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EVALUATION OF (*Tinomiscium petiolare* HOOK.F. &THOMSON) EXTRACT OINTMENT ON INFLAMMATION AND ANGIOGENESIS DURING INCISION WOUND HEALING

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ABSTRACT
Wound incidence remains high worldwide and includes surgical injuries, burns, ulcers and trauma. National reports also show that abrasions and contusions account for more than half of wound complaints. These data indicate a continuing need for effective therapeutic approaches. Wound healing depends on a regulated inflammatory phase and sufficient angiogenesis, and disturbances in these processes can delay tissue repair. Natural compounds with anti-inflammatory and pro-angiogenic activity offer potential support. Tinomiscium petiolare contains flavonoids and alkaloids with documented roles in modulating inflammation and promoting vascular growth. Evidence regarding its effects on incision wounds is limited and requires systematic evaluation. This study aimed to evaluate the wound-healing effects of Tinomiscium petiolare extract ointment by examining inflammatory and angiogenic responses in incision wounds with and without Staphylococcus aureus infection. Twenty-four male Rattus norvegicus were randomized into four groups consisting of non-infected controls, infected controls, extract-treated non-infected rats and extract-treated infected rats. Standardized incision wounds were created, infection was induced in designated groups and the extract ointment was applied to treatment groups. Tissue samples were collected on days 3 and 7 to measure TNF-α expression, macrophage infiltration and blood vessel formation. Statistical analysis included normality testing, variance homogeneity testing and comparative analyses with post-hoc procedures when required. TNF α levels showed no group differences on day 7. Temporal analysis demonstrated significant reductions from day 3 to day 7 in T3 and T4 ($p < 0.05$). Macrophage infiltration differed among groups ($p = 0.044$), and post-hoc analysis indicated significantly lower macrophage counts in T4 compared with T1 after Bonferroni correction. Blood vessel density also varied among groups ($p = 0.019$), and temporal evaluation showed a progressive increase in angiogenesis in T4 from day 3 to day 7, although pairwise comparisons did not reach statistical significance. The extract modulated inflammatory activity and supported angiogenic progression, with the strongest effects in infected wounds treated with the ointment.

Keywords: blood vessel; gamat extract; tnf-α; macrophage; wounds healing

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INTRODUCTION

Wounds occur with high frequency worldwide. In the United States, surgical wounds reach 110.30 million cases. Trauma-related injuries reach 1.60 million cases. Abrasions reach 20.40 million cases. Burns account for 10 million cases. Decubitus ulcers reach 8.50 million cases (Mitaart et al., 2017a; Sen et al., 2009a). Venous ulcers reach 12.50 million cases. Diabetic ulcers reach 13.50 million cases. Indonesia reports varying prevalence across provinces. South Sulawesi reaches 12.8 percent, while Jambi reaches 4.5 percent. Abrasions and contusions are the most common wound types at 70.9 percent (Mitaart et al., 2017b; Sen et al., 2009b; Wibowo & Comariyanti, 2017).

A wound represents a structural disruption of tissue caused by thermal, chemical or mechanical insults. Blunt trauma produces abrasions, contusions and lacerations. Sharp trauma produces incised and puncture wounds. Healing proceeds through hemostasis, inflammation, proliferation and remodeling. Cellular mediators such as neutrophils, macrophages, fibroblasts and endothelial cells regulate cytokines and growth factors that guide repair(Alsareii et al., 2023; Balderas-Cordero et al., 2023).

Medicinal plants contain secondary metabolites that influence inflammation and tissue regeneration. Tinomiscium petiolare Hook.f. & Thomson is traditionally used across Southeast Asia for musculoskeletal pain, oral lesions, postpartum recovery and wound care (Thinh et al., 2021a). Phytochemical studies report alkaloids such as 1-isocorypalmine, magnoflorine and homoaromaline, as well as clerodane diterpenes and flavonoids. These compounds show potential to modulate IL-1, TNF-α and growth factors including VEGF and FGF, which regulate inflammation, fibroblast activity and angiogenesism (Alsareii et al., 2023; Isdiyanti et al., 2021; Nugraha & Keller, 2011).

