Trop J Nat Prod Res, January 2026; 10(1): 6520 - 6525

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Topical Effects of a Combination of Bitter Melon (*Momordica charantia*) and Tamarind (*Tamarindus indica*) Leaf Extracts on Cutaneous Wound Healing in Female Wistar Rats

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ARTICLE INFO

Article history:
Received 01 October 2025
Revised 09 December 2025
Accepted 13 January 2026
Published online 01 February 2026

ABSTRACT

Tissue damage such as lacerations requires proper therapeutic intervention to minimize infection risk and accelerate the healing process. This study evaluated the wound-healing potential of a topical formulation containing combined extracts of bitter melon (*Momordica charantia*) and tamarind (*Tamarindus indica*) leaves in female Wistar rats. Twenty-five animals were distributed into five groups: a negative control given only the ointment base, two positive controls treated with Betadine and Bioplacenton, and two treatment groups receiving extract-based ointments in 1:1 and 1:2 ratios. Each preparation was applied once daily for 14 days, and wound progression was monitored using the REEDA scale supported by histopathological assessment of skin tissue. Phytochemical screening verified the presence of flavonoids, tannins, triterpenoids, and saponins in the extracts. The ointment exhibited a physiologically acceptable pH between 5.48 and 5.54. The 1:1 combination showed the fastest healing response, with a median recovery period of seven days, significantly outperforming both the negative control and Betadine ($p < 0.05$) while not differing significantly from Bioplacenton ($p > 0.05$). Histological observations demonstrated improved re-epithelialization and a more organized dermal architecture in the treated group compared with controls. These enhancements are attributed to the anti-inflammatory and regenerative activities of the bioactive compounds present in the extracts. Collectively, the results suggest that bitter melon and tamarind leaf extracts constitute a safe and promising herbal option for topical wound management.

Keywords: Cuts, herbal ointment, *Momordica charantia*, *Tamarindus indica*, wound healing.

Introduction

Wound repair is an intricate physiological event that requires the interplay of multiple cell populations, inflammatory signals, and molecular mechanisms to re-establish normal tissue function.[1] In the case of cut injuries, the healing sequence encompasses cellular migration and replication, formation and modification of the extracellular matrix, inflammatory responses, and the growth of new blood vessels, with macrophages, keratinocytes, fibroblasts, and endothelial cells serving essential roles throughout these phases.[2] When cuts are inadequately treated, they may progress to persistent inflammation or infection, increasing the likelihood of chronic wound formation or abnormal scar development.[3] Consequently, the search for therapeutic strategies that are both safe and effective in promoting faster wound closure has become a central theme in contemporary biomedical investigation.

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Citation: Masdayanti Masdayanti , Elly Wahyudin, Mardiana Ahmad, Prihantono Prihantono , Stang Stang . Topical Effects of a Combination of Bitter Melon (*Momordica charantia*) and Tamarind (*Tamarindus indica*) Leaf Extracts on Cutaneous Wound Healing in Female Wistar Rats. Trop J Nat Prod Res. 2026; 10(1): 6520 – 6526 https://doi.org/10.26538/tjnpr/v10i1.13

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

Many efforts focus on the use of naturally derived substances—such as plant-based bioactive molecules, compounds from animal sources, and nanomaterials originating from natural products—which exhibit antioxidant, anti-inflammatory, and antimicrobial properties that contribute to enhanced tissue repair.[4]

Perineal tears are a common condition experienced by mothers during childbirth due to tears in the birth canal, either spontaneously or through episiotomy, which require wound healing treatment.[5] Research by Argaw et al. at Atat Hospital, Ethiopia showed that the prevalence of perineal tears is quite high, recorded at 38.4% in mothers who gave birth vaginally. [6] The main risk factors for perineal tears include episiotomy, instrumental delivery (forceps or vacuum), high birth weight, primiparity, and augmentation procedures and fundal pressure. Perineal wounds can cause complications such as infection, dehiscence, postpartum pain, and an increased risk of maternal morbidity.[7] Episiotomy can also increase the risk of wound infection by up to threefold.[5] These complications not only disrupt maternal comfort during the postpartum period but can also increase the risk of morbidity and mortality if not managed properly, especially in countries with limited resources.[7]

