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Guava Leaf Extract and Polyvinylpyrrolidone Hydrogel for Rabbit Oral Wounds

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Abstract:
Wounds, caused by trauma, surgery, or accidents, can disrupt tissue integrity. A common complication in maxillofacial surgery is wound dehiscence. The combination of guava leaf (Psidium guajava Linn.) ethanol extract and polyvinylpyrrolidone (PVP) hydrogel is expected to accelerate oral mucosal wound healing by enhancing fibroblast proliferation, epithelialization, and VEGF levels, while reducing IL-6 levels. This research aims to evaluate the effectiveness of a combination gel of guava leaf ethanol extract and PVP hydrogel in accelerating oral mucosal wound healing. This experimental study used 28 rabbits divided into four groups: Group 1 (sutured wound + combination gel), Group 2 (unsutured wound + combination gel), Group 3 (sutured wound + placebo), and Group 4 (unsutured wound + placebo). A standardized incisional wound was created on the gingiva, and the gel was applied twice daily. Histopathological analysis was performed on days 3 and 14 to assess fibroblast count, epithelialization, VEGF, and IL-6 levels. The treatment group showed significantly higher fibroblast counts (64.50 ± 4.43 vs. 55.67 ± 4.04; p = 0.041), enhanced epithelialization, increased VEGF levels, and a 25% reduction in IL-6 levels on day 3 compared to controls. These findings support the gel's role in accelerating wound healing through angiogenesis and inflammation control. The combination of guava leaf ethanol extract and PVP hydrogel is a promising innovative therapy for accelerating wound healing, particularly in chronic or difficult-to-heal wounds, with minimal risk of excessive inflammation and scar tissue formation.

***Keywords**: Wound, guava leaf ethanol extract, oral mucosa, fibroblasts, VEGF levels, IL-16 levels*

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INTRODUCTION

Wound healing restores tissue integrity through inflammatory, proliferative, and remodeling phases, with fibroblast proliferation playing a key role (Gonzalez, 2016). Maxillofacial trauma, including mandibular fractures, requires ATLS-based management due to its impact on airway function (Demidova-Rice et al., 2012; Esmaeelinejad & Esmaeelinejad, 2018; Khan, 2022; Singh, 2012). Surgical treatment often involves ORIF via intraoral or extraoral approaches, each with benefits and risks. Intraoral techniques minimize scarring but increase infection risk, while extraoral approaches improve visualization but may cause nerve injury and scarring (Cao et al., 2025; Das et al., 2019; Hao et al., 2022; Liang et al., 2024; Wang et al., 2018; Yadav, 2021; Yang et al., 2021). A major complication is intraoral wound dehiscence, prolonging recovery and increasing costs (Oksa, 2023; Wusiman et al., 2020).

Wound dehiscence management requires meticulous care, but persistent cases impair healing and quality of life (Abdulazeem et al., 2022; Delorino et al., 2021; Ekom & Tamokou, 2018; Hakim et al., 2023; Kumar & Ravi, 2021; Maigoda et al., 2022; Naseer et al., 2018; Sutrisno et al., 2024). Herbal medicine, including guava (*Psidium guajava Linn.*) leaves, shows

potential due to antimicrobial, anti-inflammatory, and astringent properties (Budovsky et al., 2015; Carolino et al., 2022). The combination of guava leaf ethanol extract and polyvinylpyrrolidone (PVP) hydrogel is expected to accelerate traumatic wound healing in the oral mucosa by increasing fibroblast count, epithelialization, and VEGF levels, and decreasing IL-6 levels (Buchsel, 2008; Cialdai et al., 2022; Espinosa et al., 2023; Foster, 2021; Hakim et al., 2023; Liu, 2022; Mascharak, 2021; Stunová & Vištejnová, 2018).

Several previous studies have investigated the wound healing properties of guava leaf extract (Roman, 2023). Research by Bilal et al. (2024) demonstrated that *Psidium guajava* leaf extract possesses significant wound healing activity by promoting epithelialization and wound contraction, increasing hydroxyproline content, and reducing oxidative stress through the regulation of endogenous antioxidant enzymes. The study confirmed that the extract promotes wound contraction, epithelialization, angiogenesis, and fibroblast proliferation more effectively compared to controls. Similarly, Samuvel et al. (2024) found that guava leaf extracts accelerate wound healing by increasing blood circulation towards the wound site, with metabolomic profiling identifying 107 compounds responsible for their wound healing properties. Chah et al. (2006) also reported that guava leaf extracts demonstrated significant wound healing activity, with more than 90% wound healing recorded in extract-treated groups by 14 days post-surgery.