TNF-α plays a central role in neutrophil recruitment, vasodilation and endothelial activation. VEGF supports microvascular formation, which is essential for oxygen delivery and collagen deposition. The number of macrophages and new vessels strongly influences wound progression and tissue quality. This study evaluates the effect ethanol extract on TNF-α levels, macrophage counts and neovascularization in incision wounds. The study aims to determine whether the extract modulates key inflammatory and proliferative pathways involved in tissue repair(Ibrahim et al., 2018; Wilkinson & Hardman, 2023).

METHOD

This study employed a true experimental design using a Post-Test Only Control Group model. Animals were randomly assigned to the control or treatment groups, and baseline equivalence was assumed after randomization. The treatment effect was evaluated by comparing post-intervention outcomes between the groups. Leaves of *Tinomiscium petiolare* were collected and submitted for phytochemical analysis using GC–MS to identify the major secondary metabolites. Extract preparation followed the maceration method with 96% ethanol as the solvent. The concentrated extract was incorporated into an ointment formulation composed of 10 %. Gamat leaf extract, 6 % adeps lanae, 8 % white beeswax and vaseline to a final weight of 100%.

Twenty-four male Rattus norvegicus were acclimatized under controlled conditions before use. The animals were then randomized into four groups of six rats. Standard incision wounds were induced in each subject, and the treatment groups received topical application of the Gamat ointment according to the experimental protocol. Tissue samples were collected on days 3 and 7 to measure TNFα expression, macrophage infiltration and blood vessel formation, representing key parameters of the inflammatory and proliferative stages of wound repair. Data analysis included the Shapiro–Wilk test to assess normality and Levene's test to evaluate homogeneity of variance. Comparative statistical tests were applied to examine differences between groups. Posthoc analysis was performed when significant differences were observed, allowing identification of treatment effects across groups for each observation period.

RESULT

This study offers a novel contribution by providing the first GC–MS–based phytochemical profile of *Tinomiscium petiolare* (Gamat leaves). The extract was formulated into a topical ointment and evaluated for its wound-healing potential. The GC–MS analysis identified the

major secondary metabolites present in the extract, as shown in Table 1, forming the basis for interpreting its biological effects on inflammation, cell proliferation, and tissue repair.

Table 1.
GCMS Results of Gamat Extract (*Tinomiscium petiolare* Hook.f. & Thomson)