The application of herbal remedies for managing wounds has long been a fundamental component of traditional healthcare systems across many regions, including Indonesia, a country known for its vast biological diversity.[8] Botanical species such as *Momordica charantia* (bitter melon leaves) and *Tamarindus indica* (tamarind leaves) are known to contain various bioactive compounds—among them flavonoids, tannins, saponins, and alkaloids—that facilitate accelerated tissue regeneration due to their anti-inflammatory, antimicrobial, and antioxidant properties.[9] Leaf extracts of *Momordica charantia* have been shown to provide substantial antioxidant and antimicrobial activities, stimulate wound contraction, and increase collagen synthesis

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

in damaged tissue.[10] Meanwhile, Likewise, *Tamarindus indica* leaf extract demonstrates notable anti-inflammatory potential and supports the migration of fibroblasts, a key event required for effective wound healing.[9]

The development of topical preparations based on medicinal plants has become an important topic in the pharmaceutical and biomedical fields in recent years. Medicinal plants offer potential as natural anti-inflammatory, antibacterial, and antioxidant agents that support the wound healing process without causing systemic side effects.[11] Communities often favor medicinal plants because they are viewed as natural, safer alternatives that align with cultural practices and traditional knowledge. The wound-healing benefits of these plant-based therapies have been demonstrated in numerous in vivo and in vitro investigations, particularly in species rich in flavonoids, tannins, and saponins. These compounds contribute significantly to anti-inflammatory activity, antioxidant protection, and the promotion of tissue repair and regeneration.[12]

The development of topical preparations based on medicinal plants has become an important topic in the pharmaceutical and biomedical fields in recent years. Medicinal plants offer potential as natural anti-inflammatory, antibacterial, and antioxidant agents that support wound healing without causing systemic side effects.[11] Many communities choose medicinal plants because they are perceived as more natural, safer to use, and closely aligned with traditional knowledge and cultural practices.[12] Numerous in vivo and in vitro investigations have validated the ability of herbal preparations to enhance the wound-healing process, particularly those derived from plants rich in flavonoids, tannins, and saponins. These bioactive constituents are known to contribute to anti-inflammatory actions, antioxidant protection, and the activation of tissue regeneration pathways.[13]

Several previous studies, such as those conducted by Yazarlu et al., Vitale et al., dan Herman and Herman, showed that topical use of herbal plant extracts can accelerate re-epithelialization, increase angiogenesis, and reduce local inflammation in the wound area through mechanisms such as growth factor stimulation, anti-inflammatory activity, and increased collagen synthesis.[11,14,15] This study aimed to evaluate the effectiveness of a combination of bitter melon (*Momordica charantia*) and tamarind (*Tamarindus indica*) leaf extract on wound healing in female Wistar rats

Materials and Methods

Research Design

This study employed a laboratory-based experimental design using a post-test–only control group approach to assess the wound-healing effects of an ointment formulated from combined extracts of bitter melon (*Momordica charantia*) and tamarind (*Tamarindus indica*) leaves. The research was carried out between March and June 2025 across five laboratories within the Faculty of Pharmacy, Hasanuddin University, Makassar—specifically the Biopharmacy, Phytochemistry, Pharmaceutics, Pharmacology, and Toxicology Laboratories—along with the Anatomical Pathology Laboratory at Hasanuddin University Hospital. Ethical clearance for the study was granted by the Research Ethics Commission of the Faculty of Pharmacy, Hasanuddin University, under approval letter number 1935/UN4.17/KP.06.05/2025 and protocol number UHO12502133.

Plant Materials and Extractions

Fresh bitter melon (*Momordica charantia*) and tamarind (*Tamarindus indica*) leaves were obtained from Bone Regency, South Sulawesi. The plant specimens were identified by botanists from the Faculty of Forestry, Hasanuddin University, and stored in the herbarium under voucher numbers MCH-001 (bitter melon) and TAM-002 (tamarind).

The extraction was performed by maceration employing 70% ethanol as the extracting solvent. Precisely 100 grams of dried leaf powder were soaked in 1000 mL of solvent for 48 hours, protected from light and periodically agitated. The obtained filtrate was then concentrated using a rotary evaporator to yield a thick extract, which was subsequently stored in a dark container and maintained at 4°C.

Preparation of Combination Ointment Preparations

The ointment base was made from white Vaseline with added lanolin to increase spreadability. The base was heated to 60°C, then cooled to 45°C. The extract was added to the ointment base in a combination ratio of bitter melon: tamarind of 1:1 and 1:2 (each at 10% concentration), then stirred until homogeneous and packaged in sterile containers.