Regarding hydrogel-based wound dressings, Waresindo et al. (2021) successfully fabricated a polyvinyl alcohol (PVA) hydrogel loaded with guava leaf extract with potential applications as a wound dressing, demonstrating good antibacterial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The zone of inhibition demonstrated antibacterial activity of 17.93% and 15.79% against these pathogens, respectively. Research by Zheng et al. (2025) on PVA/PVP hydrogels showed that these biomaterials have excellent biocompatibility, with the survival rate of cells cultured in hydrogel extract reaching 96.18%. Lee et al. (2024) investigated chitosan-PVP hydrogels and found that they can modulate human gingival fibroblast and oral keratinocyte growth, suggesting potential applications in oral and maxillofacial wound healing.

In the context of polyherbal formulations, Manhas et al. (2025) developed a polyherbal gel containing *Psidium guajava* along with other medicinal plants for diabetic foot ulcers, demonstrating enhanced wound closure rates of 86.04% in cell-based assays and significant efficacy in diabetic rat models. The formulation showed remarkable α-amylase inhibitory activity and notable antibacterial efficacy against a spectrum of tested pathogens.

Despite these promising findings, research on the specific combination of guava leaf ethanol extract with PVP hydrogel for oral mucosal wound healing remains limited. Jayaningrum et al. (2025) conducted a study on this combination using 28 rabbits divided into four treatment groups, demonstrating significant increases in fibroblast count (64.50 ± 4.43) compared to controls (55.67 ± 4.04), with $p = 0.041$, as well as increased epithelialization and VEGF levels, and decreased IL-6 levels by 25% on day 3. However, there is a research gap in systematically evaluating the synergistic effects of this combination across all phases of wound healing, particularly regarding the modulation of inflammatory markers and long-term tissue regeneration.

This study aims to explore the synergistic effects of guava leaf ethanol extract and PVP hydrogel combination in promoting oral wound healing. By integrating the bioactive compounds from guava leaves with the moisture-retaining and biocompatible properties of PVP hydrogel, this combination therapy is expected to provide an innovative approach for accelerating wound healing, particularly in chronic or difficult-to-heal wounds, with minimal risk of excessive inflammation and scar tissue formation.

RESEARCH METHOD

This experimental study used a randomized post-test only control group design with 28 rabbits divided into four groups: Group I (guava leaf extract + PVP hydrogel + suturing), Group II (extract without suturing), Group III (placebo + suturing), and Group IV (placebo without suturing). Rabbits were housed under controlled conditions, receiving standard feed and care. Anesthesia was administered intramuscularly using a Ketamine-Xylazine-Acepromazine mixture. Standardized incisional wounds were created on the gingival mucosa, with suturing using 5-0 Vicryl where applicable. The guava leaf extract gel was prepared through ethanol maceration, followed by formulation with Na-CMC, propylene glycol, nipagin, glycerin, and triethanolamine. The gel was applied twice daily. Euthanasia was performed on day 14 using high-dose Ketamine-Xylazine, with tissue samples collected for histopathological analysis of IL-6, VEGF, and fibroblast count. Statistical analysis included Shapiro-Wilk for normality, Levene's test for homogeneity, and one-way ANOVA with post-hoc comparisons using Tukey's or Games-Howell tests. Data were analyzed in IBM SPSS 26.0, with significance set at $p < 0.05$. The study was conducted at Udayana University, Indonesia, from November–December 2024.

RESULT AND DISCUSSION

The 28 male rabbits were divided into four groups. On day 3, fibroblast count was highest in P1 (64.50±4.43) and lowest in K1/P2 (55.67±4.04). By day 14, P1 increased to 76.75±7.68, while K1/P2 remained at 66.67±1.53. Epithelialization in P1 was 131.34±3.88 on day 3, rising to 176.95±11.99 by day 14, whereas K2 remained the lowest (83.21±16.87 to 94.65±14.37).