Peak	R. Time	Compound Name	Chemical Formula	Molecular weight	Peak Area %
1.	13.261	Hexadecanoid acid, methyl ester	$C17H34O2$	270	0,71
2.	15.262	6-Octadecenoid Acid	$C_{19}H_{36}O_2$	296	15,56
3.	15.919	Octadecanoic Acid, Methyl Ester	$C_{19}H_{38}O_2$	298	6,68
4.	16.879	9-Octadecenoid Acid	$C_{18}H_{34}O_2$	282	35,45
5.	17.258	Hexadecanoic Acid, 2-hydroxy-1-(hydroxymethyl) ethyl ester	$C_{19}H_{38}O_4$	330	9,06
6.	17.747	Hexadecanoic acid, 2-hydroxyl-1,3-propanediyl ester	$C_{35}H_{68}O_5$	569	4,28
7.	17.908	Eicosanoic Acid, Methyl Ester	$C_{21}H_{42}O_2$	326	2,29
8.	18.458	9-Octadecenamide	$C_{18}H_{35}NO$	281	0,14
9.	18.863	Oleic Acid, 3-hydroxypropyl Ester	$C_{21}H_{40}O_3$	340	3,12
10.	19.043	N,N'-bis(trifluoroacetyl)-N,N'-ethylene-Bis(stearamide)	$C_{42}H_{72}F_6N_2O_4$	783	0,60
11.	19.282	DI-(9-Octadecenoyl)-Glycerol	$C_{39}H_{72}O_5$	621	5,60
12.	19.441	Octadecanoic Acid, 2-hydroxyl-1,3-propanediyl Ester	$C_{39}H_{76}O_5$	625	1,05
13.	19.600	Decosanoic Acid, Methyl Ester (CAS) Methyl Behenate	$C_{23}H_{46}O_2$	354	0,09
14.	20.246	Acetic Acid 13-Hydroxyl-4,4,6A,6B,8A,11,11,14B-Octamethyl-Docosahydro-Picen-3-Yl	$C_{32}H_{54}O_3$	486	0,09
15.	20.645	1,3-Dioxolane,4-[[2-Methoxy-4-hexadecenyl)oxy]-2,2-Dimethyl	$C_{23}H_{44}O_4$	384	0,64
16.	20.809	Eicosanoic Acid, 2,3-bis (trimethylsilyl)oxy]Propyl Ester	$C_{29}H_{62}O_4Si_2$	530	0,32
17.	21.586	Cyclohexylsulfide, decyl	$C_{16}H_{32}S$	256	0,42
18.	21.733	9-Octadecenoid Acid, 2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl Ester	$C_{22}H_{44}O_6$	440	0,17
19.	22.125	Ketone, 5-Hydroxy-8-methyoxy-2-methyl-2-(4-methyl-3-pentenyl)-2H-1-benzppyran-6-yl Methyl	$C_{19}H_{24}O_4$	316	0,13
20.	22.948	9-Octadenecel	$C_{18}H_{34}O$	266	0,94
21.	23.073	Decanoid Acid, Octadecyl Ester	$C_{28}H_{56}O_2$	424	0,34
22.	24.973	16-Hentriacontanone	$C_{31}H_{62}O$	450	0,26
23.	26.261	1,3-Undecafluorocyclohexylpropan-1,3-Dione	$C_{15}H_2F_{22}O_2$	632	0,89
24.	26.433	9-Octadecanel	$C_{18}H_{34}O$	266	3,95
25.	26.545	16-Hentriacontanone	$C_{31}H_{62}O$	310	0,52
26.	27.643	1,3-Undecafluorocyclohexylpropan,1-3- Diane	$C_{15}H_2F_{22}O_2$	632	0,43
27.	28.273	Tricyclo[20.8.0.0E7]Triacontan, 1(22), 7(16)-Diepoxy	$C_{30}H_{52}O_2$	444	4,17
28.	28.400	Borane, diethylmethyl-	$C_5H_{13}O$	84	1,59
29.	28.525	Octadecanoic Acid, Ethenyl Ester	$C_{20}H_{38}O_2$	310	0,23
30.	29.576	10-Undecenoyl Chloride	$C_{11}H_{19}CLO$	202	0,23

Immunohistochemical examination showed clear TNF-α staining marked by arrow indicators in the tissue sections. Figure 1 shows stronger TNF-α expression on day three, as indicated by the arrows pointing to areas of intense immunoreactivity. Figure 2 shows reduced TNF-α staining on day seven with fewer and lighter arrow-marked regions. This pattern reflects the expected decline in inflammatory cytokine activity as the wound progresses toward the proliferative phase.