Test Animals and Injury Procedures

A total of twenty-five female Wistar rats, aged 8–12 weeks and weighing 120–200 grams, were utilized in this experiment. Prior to treatment, the animals underwent a 14-day acclimatization period, during which they were housed in partitioned plastic cages and provided with standard laboratory chow and ad libitum water. Cage maintenance was performed by cleaning them three times weekly.

After acclimation, anesthesia was induced using intramuscular ketamine at a dose of 20 mg/kg. Approximately 5–10 minutes later, the dorsal surface of each rat was sterilized with 70% alcohol, and a 1 cm incision was made using a sterile scalpel. The induced wound was left open, without bandaging, to allow direct observation of the healing progression.

Treatment Group

The rats were randomly assigned to five groups, with each group comprising five animals. The negative control group did not receive any topical intervention and was treated only by rinsing the wound with a 0.9% NaCl solution. The first positive control group was given povidone–iodine ointment, while the second positive control group received bioplacenton ointment. The two treatment groups were administered combination ointments composed of bitter melon and tamarind extracts in ratios of 1:1 and 1:2, respectively. Wound care was carried out daily for 14 days, starting from the first day the wound was made. Before applying the ointment, the wound was cleaned using sterile NaCl solution without covering the wound to speed up the healing process.

Wound Care and Monitoring

Wounds in all groups were treated daily for 14 days between 8:00 and 16:00 WIB. Before applying the ointment, the wounds were cleaned with sterile 0.9% NaCl. Wound observations were performed daily using the REEDA scale, which assesses five parameters: Redness, Edema, Ecchymosis, Discharge, and Approximation. Wounds were considered completely healed if the total REEDA score was 0. On day 14, skin samples were taken for histopathological analysis.

Instrument

Skin tissue samples from the wound area were collected on day 14 and immediately fixed in 10% neutral buffered formalin (NBF) for 24 hours. After fixation, the tissues were processed following standard paraffin-embedding procedures. The samples were dehydrated using a graded ethanol series (70%, 80%, 90%, and 100%), followed by clearing with xylene, and then embedded in paraffin blocks. Tissue sections with a thickness of 4–5 µm were subsequently prepared using a rotary microtome. For histopathological evaluation, the sections were placed on glass slides, deparaffinized with xylene, rehydrated through decreasing concentrations of ethanol, and stained using the Hematoxylin–Eosin (HE) method. Hematoxylin was applied to highlight cell nuclei, followed by eosin to stain the cytoplasm and extracellular matrix. The stained slides were then dehydrated, cleared, and mounted with coverslips for microscopic examination.

Microscopic examination was conducted using a light microscope (Olympus CX23) at magnifications of 100× and 400× to observe epithelialization, fibroblast density, collagen arrangement, and inflammatory cell infiltration. All histopathological examinations were carried out at the Anatomical Pathology Laboratory of Hasanuddin University Hospital following standard procedures.

Data Collection and Analysis

All REEDA scale observational data were documented on observation sheets and subsequently processed using SPSS version 24.0. Data normality was evaluated with the Kolmogorov–Smirnov test. If the dataset fulfilled the assumptions of normality and homogeneity, a one-way ANOVA was employed; otherwise, the Kruskal–Wallis test was

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

conducted. A p-value of <0.05 was interpreted as statistically significant.

Ethical Considerations and the 3R Principles
To comply with animal research ethics, this study adopted the 3R principle: replacement (avoiding the use of animals whenever possible), reduction (using a minimum number of test animals based on Federer's formula, namely 5 animals per group), and refinement (reducing pain and stress through the use of anesthesia and non-invasive wound care methods). All procedures were carried out by qualified personnel and adhered strictly to established standard operating protocols.

