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EFFECT OF *FICUS DELTOIDEA* JACK. TO NEUTROPHIL AND MACROPHAGE CELLS IN ORAL WOUND HEALING

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ABSTRACT

Background*: Oral mucosal wounds require effective inflammatory control for optimal healing. However, conventional agents such as povidone-iodine may cause irritation and cytotoxicity, limiting their use. Ficus deltoidea, a medicinal plant from Kalimantan, possesses antimicrobial, antioxidant, and anti-inflammatory properties, making it a promising alternative for oral wound therapy.* ***Objectives:*** *To evaluate the effect of Ficus deltoidea leaf extract gel on neutrophil and macrophage cells in oral mucosal wound healing.* ***Methods****: A true experimental posttest-only control group study was conducted on 48 male Wistar rats. Standardized buccal mucosal wounds were treated with Ficus deltoidea J. leaf extract gel (GEDTB) 5%, 10%, 15% or gel base (control). Animals were sacrificed on days 1, 3, and 7, and neutrophil and macrophage counts were assessed histopathologically. Data were analyzed using two-way ANOVA with Bonferroni post hoc.* ***Results****: Neutrophil counts decreased significantly over time in all groups, with a faster reduction in extract-treated groups, particularly at 15%. On day 1, the control group had the highest neutrophil count, significantly greater than the 15% group ($p<0.05$), while by day 7, all treatment groups showed significantly lower neutrophil levels than control. Macrophage counts increased from day 1, peaked on day 3—highest in the 15% group—and declined significantly by day 7. Both treatment and time had significant effects on neutrophil and macrophage counts ($p<0.05$), with a significant interaction observed for macrophages.* ***Conclusion****: Ficus deltoidea J. leaf extract gel effectively modulates inflammatory cell by accelerating neutrophil reduction and enhancing macrophage activity in oral wound healing.*

Keywords: Anti-inflammatory activity, *Ficus deltoidea* jack.,Macrophages, Neutrophils, Oral wound healing

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INTRODUCTION

Oral and dental treatments frequently induce mucosal injuries, commonly referred to as stomatitis, which present as open lesions within the oral cavity. These lesions often interfere with mastication, speech, and oral hygiene practices due to associated pain and discomfort. The global prevalence of stomatitis ranges from 5% to 25%.[1] Although the exact etiology of oral mucosal inflammation remains unclear, it is multifactorial, involving trauma (e.g., accidental biting or mechanical injury), infections, hematological disorders, immunological disturbances, nutritional deficiencies, hormonal imbalance, psychological factors, and systemic conditions such as HIV infection. Current management strategies primarily focus on symptomatic relief, particularly reducing inflammation and pain, to accelerate healing and tissue recovery.[2]

Conventional treatments for stomatitis include antibiotics, antiseptics, and antimicrobial agents such as povidone-iodine. Although widely used and generally safe for minor wounds, povidone-iodine may induce local irritation and exert cytotoxic effects on fibroblasts and leukocytes. Consequently, there is increasing interest in alternative therapies using natural products with fewer adverse effects.[2,3] One such potential candidate is *Ficus deltoidea* Jack., locally known as Tabat Barito, a medicinal plant native to Kalimantan, Indonesia.[4] Ethnobotanical evidence suggests that this plant possesses anti-inflammatory and antioxidant properties, supporting its use in wound management.[5]

Phytochemical analyses have demonstrated that *Ficus deltoidea* leaves contain significant amounts of bioactive compounds, including alkaloids (154.31 ± 5.85 mg/ml), phenolics (99.689 ± 0.139 mg/ml), flavonoids (62.917 ± 0.382 mg/ml), and steroids (49.036 ± 0.473 mg/ml).[6] These compounds contribute to its antimicrobial, anti-inflammatory, antioxidant, and wound healing activities.[5] Previous studies have shown that *Ficus deltoidea* extract at concentrations of 5%, 10%, and 15% exhibits antifungal activity against *Candida albicans,* while higher concentrations (15%) demonstrate strong antibacterial effects against *Bacillus subtilis* and *Staphylococcus aureus,*[7] which are commonly implicated in oral infections such as stomatitis and gingivitis. The antimicrobial properties of plant-derived compounds are considered highly beneficial in enhancing wound healing by reducing microbial burden.