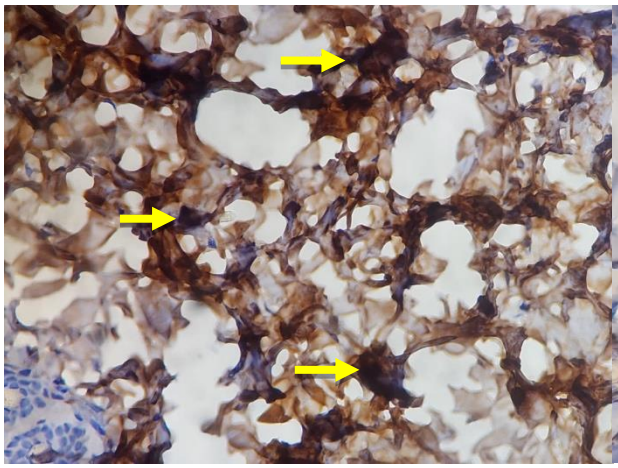


Figure 1. TNF-α expression on day three

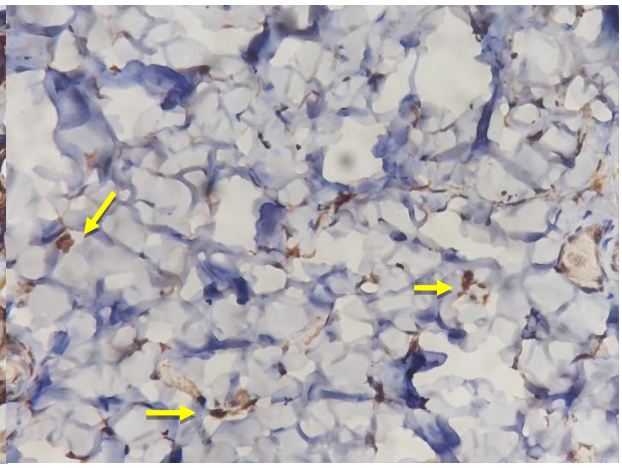


Figure 2. TNF-α staining on day seven

Histological analysis of HE stained sections demonstrated clear visualization of macrophages and vascular structures through arrow indicators. Figure 3 illustrates the day three morphology, with yellow arrows identifying concentrated macrophage infiltration and red arrows highlighting early endothelial vascular formations within the wound bed. Figure 4 depicts the day seven tissue profile, showing fewer yellow arrow macrophages and more defined red arrow vascular structures indicative of progressing neovascularization. These observations collectively reflect the expected shift from inflammatory activity to proliferative tissue responses during wound repair.

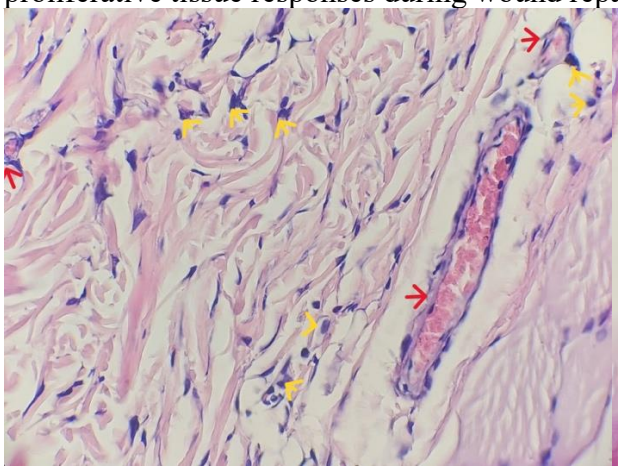


Figure 3. Macrophage (yellow arrows) and blood vessel (red arrows) day trhree

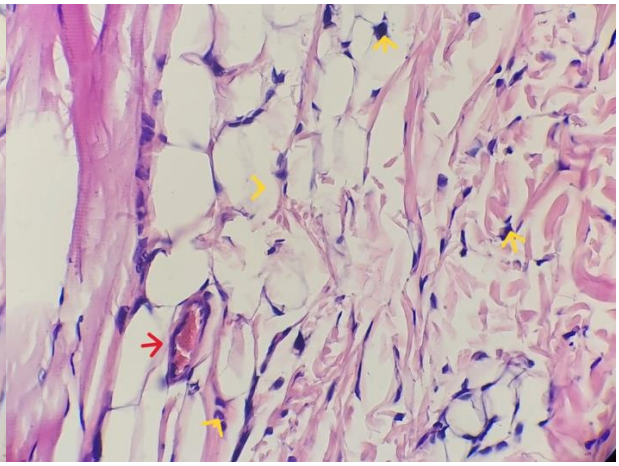


Figure 4. Macrophage (yellow arrows) and blood vessel (red arrows) day seven

The wound healing observations presented in Table 2 show a progressive reduction in wound size across all groups from day zero to day seven. The incision sites remained clearly visible at the initial observation but demonstrated narrowing and partial closure by day three. By day seven, all groups exhibited complete wound closure with smooth surface contours, indicating successful epithelialization and tissue recovery regardless of treatment condition. The uniform closure across groups suggests effective progression through the inflammatory and proliferative phases of wound healing.