Results and Discussion

Initial Characterization and Macroscopic Progress of Wound Healing
Phytochemical evaluation demonstrated that the extracts obtained from bitter melon and tamarind leaves contain several bioactive metabolites, including flavonoids, tannins, triterpenoids, and saponins, whereas alkaloid compounds were identified only in the bitter melon leaf extract (Table 1). These metabolites are closely associated with anti-inflammatory, antioxidant, and tissue-regenerative functions that facilitate wound repair. In particular, the flavonoids and triterpenoids present in bitter melon leaves are known to inhibit major inflammatory signaling pathways, including NF-κB and the NLRP3 inflammasome, thereby reducing the release of pro-inflammatory cytokines such as TNF-α and IL-6. Concurrently, these compounds enhance fibroblast activity and support collagen synthesis through the activation of TGF-β.[16,17] Collectively, these molecular actions accelerate tissue recovery and contribute to more effective wound-healing responses.
The combination ointments exhibited pH values between 5.48 and 5.54 (Table 2), which fall within the normal skin pH range of 4.5–6.5. Maintaining a pH close to physiological conditions is important because it supports skin homeostasis and reduces the likelihood of irritation. Formulations with a pH similar to that of healthy skin help preserve the integrity of the skin barrier and optimize the activity of wound-healing enzymes such as metalloproteinases, which mediate extracellular matrix degradation and remodeling during tissue repair.[18] An appropriate pH environment also promotes keratinocyte migration and sustains epidermal architecture—processes that are fundamental to the wound-healing sequence.[19] Findings reported by Martins et al. indicate that metalloproteinase function and keratinocyte mobility are highly influenced by the skin's microenvironment, including its pH. Consequently, topical preparations formulated near physiological pH can accelerate re-epithelialization and enhance the overall quality of wound recovery.[18]

Table 1: Results of phytochemical screening of bitter melon and tamarind leaf extracts

Phytochemical Compounds	Bitter Melon Leaf Extract	Tamarind Leaf Extract
Alkaloid	(+)	(–)
Flavonoid	(+)	(+)
Tannin	(+)	(+)
Triterpenoid	(+)	(+)
Saponin	(+)	(+)

Table 2: PH value of ointment preparation combining bitter melon and tamarind leaf extracts

Topical Dosage Formulation	pH value
1:1 Combination Ointment	5.54
1:2 Combination Ointment	5.48

The Effect of Extract Combinations on the Wound Healing Process
The median duration of wound closure revealed that the 1:1 combination of bitter melon and tamarind leaf extracts produced the quickest recovery, with healing occurring within 7 days. This was followed by the 1:2 combination and Bioplacenton, both requiring 8 days (Table 3). In comparison, Betadine required 9 days to achieve wound closure, whereas the negative control group (ointment base) exhibited the slowest recovery, taking 14 days. These results indicate that both herbal extract formulations are more efficient in accelerating the inflammatory phase and promoting the transition to the proliferative stage of wound healing. *Momordica charantia* has also been documented to stimulate angiogenesis and enhance fibroblast migration, which aligns with the findings observed in this study.
The Kruskal–Wallis analysis revealed a significant difference across the treatment groups (p = 0.000), with the greatest disparity observed between the combination-ointment groups and the negative control (Table 4). The 1:1 Combination group recorded the lowest mean rank, reflecting the most rapid wound healing, whereas the Ointment Base group displayed the highest mean rank, indicating a marked delay in the healing progression. These results align with previous findings by Chairul et al. and Manjula & Thirumal who reported that herbal combination ointments enriched with bioactive compounds such as flavonoids and polyphenols provide superior benefits compared to conventional antiseptic formulations by enhancing granulation tissue formation, accelerating epithelialization, and markedly increasing the rate of wound closure.[20,21]

Table 3: Median distribution of incision wound healing time

Treatment Group	n	Median Duration of Healing (Days)
Combination of Bitter Melon Leaves and Tamarind Leaves (1:1)	5	7
Combination of Bitter Melon Leaves and Tamarind Leaves (1:2)	5	8
Bioplacenton	5	8
Betadine	5	9
Ointment Base (Negative Control)	5	14

Table 4: Length of wound healing based on ointment treatment group on female Wistar rats

Variables	n	Mean rank	Chi-Square	df	p-value*
Combination of Bitter Melon Leaves and Tamarind Leaves (1:1)	5	4.20	20.013	4	0.000
Combination of Bitter Melon Leaves and Tamarind Leaves (1:2)	5	10.50			
Ointment Base	5	23.00			
Betadine	5	16.80			
Bioplacenton	5	10.50			