Wound healing is a complex physiological process involving coordinated vascular and cellular responses, generally categorized into three overlapping phases: inflammation, proliferation, and remodeling. Neutrophils and macrophages play critical roles in regulating the inflammatory phase. Neutrophils are the first immune cells recruited to the injury site, appearing within 4–12 hours post-injury and peaking at 24–48 hours, followed by a gradual decline as they undergo apoptosis and are replaced by macrophages within approximately 72 hours.[8,9] Macrophages become dominant during days 2–3 and subsequently decrease between days 5 and 7. However, progression to the proliferative phase can only occur after the resolution of inflammation; thus, excessive or prolonged inflammatory responses can significantly impair wound healing.[10]

Bioactive compounds such as alkaloids, flavonoids, and phenolics are found in *Ficus deltoidea* J. and known to modulate inflammatory responses and promote healing. Alkaloids exhibit antimicrobial activity by disrupting bacterial metabolism and enhancing neutrophil function.[11] Phenolic compounds act as antioxidants by scavenging reactive oxygen species (ROS), thereby reducing oxidative stress while maintaining their role in bacterial phagocytosis.[12] Flavonoids have been shown to inhibit cyclooxygenase and lipoxygenase pathways, leading to reduced production of prostaglandins and leukotrienes, which in turn decreases neutrophil migration and shortens the inflammatory phase.[13] Based on these findings, *Ficus deltoidea* leaf extract demonstrates promising anti-inflammatory, antimicrobial, and antioxidant properties that may enhance oral wound healing. However, its effects on inflammatory cell dynamics, particularly neutrophil and macrophage responses, remain insufficiently explored. Therefore, this study aimed to evaluate the effect of *Ficus deltoidea* leaf extract gel at concentrations of 5%, 10%, and 15% on neutrophil and macrophage counts during oral mucosal wound healing in male Wistar rats (*Rattus norvegicus*) on days 1, 3, and 7.

MATERIALS AND METHODS

This study employed a true experimental design using a posttest-only control group approach . Ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Dentistry, Universitas Lambung Mangkurat, Banjarmasin (No. 094/KEPKG-FKGULM/EC/IX/2023). The study was conducted from September to November 2023 at the Laboratory of Mathematics and Natural Sciences, Universitas Lambung Mangkurat; the Laboratory of Chemistry and Pharmaceutical Technology, Universitas Sari Mulia; and the Anatomical Pathology Laboratory, RSUD Ulin Banjarmasin.

Sample size was calculated using the analytical formula for numerical data with more than two independent groups,[14] resulting in 48 male Wistar rats. Inclusion criteria were male sex, age 2–3 months, and healthy condition characterized by normal feeding, drinking, and activity without visible defects. Exclusion criteria included death during the study and clinical signs of illness such as inactivity, anorexia, or dull and shedding fur.

Preparation of *Ficus deltoidea* Leaf Extract

Fresh mature leaves (2 kg) were collected, washed, and oven-dried at 40–50°C for 4 hours to obtain 200 g of dried material. The dried leaves were ground and sieved to produce 130 g of simplicia powder. Extraction was performed using the maceration method with 98% methanol for 3 × 24 hours under intermittent agitation, followed by daily filtration using WH40 filter paper. The filtrate was concentrated using a rotary evaporator at 50–60°C for 4–6 hours and further evaporated in a water bath to obtain 13.44 g of crude extract. Methanol-free verification was conducted using UV/VIS spectrophotometry; the absence of ester odor indicated successful removal of methanol.

Preparation of Gel Base and Extract Formulations

The gel base composition was prepared following Handbook of Pharmaceutical Excipient 5th Edition and Remington: The Science and Practice of Pharmacy by heating distilled water (ad 100 mL) at 50°C, followed by the addition of Na-CMC (5 g), glycerin (10 g), and propylene glycol (5 g), and mixing until a homogeneous gel was formed.[15,16] The extract was incorporated into the gel base to produce concentrations of 5%, 10%, and 15%, with each formulation prepared in 25 g batches. A gel base without extract was used as the control.

Animal Treatment

Forty-eight Wistar rats were randomly assigned into 12 groups (n = 4 per group) and acclimatized for 7 days under controlled conditions (25–28°C, adequate ventilation) with standard diet (BR2 Comfeed) and water ad libitum. Prior to wounding, animals were anesthetized via intramuscular injection of xylazine hydrochloride (2 mg/kg) and ketamine hydrochloride (20 mg/kg). A standardized incision (±10 mm length, ±1 mm depth) was

created on the left buccal mucosa using a sterile scalpel (blade No. 11). The wound was cleaned with sterile cotton soaked in distilled water and dried using sterile cotton buds.