Table 3 presents the observed values of TNF-α expression, macrophage counts, and blood vessel density measured across four treatment groups. These variables capture key aspects of the inflammatory and angiogenic responses during wound healing. The mean values and standard deviations provide a descriptive overview of how each group differed in cytokine activity, inflammatory cell presence, and vascular formation.

Table 3.
wound healing process in the rats treatment groups

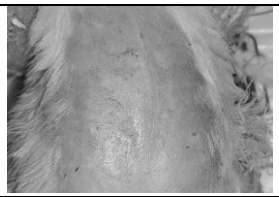
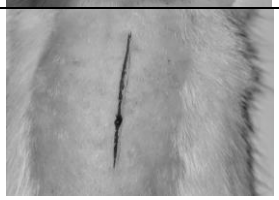
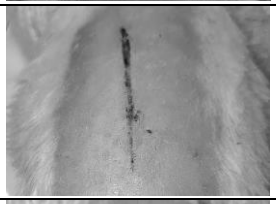
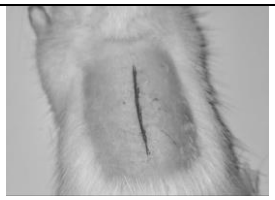
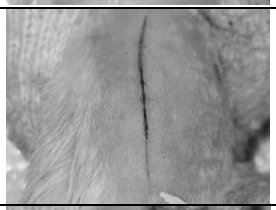
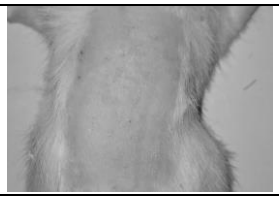
Times/ Cluster	W0	W3	W7
T1			
T2			
T3			
T4			

Table 4
Inflammatory and Angiogenic Parameters Across Treatment Groups

Group	TNF-α %		Macrophage cell		Blood Vessle Vascular count/HPF	
	Mean	SD	Mean	SD	Mean	SD
T1	37.50	7.932	3.67	1.145	18.17	3.719
T2	45.00	6.191	4.67	0.715	25.17	3.781
T3	39.17	13.192	4.33	0.333	22.17	3.478
T4	45.83	12.677	6.50	0.764	30.33	2.499

Table 5.
Results of normality and homogeneity tests

Variable	Treatment Group	Normality and Homogeneity Tests	
		Shapiro-Wilk	Levene Test
TNF-α	T1	0.316	0.029
	T2	0.389	
	T3	0.046	
	T4	0.061	
Macrophage	T1	0.102	0.010
	T2	0.059	
	T3	0.091	
	T4	0.961	
Blood Vessle	T1	0.012	0.008
	T2	0.205	
	T3	0.166	
	T4	0.472	

The results of the normality and homogeneity tests are presented in Table 4. Shapiro–Wilk

analysis showed that the dataset did not fully meet the assumption of normality. TNF-α values in the T3 group and blood vessel counts in the T1 group deviated from a normal distribution. Macrophage counts met the normality assumption across all treatment groups. The Levene test showed heterogeneous variances for all variables, as indicated by p-values below 0.05. These findings indicate that the dataset does not meet the assumptions of normality and variance homogeneity required for parametric analysis. The study therefore applied non-parametric statistical methods for subsequent testing.

Table 6.
Kruskal–Wallis Test Results for Inflammatory and Angiogenic Variables

Variabel	Kruskal-Wallis
	P-Value
TNF-α	0.170
Macrophage	0.044*
Blood Vessle	0.019*

Table 5 shows the Kruskal–Wallis analysis for TNF-α expression, macrophage counts, and blood vessel density across the treatment groups. TNF-α levels did not differ significantly among groups, indicated by a p-value of 0.170. Macrophage counts showed a significant difference, with a p-value of 0.044, reflecting variation in inflammatory cell infiltration. Blood vessel density also differed significantly, with a p-value of 0.019, showing measurable effects on angiogenesis. These significant findings for macrophages and blood vessels warranted post-hoc analysis to determine the specific group comparisons contributing to the observed differences.