* Kruskal–Wallis test

The Mann–Whitney test results (Table 5) confirmed the significant difference between the (1:2) Combination with Ointment Base (p = 0.007), and the (1:2) Combination with Betadine (p = 0.032), but not significantly with Bioplacenton (p = 1.000). This indicates that the effectiveness of the herbal extract combination is equivalent to Bioplacenton, which has been used as a standard therapy for wounds. This difference also reflects that the healing effect does not solely depend on antiseptic properties, but also on tissue regenerative capacity. Another study by oleh Mulyati et al. showed that the combination of *Tinospora crispa* extract and natural zeolite significantly accelerated wound closure in a diabetic ulcer model (p = 0.002), confirming the potential of the herbal combination in accelerating the tissue regeneration process.[22] The use of *panchavalkala* extract has also been clinically proven to reduce infection and accelerate wound debridement, making it an effective alternative to conventional allopathic ointments.[23]

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 5: Post hoc test of wound healing time based on ointment treatment group on female Wistar rats

Variables	Mean Rank A	Mean Rank B	p-value*
Combination of bitter melon leaves and tamarind leaves (1:1) vs Combination of bitter melon leaves and tamarind leaves (1:2)	3.60	7.40	0.031
Combination of bitter melon leaves and tamarind leaves vs basic ointment	3.00	8.00	0.007
Combination of bitter melon leaves and tamarind leaves vs betadine	3.00	8.00	0.007
Combination of bitter melon leaves and tamarind leaves vs bioplacenton	3.60	7.40	0.031
Combination of bitter melon leaves and tamarind leaves (1:2) vs Basic Ointment	3.00	8.00	0.007
Combination of bitter melon leaves and tamarind leaves (1:2) vs Bethadin	3.60	7.40	0.032
Combination of bitter melon leaves and tamarind leaves (1:2) vs Bioplacenton	5.50	5.50	1.000
Ointment Base vs Betadine	8.00	3.00	0.007
Ointment Base vs Bioplacenton	8.00	3.00	0.007
Betadine vs Bioplacenton	7.40	3.60	0.32

* Mann-Whitney test

Histopathological Evaluation and Pharmacological Mechanism

The histopathological results supported the quantitative and macroscopic data. On day 14, the tissues from the Combination (1:1) and (1:2) groups showed good morphology with almost perfect epithelial layers and regular dermis formation (Figures a and b). Collagen fibers appeared dense, parallel, and dominant, and the number of fibroblasts increased significantly compared to the control group (Figure c). The Bioplacenton group also showed good tissue structure (Figure e), while the Betadine (Figure d) and Ointment Base (Figure c) groups still showed signs of inflammation and immature granulation tissue.

The flavonoid constituents of bitter melon together with the tannins present in tamarind exert complementary actions in modulating inflammation and promoting tissue repair. Flavonoids have been shown to upregulate VEGF, stimulate angiogenesis, and support re-epithelialization and collagen formation through activation of key molecular pathways, including TGF-β, PI3K/Akt, and MAPK/ERK.[24] These compounds also downregulate pro-inflammatory cytokines such as TNF-α and IL-6, inhibit NF-κB signaling, and attenuate oxidative stress by increasing antioxidant enzyme activity and decreasing ROS levels.[25] Additionally, tannins contribute an astringent effect that enhances wound contraction, reinforces tissue strength, and functions as both an antioxidant and anti-inflammatory agent, thereby promoting cell migration and facilitating extracellular matrix remodeling.[26] The synergistic antioxidant properties of flavonoids and tannins are essential in diminishing oxidative stress—one of the primary barriers to the healing of chronic wounds—and collectively contribute to a faster and more effective tissue-repair process.[24–26]

Triterpenoids such as *cucurbitacin B*, found in bitter melon leaves, have been reported to enhance fibroblast activity and prevent collagen degradation, thereby promoting the synthesis and maintenance of type I collagen—an essential structural component required for connective tissue maturation and the reinforcement of skin architecture after injury. Lou et al. further demonstrated that *cucurbitacin B* mitigates inflammation and oxidative damage through activation of the Nrf2/HO-1 signaling pathway, contributing to tissue protection and improved regenerative capacity.[27] In addition, coordinated interactions between fibroblasts and keratinocytes are fundamental to the wound-repair process: fibroblasts secrete growth factors and extracellular matrix elements, while keratinocytes facilitate re-epithelialization and restore the integrity of the skin surface.