Animals received topical applications of *Ficus deltoidea* extract gel (GEDTB): 5% (groups 1–3), 10% (groups 4–6), 15% (groups 7–9), and gel base control (groups 10–12). Treatments were applied twice daily (0.5 g at 08.00 in the morning and 0.5 g at 16.00 in the afternoon) on days 1, 3, and 7.

Euthanasia was performed using intraperitoneal administration of ketamine (60 mg/kg) and xylazine (6 mg/kg) at three times the anesthetic dose, following AVMA guidelines.[17] Tissue samples were collected on day 1 (groups 1, 4, 7, 10), day 3 (groups 2, 5, 8, 11), and day 7 (groups 3, 6, 9, 12). Buccal mucosal tissue was excised using biopsy techniques,[18] and carcasses were disposed of according to laboratory animal handling protocols.[19]

Histopathological Preparation

Tissue samples were fixed in 10% buffered neutral formalin for approximately 24 hours, followed by dehydration using tissue processing for ±18 hours. Samples were embedded in paraffin using base molds and cooled, then sectioned at 5 µm thickness using a microtome. Sections were placed in a water bath (37–47°C), mounted on glass slides, dried, and stained using hematoxylin–eosin (HE).[20]

Observation and Cell Counting

Histopathological evaluation was performed using a light microscope (Leica DM 1000). Neutrophils and macrophages were counted under 400× magnification (40× objective and 10× ocular) across five fields of view. The number of cells in each field was recorded, and the mean count for each group was calculated based on the average of observations from three blinded independent observers with backgrounds in biomedical laboratory science and oral biology. Neutrophils were morphologically characterized by neutrophils are characterized by a multilobed nucleus (typically 2–5 lobes) and pale pink to lightly stained cytoplasm containing fine granules. Macrophages characterized by an oval or kidney-shaped nucleus with a reddish-stained cytoplasm, indicating early differentiation of monocytes into macrophages.

Statistical Anlysis

The research data were first tested for normality using the Shapiro–Wilk test, as the sample size consisted of 48 observations (<50), and for homogeneity of variances using Levene's test. Data that were normally distributed and homogeneous ($p > 0.05$) were further analyzed using a parametric two-way ANOVA to determine significant differences between treatment groups. Post-hoc analysis was performed using the Bonferroni test to identify which groups showed significant differences. All statistical analyses were conducted using SPSS software.[14]

RESULTS

Histopathological examination using hematoxylin–eosin staining revealed the presence of neutrophils and macrophages in all experimental groups at each observation time. On day 1, neutrophil accumulation was prominent as part of the acute inflammatory response, with the highest counts observed in the control (base gel) group. Over time, neutrophil numbers decreased by day 3 across all groups, indicating a transition from the inflammatory to the proliferative phase. This decline became more pronounced by day 7, when neutrophil counts were minimal due to resolution of inflammation, with the greatest reduction observed in the GEDTB 15% group.

