiting oxygen diffusion and absorption of active substances into wound tissue, which in turn can slow the healing process. [19,28,29]

Table 3: Comparison of the average healing time of incision wounds between pairs of female rats (n=25)

Variables	Mean Rank 1	Mean Rank 2	p-value*
Basic ointment vs Betadine ointment	8.00	3.00	0.007
Basic ointment vs 5% bitter melon leaf extract ointment	8.00	3.00	0.006
Basic ointment vs 10% bitter melon leaf extract ointment	8.00	3.00	0.007
Basic ointment vs 15% bitter melon leaf extract ointment	6.00	5.00	0.513
Betadine ointment vs 5% bitter melon leaf extract ointment	3.40	7.60	0.018
Betadine ointment vs 10% bitter melon leaf extract ointment	7.00	4.00	0.100
Betadine ointment vs. 15% bitter melon leaf extract ointment	3.00	8.00	0.006
Bitter melon leaf ointment 5% vs. Bitter melon leaf extract ointment 10%	8.00	3.00	0.006
Bitter melon leaf ointment 5% vs. Bitter melon leaf extract ointment 15%	3.00	8.00	0.005
Bitter melon leaf ointment 10% vs. Bitter melon leaf extract ointment 15%	3.00	8.00	0.006

* p-values are derived from the Mann–Whitney test for pairwise comparisons between groups.

Histopathological Observation of Skin Tissue

Histopathological analysis of skin tissue on the 15th day after treatment showed significant differences between groups (Figure 1). In the negative control group (Figure 1a), the tissue showed active inflammation, necrosis, and no evidence of new tissue formation. In contrast, tissue repair began to appear in the Betadine-treated group (Figure 1b), characterized by the formation of granulation tissue and increased fibroblasts. However, the level of inflammation remained relatively high. These findings align with research by Malarvizhi *et al*. [30] This study showed that betadine application can accelerate granulation tissue formation and increase fibroblast activity during the wound healing phase, although the inflammatory process has not yet fully resolved. The group receiving 5% bitter melon leaf extract ointment (Figure 1c) showed increased new blood vessel formation (angiogenesis) and fibroblast activity, although the re-epithelialization and tissue remodeling processes were still suboptimal. In the group receiving 10% extract (Figure 1d), the tissue structure appeared to be the best, indicated by the highest scores for re-epithelialization, fibroblast count, remodeling processes, and minimal levels of inflammation. Meanwhile, the group receiving 15% extract (Figure 1e) showed a similar pattern, but with fewer areas of necrosis, indicating its slightly lower effectiveness than the 10% concentration.

These histological results support the clinical findings that the 10% concentration of bitter melon leaf extract ointment provided optimal wound healing. This was characterized by complete granulation tissue formation, maximal re-epithelialization, and reduced inflammation and necrosis. The high fibroblast activity in this group reflects intense stimulation of the proliferation phase, which plays a crucial role in the synthesis and reorganization of the extracellular matrix. This indicates that the wound healing process has entered a more mature remodeling phase, where fibroblasts not only proliferate but also regulate the formation of new tissue and increase the structural strength of the tissue being repaired, thereby accelerating recovery and improving the quality

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of wound healing compared to other groups.[31] The wound-healing effects observed in this study are likely attributable to the flavonoid and triterpenoid compounds present in bitter melon leaves, which possess well-documented anti-inflammatory and antioxidant properties that promote tissue regeneration.[32] Flavonoids are particularly important because they enhance the expression of growth factors such as Vascular Endothelial Growth Factor (VEGF) and Transforming Growth Factor-Beta (TGF-β), both of which play key roles in angiogenesis and fibroblast proliferation during the healing process.[24] Additionally, the saponins found in bitter melon leaves help accelerate collagen production and granulation tissue formation, thereby supporting faster restoration of damaged skin tissue.[32]

Several studies by Almasian et al., Lyggitsou *et al*., and Ugoeze et al. [33–35] Showed that increasing the concentration of herbal extracts is not always directly proportional to the effectiveness of wound healing. Interestingly, the 15% concentration group produced a histological picture almost equivalent to the 10% group, but with slight necrosis. This indicates that increasing the extract dose above the optimal level can cause side effects, such as cytotoxicity due to the high content of secondary metabolites at high concentrations, thus potentially inhibiting tissue regeneration.[33] This phenomenon emphasizes the importance of determining the optimal threshold concentration of herbal extracts for topical application in wound healing. Concentrations that are too high can reduce effectiveness or even cause detrimental effects on tissue.[36]