The saponins present in various plants further enhance tissue regeneration by increasing cell membrane permeability and promoting mitotic activity in keratinocytes, thus facilitating faster wound closure through stimulated cell proliferation and migration.[28]

A comparison with Bioplacenton and Betadine shows that although both commercial preparations have healing activity, the herbal combination offers a broader regenerative effect. Bioplacenton contains placental extract and neomycin, which act as anti-inflammatory and antibacterial agents, making it effective in reducing inflammation and preventing wound infection.[29] However, Bioplacenton does not have a direct stimulatory effect on fibroblast proliferation as found in certain herbal combinations, which can increase fibroblast activity and accelerate new tissue formation.[30] Meanwhile, Betadine is indeed effective as an antiseptic, but its long-term use can cause tissue irritation and does not actively accelerate the process of epithelialization or skin tissue regeneration.[31]

Flavonoids primarily exert their effects during the inflammatory and proliferative stages of wound repair, whereas vitamin C and tannins play a major role in the remodeling process and in promoting collagen formation. Evidence from Riaz et al. further demonstrates that formulations incorporating multiple phytochemicals provide an effective therapeutic strategy for managing both acute and chronic wounds because of their diverse mechanisms of action. A synergistic blend of compounds—including β-sitosterol, tannic acid, gallic acid, quercetin, and ellagic acid—can enhance angiogenesis, stimulate granulation tissue formation, boost collagen production, regulate oxidative balance, and facilitate cell migration, proliferation, and differentiation throughout the wound healing cascade.[32]

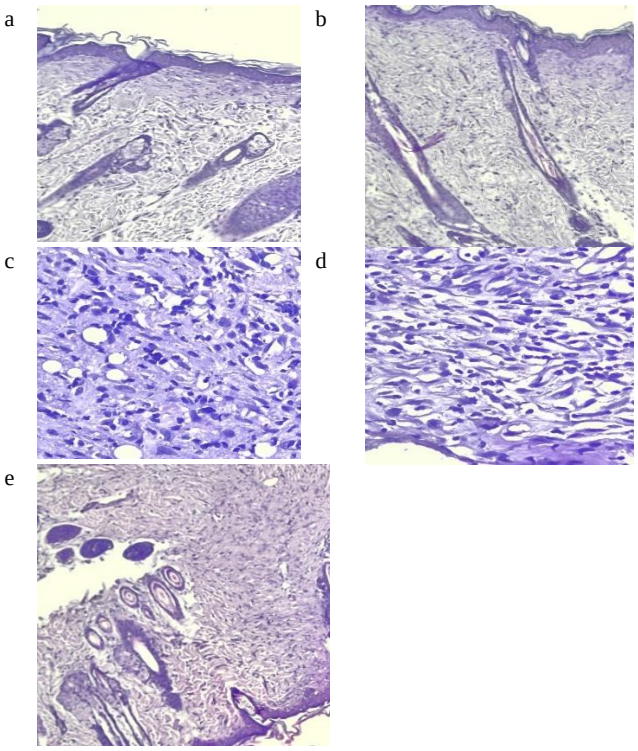

Figure 1: Histological characteristics of wound tissue after 14 days of treatment.
Panels: (a) Combination ointment 1:1 showing re-epithelialization and dense collagen fibers; (b) Combination ointment 1:2 showing well-organized dermal structure; (c) Basic ointment showing incomplete epithelialization and persistent inflammation; (d) Betadine group showing moderate epithelial layer formation; (e)

Bioplacenton group showing mature collagen bundles. All micrographs at 400× magnification.

Conclusion

A topical ointment formulated with combined extracts of bitter melon (*Momordica charantia*) and tamarind (*Tamarindus indica*) leaves markedly enhanced the wound healing process in female Wistar rats. The observed therapeutic benefits included shortened healing duration, greater re-epithelialization, and improved histological characteristics of the regenerating tissue. The extract mixture at a 1:1 ratio produced the most optimal outcome, demonstrating effectiveness comparable to Bioplacenton and significantly outperforming Betadine as well as the untreated control group. These healing properties are believed to arise from the actions of flavonoids, tannins, and triterpenoids, which mediate anti-inflammatory, antioxidant, and collagen-promoting mechanisms. Further investigations are advised to elucidate the specific molecular mechanisms governing these phytochemical interactions and to assess their potential effectiveness within clinical wound-healing settings in humans.

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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ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

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