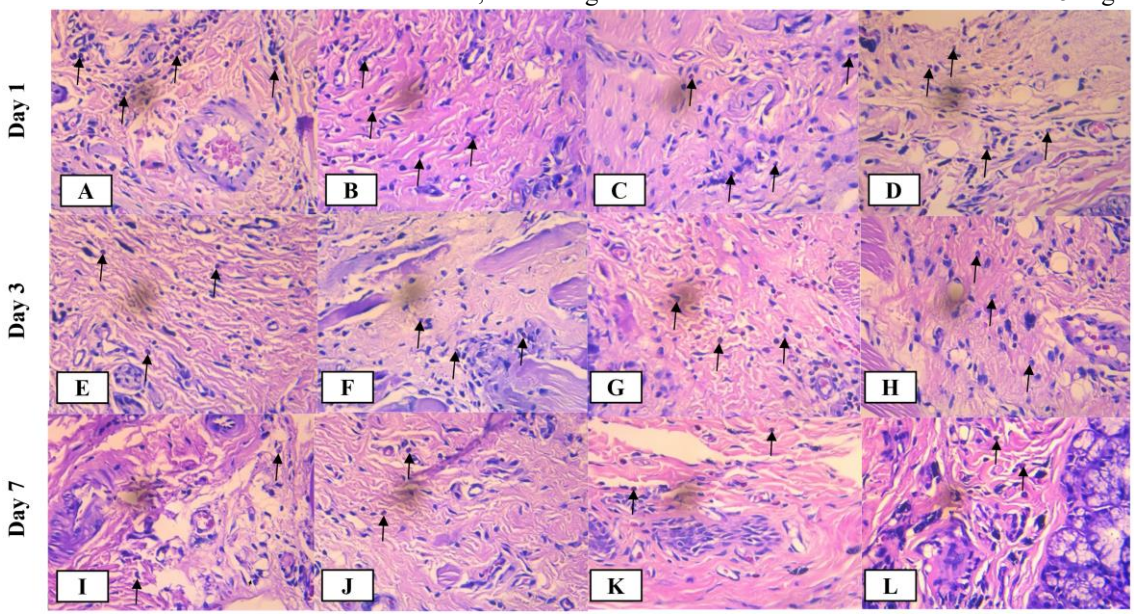

Figure 1. Representative histopathological images of neutrophil cells in GEDTB 5% (A, E, I), GEDTB 10% (B, F, J), GEDTB 15% (C, G, K), and control (base gel) (D, H, L) groups at different observation times: day 1 (I–L), day 3 (E–H), and day 7 (A–D) (hematoxylin–eosin staining, 400× magnification); black arrows indicate neutrophils.

Quantitatively, the mean neutrophil count demonstrated a decreasing trend from day 1 to day 7 in all groups (Table 1). Shapiro–Wilk testing confirmed normal data distribution ($p > 0.05$), and Levene's test indicated homogeneity of variance ($p > 0.05$). Bonferroni post hoc analysis demonstrated significant differences between day 1 and day 7, as well as between day 3 and day 7 across all groups ($p < 0.05$), although some intergroup comparisons were not statistically significant. On day 1, the control group showed the highest neutrophil count (11.00 ± 1.60^{b}), which was significantly higher than the GEDTB 15% group (9.25 ± 0.50^{a}) ($p < 0.05$), while the GEDTB 5% and 10% groups (9.80 ± 2.02^{ab} and 9.50 ± 0.47^{ab}, respectively) were not significantly different from either group. On day 3, the control group (9.15 ± 1.06^{b}) remained significantly higher than all treatment groups (GEDTB 5%, 10%, and 15%), which showed no significant differences among themselves (all ^{a}). By day 7, neutrophil counts were lowest in the GEDTB-treated groups (GEDTB 5%, 10%, and 15%; all ^{b}), with no significant differences among them. However, these values were significantly lower than the control group (4.55 ± 1.20^{c}) ($p < 0.05$). Overall, neutrophil counts declined more rapidly in the GEDTB-treated groups compared to the control, indicating a faster resolution of the inflammatory phase. Two-way ANOVA revealed significant differences based on treatment group ($p = 0.014$) and observation time ($p = 0.000$), with no significant interaction between the two factors ($p > 0.05$).

Table 1. Mean ± standard deviation (SD) of neutrophil and macrophage counts in each treatment group (GEDTB 5%, GEDTB 10%, GEDTB 15%, and control [base gel]) on days 1, 3, and 7.

Group	Neutrophils			Macrophages		
	Day 1	Day 3	Day 7	Day 1	Day 3	Day 7
GEDTB 5%	9,80 ± 2,02^{ab}	7,95 ± 1,07^{a}	3,35 ± 1,50^{b}	6,01 ± 1,90^{b}	11,00 ± 0,99^{b}	4,01 ± 0,91^{b}
GEDTB 10%	9,50 ± 0,47^{ab}	7,65 ± 1,87^{a}	2,80 ± 1,48^{b}	7,00 ± 1,22^{b}	12,16 ± 2,47^{b}	3,21 ± 0,67^{a}
GEDTB 15%	9,25 ± 0,50^{a}	7,30 ± 2,57^{a}	2,25 ± 0,25^{b}	8,05 ± 2,89^{c}	14,99 ± 1,91^{c}	2,63 ± 0,34^{a}
Control (BG)	11,00 ± 1,60^{b}	9,15 ± 1,06^{b}	4,55 ± 1,20^{c}	5,48 ± 1,83^{a}	7,08 ± 1,30^{a}	4,45 ± 1,38^{b}