Table 7
Pairwise Comparisons of Macrophage and Blood Vessel Counts Across Treatment Groups

Group Comparisons	Macrophages		Blood Vessels	
	P-value	Bonferroni Correction	P-value	Bonferroni Correction
T1-T3	0.303	1.000	0.138	0.826
T1-T2	0.059	0.354	0.023*	0.139
T1-T4	0.002*	0.015*	0.025*	0.149
T3-T2	0.391	1.000	0.052	0.314
T3-T4	0.045*	0.281	0.038*	0.230
T2-T4	0.252*	1.000	0.173	1.000

The results of the post-hoc analysis are summarized in Table 6**.** For macrophage counts, only the comparison between T1 and T4 remained statistically significant after Bonferroni correction, with an adjusted p-value of 0.015. This finding indicates that the most substantial reduction in macrophage numbers occurred in the T4 group. All other pairwise comparisons showed non-significant adjusted p-values, demonstrating that differences among T1, T2, and T3 were not statistically meaningful. For blood vessel counts, several uncorrected p-values suggested possible group differences, particularly in the T1–T2, T1–T4, and T3–T4 comparisons. However, none of these comparisons retained significance after Bonferroni adjustment.

Table
Kruskal–Wallis Test Results for TNF-α, Macrophages, and Blood Vessels on Day Seven

Variable	Kruskal-Wallis
	P-Value
TNF-α	0.112
Sel Makrofag	0.709
Pembuluh darah	0.664

The Kruskal–Wallis analysis (Table 8) on day seven showed no significant differences among treatment groups for all measured variables. TNF-α levels demonstrated a p-value of 0.112, indicating that cytokine expression had stabilized and no longer differed across groups. Macrophage counts also showed no significant variation, with a p-value of 0.709, suggesting

that inflammatory cell infiltration had declined uniformly as the wound approached the late inflammatory-to-remodeling transition. Blood vessel counts exhibited a p-value of 0.664, reflecting comparable angiogenic activity among groups at this stage.

Table 9.
Temporal Comparison of TNF-α, Macrophages, and Blood Vessels Between Day Three and Day Seven Across Treatment Groups

Groups	Variabel		
	TNF-α	Macrophage	Blood Vessels
T1	0.817	0.658	0.658
T2	0.817	0.658	0.658
T3	0.046*	0.346	0.275
T4	0.043*	0.050*	0.077

The temporal analysis in Table 9 shows distinct patterns of change between day three and day seven for each treatment group. In T1 and T2, all variables exhibited non-significant p-values, indicating that TNF-α levels, macrophage counts, and blood vessel formation progressed consistently over time without detectable shifts. In T3, TNF-α decreased significantly with a p-value of 0.046, while macrophage and blood vessel counts remained unchanged, suggesting partial modulation of the inflammatory phase. The most prominent changes occurred in T4, where TNF-α and macrophage counts declined significantly, with p-values of 0.043 and 0.050. Blood vessel counts in T4 showed a near-significant trend with a p-value of 0.077, suggesting increased angiogenic activity as the wounds transitioned toward proliferation.

DISCUSSION

The GC-MS profiling of *Tinomiscium petiolare* (Gamat leaves) identified several dominant secondary metabolites. These include 9-octadecenoic acid (oleic acid), hexadecanoic acid derivatives, and octadecanoic acid esters (Thinh et al., 2021). These lipid-based compounds have bioactivities that affect inflammatory regulation, microbial control, oxidative balance, and stromal cell activation during wound healing (Arundina et al., 2024; Cardoso et al., 2011). Oleic acid modulates inflammatory signaling by inhibiting the MAPK and NF-κB pathways. This reduces ERK, p38, and JNK phosphorylation. It also suppresses the expression of inducible nitric oxide synthase and COX-2. Oleic acid also shows antimicrobial effects against Staphylococcus aureus and other Gram-positive pathogens (Hammad et al., 2025; Salem et al., 2022).