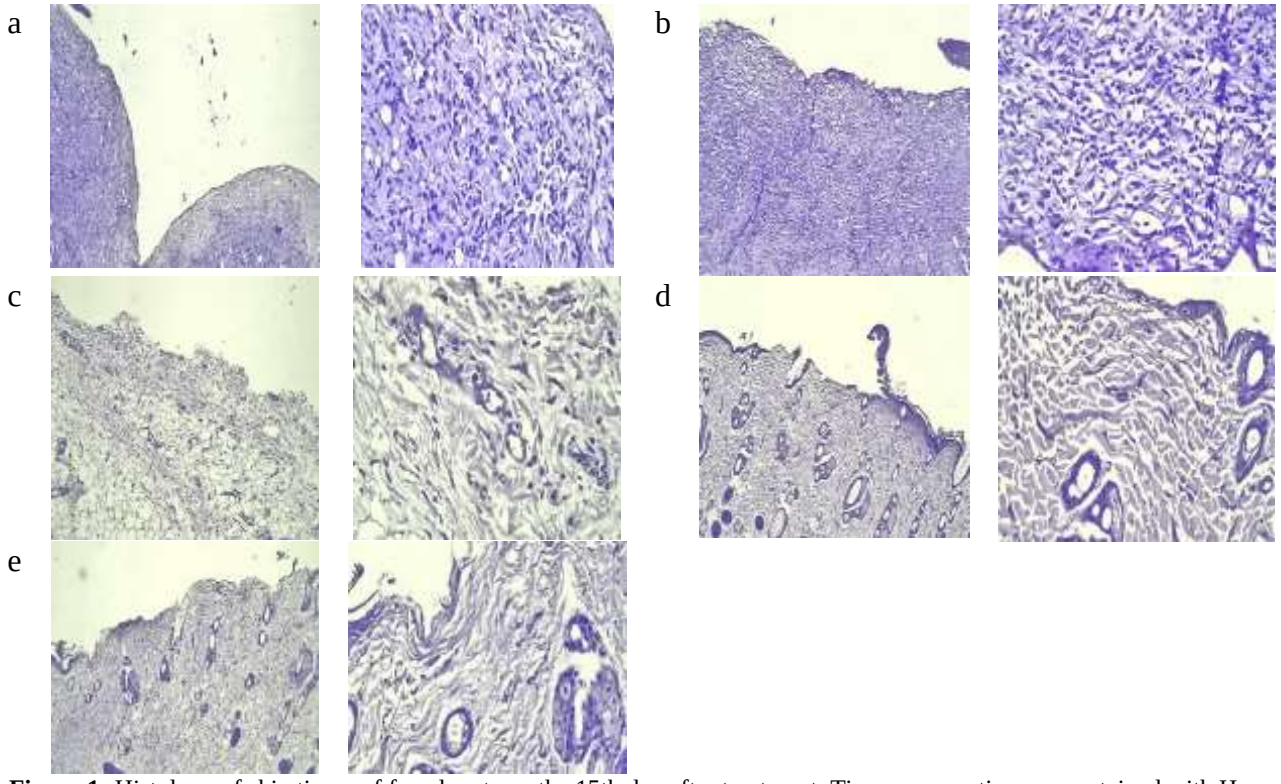

Figure 1: Histology of skin tissue of female rats on the 15th day after treatment. Tissue preparations were stained with Hematoxylin-Eosin (HE) and observed at 10× and 40× magnification. The image shows the differences in skin tissue structure between treatment groups: (a) negative control group (ointment base), (b) positive control group (Betadine Ointment), (c) treatment group with 5% bitter melon leaf extract ointment, (d) 10% bitter melon leaf extract, and (e) 15% bitter melon leaf extract).

Conclusion

A topical ointment formulated with *Momordica charantia* L. leaf extract was shown to significantly accelerate wound healing in female rats, particularly at a concentration of 10%, likely through enhanced re-epithelialization, fibroblast activity, tissue remodeling, and reduced inflammation and necrosis. The non-linear dose–response pattern observed indicates the importance of determining an optimal concentration to prevent reduced effectiveness or potential cytotoxic effects. To advance these findings, future research should explore alternative extraction methods and phytochemical standardization, evaluate larger sample sizes with extended observation periods, and incorporate molecular-level assessments such as collagen synthesis markers, inflammatory cytokines, and antioxidant profiles to better elucidate underlying mechanisms. Further formulation optimization, comparison of different ointment bases, and comprehensive safety, irritation, and stability testing are also recommended to support the development of *M. charantia* extract ointment toward potential preclinical application as a plant-based wound-healing therapy.

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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