^{a}significantly different from groups with superscripts b and c ($p < 0.05$); ^{b}significantly different from groups with superscripts a and c ($p < 0.05$); ^{c}significantly different from groups with superscripts a and b ($p < 0.05$); same superscript letters within the same column are not significantly different

Macrophages were also observed in all groups starting from day 1. By day 3, macrophage counts increased in all groups and reached their peak, particularly in the GEDTB 15% group, reflecting their active role in the late inflammatory phase and transition to the proliferative phase. On day 7, macrophage counts declined across all groups, indicating resolution of inflammation and progression toward the proliferative and early remodeling phases of wound healing

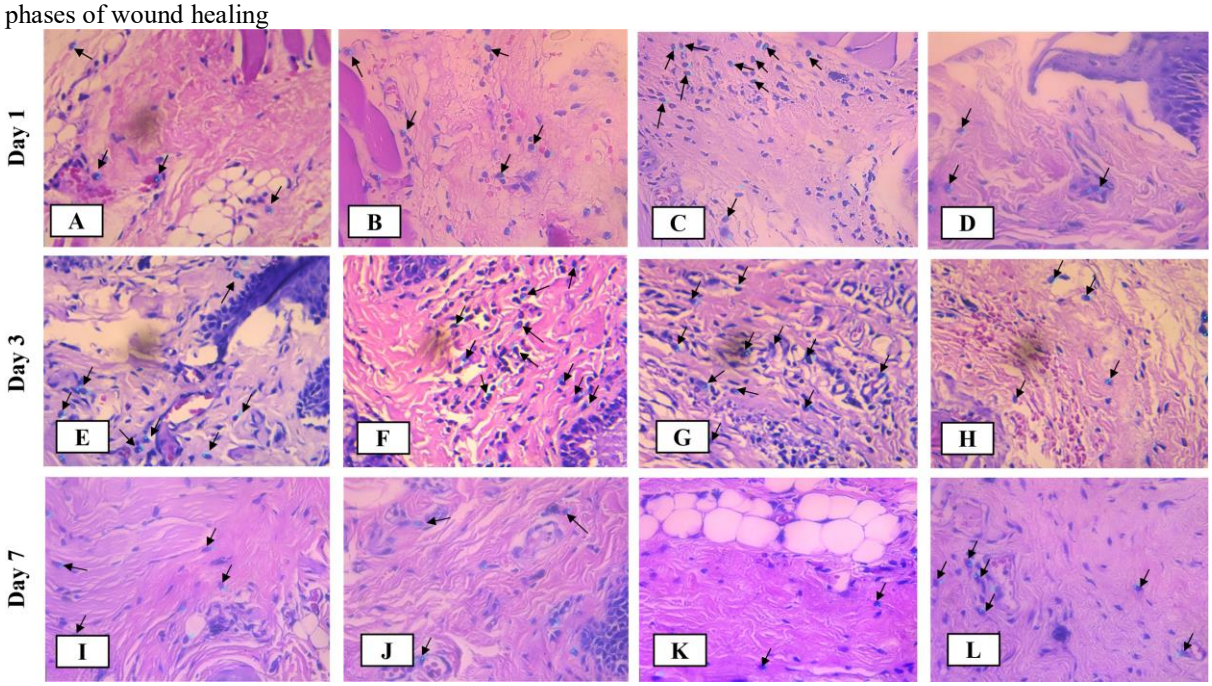

Figure 2. Representative histopathological images of macrophage cells in GEDTB 5% (A, E, I), GEDTB 10% (B, F, J), GEDTB 15% (C, G, K), and control (base gel) (D, H, L) groups arranged by observation time: day 1 (A–D), day 3 (E–H), and day 7 (I–L) (hematoxylin–eosin staining, 400× magnification); black arrows indicate macrophages.