Hexadecanoic acid derivatives provide additional anti-inflammatory, antioxidant, and antimicrobial activities that improve extracellular matrix stability and fibroblast function. Octadecanoic acid methyl ester contributes antioxidant and antimicrobial effects that protect tissue and aid regeneration. These metabolites play a role in several phases of tissue repair. Their anti-inflammatory actions reduce TNF-α and IL-6 expression during the early phase of healing. This reduction helps transition to the proliferative stage (Silva et al., 2018; Weimann et al., 2018; Zong et al., 2020). Antioxidant activity protects fibroblasts and keratinocytes from reactive oxygen species, which supports granulation and re-epithelialization. Antimicrobial properties lower bacterial load at the wound site, which reduces infection-related delays (Comino-Sanz et al., 2021; Fadilah et al., 2023). Oleic acid and methyl hexadecanoate also promote fibroblast proliferation, collagen deposition, and matrix formation. This process strengthens tissue regeneration (Alsareii et al., 2023; Rodrigues et al., 2012; Saravanan et al., 2023).Together, these mechanisms suggest that *T. petiolare* metabolites play a coordinated role in resolving inflammation, promoting angiogenesis, and

repairing the matrix (Ashcroft et al., 2012; Li et al., 2022). Macroscopic evaluation showed consistent wound contraction in all groups from baseline to day seven. Each group achieved complete epithelial closure.

The similar transition from inflammatory to proliferative phases across groups indicates that the *Tinomiscium petiolare* ointment did not disrupt epithelial repair. TNF alpha levels did not differ among groups on day seven. Temporal analysis showed significant reductions in TNF alpha from day three to day seven in T3 and T4, suggesting faster inflammatory resolution at higher concentrations (Ritsu et al., 2017; Yusuf, 2024). This pattern aligns with studies showing that oleic acid suppresses MAPK and NF-κB signaling and reduces cytokine release in macrophages (Balderas-Cordero et al., 2023; Dekebo et al., 2024). It also matches evidence that n-9 fatty acids speed up wound repair and lower inflammatory cell infiltration. Macrophage counts varied among treatment groups, and post hoc testing confirmed significantly lower macrophage infiltration in T4 compared to T1 after Bonferroni correction. This response aligns with findings that methyl palmitate reduces macrophage activation and limits cytokine production. The reduction in macrophages also aligns with studies reporting decreased neutrophil and macrophage migration after topical application of palmitoleic and related fatty acids (Kim & Nair, 2019; Koh & DiPietro, 2011; Yin et al., 2025).

Blood vessel density varied among the groups, but no pairwise comparison was significant after correction. The data showed a clear rise in vessel formation in T4 from day three to day seven. This aligns with studies reporting that fatty acid extracts promote the growth of endothelial cells and encourage blood vessel formation by activating the AKT, ERK, and TGF beta Smad3 pathways. Research on natural oils rich in oleic and palmitic acids also shows they boost fibroblast migration and improve blood vessel formation (Rodrigues et al., 2010 (Krzyszczyk et al., 2018)).

In summary, the findings suggest that the highest dose of *T. petiolare* extract speeds up the shift from inflammation to growth. Reductions in TNF alpha and macrophage infiltration, along with an increase in blood vessel formation, back up earlier studies that describe the anti-inflammatory, antioxidant, and pro-angiogenic effects of oleic acid, palmitic acid derivatives, and mixed fatty acid extracts. These results support a model where fatty acids affect MAPK and NF kappa B activity, reduce oxidative stress, and improve endothelial and fibroblast function. One study noted an early stimulating effect of oleic and linoleic acids on acute inflammation. This suggests that the impact of fatty acids depends on the dose, timing, and formulation. The current study confirms the anti-inflammatory and pro-growth benefits of higher concentrations of *T. petiolare* extract during wound healing (Agyare et al., 2019; Kim & Nair, 2019; Tonnesen et al., 2000).

CONCLUSION

The treatment did not alter TNF-α levels but influenced macrophage counts and angiogenesis, with the strongest effects observed in T4, the group receiving the highest extract concentration. By day seven all groups showed similar inflammatory and angiogenic profiles, and only T4 demonstrated meaningful changes over time.

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