Quantitatively, macrophage counts increased from day 1 to day 3 and decreased by day 7 (Table 1). Normality testing indicated normally distributed data ($p = 0.087$), and homogeneity testing showed homogeneous variance ($p = 0.053$). On day 1, the GEDTB 15% group exhibited the highest macrophage count (8.05 ± 2.89^{c}), which was significantly higher than the GEDTB 5% and 10% groups (6.01 ± 1.90^{b} and 7.00 ± 1.22^{b}, respectively), as well as the control group (5.48 ± 1.83^{a}) ($p < 0.05$). The GEDTB 5% and 10% groups were not significantly different from each other but were both significantly higher than the control. A similar pattern was observed on day 3, where the GEDTB 15% group (14.99 ± 1.91^{c}) remained significantly higher than the GEDTB 5% and 10% groups (11.00 ± 0.99^{b} and 12.16 ± 2.47^{b}, respectively), which in turn were significantly higher than the control group (7.08 ± 1.30^{a}) ($p < 0.05$). By day 7, macrophage counts decreased in all groups. The GEDTB 10% and 15% groups (3.21 ± 0.67^{a} and 2.63 ± 0.34^{a}, respectively) showed no significant difference between them but were significantly lower than the GEDTB 5% group (4.01 ± 0.91^{b}) and the control group (4.45 ± 1.38^{b}) ($p < 0.05$). Overall, macrophage counts increased in a dose-dependent manner during the early phase (days 1–3) and declined more rapidly in the higher concentration groups (10% and 15%) by day 7, suggesting enhanced inflammatory response followed by accelerated resolution. Two-way ANOVA demonstrated significant differences based on treatment group ($p = 0.002$) and observation time ($p = 0.000$), with significant interaction between treatment*observation time ($p < 0.05$).

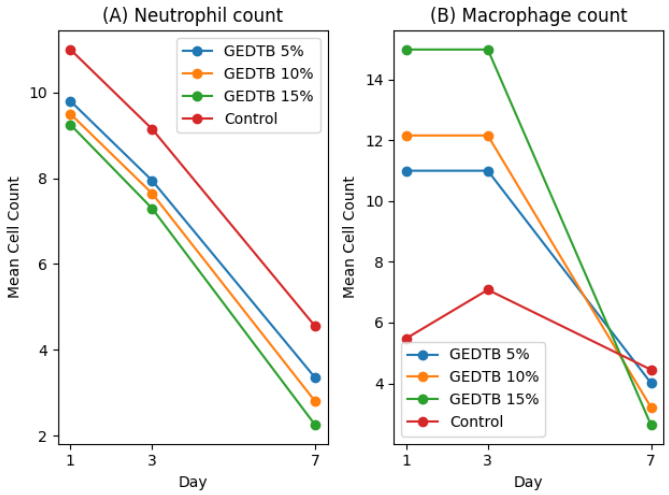

Figure 3. Mean number of inflammatory cells during wound healing. (A) Neutrophil count and (B) macrophage count in each treatment group on days 1, 3, and 7.

Overall, the administration of *Ficus deltoidei* J. leaf extract gel demonstrated a concentration-dependent effect on inflammatory cell dynamics. Higher concentrations, particularly 15%, were more effective in reducing neutrophil counts and enhancing macrophage responses during the early phase of wound healing, thereby accelerating the transition from the inflammatory phase to the proliferative phase.

DISCUSSION

The Two-Way ANOVA results demonstrated that the administration of *Ficus deltoidea* leaf extract gel (GEDTB) exerted a significant effect on neutrophil and macrophage counts during the wound healing process of Wistar rat oral mucosa on days 1, 3, and 7. On day 1, an increase in neutrophil count was observed across all groups, with the highest value in the control (gel base) group (11.00). This finding is consistent with Kurniawati et al. (2020), who reported that the highest neutrophil levels during the early inflammatory phase occur in control groups. Notably, the neutrophil response in the treatment groups had already peaked earlier, within 6–12 hours post-injury,[21–23] resulting in a lower neutrophil count at the 24-hour observation compared to the control.[23,24] This pattern reflects the typical acute inflammatory response, in which neutrophils are the first responders, rapidly peak, and subsequently decline due to apoptosis and macrophage-mediated phagocytosis.

The more rapid reduction in neutrophil count observed in the GEDTB groups, particularly at the 15% concentration, is likely associated with the presence of bioactive compounds such as alkaloids and phenolics. Alkaloids are known to accelerate the resolution of inflammation by modulating enzymatic activity and promoting tissue repair.[25] Meanwhile, phenolic compounds inhibit the leakage of macromolecules from the microcirculation and reduce edema, thereby limiting neutrophil infiltration.[26] These mechanisms facilitate a faster transition from the inflammatory to the proliferative phase.

By day 3, neutrophil counts in the GEDTB 5%, 10%, and 15% groups were significantly lower than in the control group, with the greatest reduction observed at 15% concentration. This indicates that GEDTB effectively suppresses excessive inflammatory responses. The reduction is associated with the antioxidant activity of alkaloids, which inhibit the synthesis of pro-inflammatory cytokines such as IL-1 and TNF-α, thereby reducing

vasodilation, capillary permeability, and neutrophil adhesion to the vascular endothelium.[27] Consequently, decreased adhesion leads to reduced neutrophil infiltration into the wound site, accelerating the resolution of inflammation.

Concomitant with the decrease in neutrophils, macrophage counts increased on day 1 and peaked on day 3. Macrophages typically appear within 5–6 hours after the onset of inflammation and play a central role in the later inflammatory phase.[8–10] In this study, the highest macrophage count was observed in the GEDTB 15% group, suggesting that the bioactive compounds in *Ficus deltoidea* extract enhance macrophage activity. This is supported by Noor et al. (2015),[28] who reported that alkaloids exhibit antimicrobial properties that enhance macrophage phagocytosis through nitric oxide (NO) production. Furthermore, macrophages secrete cytokines and growth factors that facilitate pathogen clearance and accelerate the inflammatory phase.

The antioxidant activity of alkaloids also contributes to the neutralization of reactive oxygen species (ROS), thereby inhibiting the activation of inflammatory mediators such as TNF-α, COX-2, and NF-κB.[21] In addition, alkaloids promote growth factor secretion and fibroblast recruitment, enhancing epithelialization.[29] Flavonoids further contribute through their antioxidant and anti-inflammatory properties by inhibiting cyclooxygenase and lipoxygenase enzymes, reducing inflammatory mediators and facilitating progression to the proliferative phase.[13]

On day 3, elevated macrophage levels indicate peak activity in angiogenesis, fibroplasia, and granulation tissue formation. Reduced macrophage counts are associated with delayed wound healing due to decreased growth factor production and collagen synthesis.[29] Alkaloids have also been shown to enhance IL-1 secretion by monocytes, a key mediator in accelerating wound healing.[11]

By day 7, both neutrophil and macrophage counts decreased across all groups. The reduction in neutrophils is attributed to their short lifespan (24–48 hours) and subsequent phagocytosis by macrophages,[9] while the decline in macrophages indicates the resolution of inflammation and transition to the proliferative phase.[8–10] This decrease is essential, as prolonged inflammatory cell presence may impair healing. Phenolic compounds in *Ficus deltoidea* extract further support inflammation resolution by inhibiting TNF-α and NF-κB signaling pathways.[12]

In normal acute wound healing, macrophage populations increase rapidly within the first 2–3 days and remain elevated until approximately day 5, after which their numbers progressively decrease as inflammation resolves and tissue repair begins.[8–10] This decline is associated with reduced inflammatory activity and the shift of macrophage phenotype from pro-inflammatory (M1) to pro-healing (M2), facilitating fibroblast activation, angiogenesis, and epithelial regeneration.[30] Therefore, the earlier reduction in macrophage count observed in this study may indicate that *Ficus deltoidea* extract accelerates inflammation resolution and promotes faster progression to the proliferative phase, resulting in earlier tissue repair dynamics compared to the typical healing timeline. Despite these findings, this study has several limitations. The assessment of wound healing dynamics was limited to neutrophil and macrophage counts, which primarily reflect the inflammatory phase and do not fully represent the complexity of the healing process especially the faster inflammatory resolution in this study. Therefore, future studies incorporating histomorphometric, immunohistochemical, and molecular analyses are needed to provide a more comprehensive understanding of the wound healing process and the therapeutic potential of *Ficus deltoidea* extract.

Overall, GEDTB—particularly at 15% concentration—demonstrated the most optimal effect in modulating inflammatory cell dynamics by accelerating neutrophil reduction and promoting controlled macrophage activity. These effects are attributed to bioactive compounds such as alkaloids, flavonoids, and phenolics, which exhibit antimicrobial, antioxidant, and anti-inflammatory properties. This finding is consistent with Rahayu et al. (2022),[7] who reported that higher extract concentrations yield greater antimicrobial efficacy. Compared to the control, GEDTB treatment resulted in a more regulated inflammatory response, thereby enhancing the efficiency and progression of wound healing. In conclusion, *Ficus deltoidea* leaf extract gel, particularly at 15% concentration, effectively modulates inflammatory cell dynamics by accelerating neutrophil resolution and optimizing macrophage activity, thereby promoting a more efficient and controlled wound healing process.

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