VEGF levels in P1 were highest (day 3: 68.99±4.77; day 14: 81.95±5.23), while K2 had the lowest increase (53.17±8.26 to 58.87±6.02). IL-6 levels in P1 were the lowest (day 3: 38.28±0.95; day 14: 23.87±1.88), while K1/P2 remained elevated (48.56±1.10 to 47.40±1.21). The results indicate significant improvements in fibroblast proliferation, epithelialization, and VEGF levels while reducing IL-6.

Table 1. Data Characteristics, Normality Test, and Homogeneity test

Variable	Time	P1 Mean ± SD	K1 Mean ± SD	P2 Mean ± SD	K2 Mean ± SD	*Shapiro-Wilk* and *Levene Test (p)*
Fibroblast	Day 3	64.50±4.43	55.67±4.04	55.67±4.04	65.00±3.61	>0,05
	Day 14	76.75±7.68	66.67±1.53	66.67±1.53	69.00±4.36	>0,05

Variable	Time	P1 Mean ± SD	K1 Mean ± SD	P2 Mean ± SD	K2 Mean ± SD	*Shapiro-Wilk* and *Levene Test (p)*
Epithel	Day 3	131.34±3.88	109.49±5.03	109.49±5.03	83.21±16.87	>0,05
	Day 14	176.95±11.99	129.48±7.29	129.48±7.29	94.65±14.37	>0,05
VEGF	Day 3	68.99±4.77	57.34±1.54	57.34±1.54	53.17±8.26	>0,05
	Day 14	81.95±5.23	46.48±1.31	46.48±1.31	58.87±6.02	>0,05
IL-16	Day 3	38.28±0.95	48.56±1.10	48.56±1.10	49.37±2.01	>0,05
	Day 14	23.87±1.88	47.40±1.21	47.40±1.21	28.92±2.98	>0,05

Source: Primary data processed, 2025

The analysis in Table 2 ANOVA showed significant differences in fibroblast counts among groups on day 3 (p = 0.009) and day 14 (p = 0.035). On day 3, P1 had a significantly higher fibroblast count than K1 (mean difference: 8.833, p = 0.041, 95% CI: 0.33–17.34). K1 had significantly lower counts than P2 (-12.083, p = 0.007, 95% CI: -20.59 to -3.58) and K2 (-9.333, p = 0.044, 95% CI: -18.42 to -0.24).

By day 14, P1 maintained the highest fibroblast count, though differences with K1 (10.083, p = 0.33) and other groups were not significant. K1 remained lower than P2 (-17.833, p = 0.042, 95% CI: -35.01 to -0.66), but no significant differences were found between K1 and K2 (p = 0.979) or P2 and K2 (p = 0.08).

Table 2. One-Way ANOVA and Tukey HSD in Fibroblast

Group I	Group II	*Mean Difference*	*p-value*	*95% CI Lower Bound*	*95% CI Upper Bound*	*ANOVA p-value*
Fibroblast Day-3						
P1	K1	8.833	0.041	0.33	17.34	0,009
P1	P2	-3.25	0.604	-11.12	4.62	
P1	K2	-0.5	0.998	-9.01	8.01	
K1	P2	-12.083	0.007	-20.59	-3.58	
K1	K2	-9.333	0.044	-18.42	-0.24	
P2	K2	2.75	0.759	-5.75	11.25	
Fibroblast Day-14						
P1	K1	10.083	0.33	-7.09	27.26	0,035
P1	P2	-7.75	0.477	-23.65	8.15	
P1	K2	7.75	0.538	-9.47	24.97	
K1	P2	-17.833	0.042	-35.01	-0.66	
K1	K2	-2.333	0.979	-20.7	16.03	

P2	K2	15.5	0.08	-1.68	32.68

Source: Primary data processed, 2025

Table 3 analysis showed significant differences in epithelial length on day 3 (p = 0.001) and day 14 (p = 0.000), confirming the efficacy of P1 in accelerating epithelialization. On day 3, P1 had significantly longer epithelium than P2 (-40.57, p = 0.003, 95% CI: 15.34–65.79) and K2 (-48.13, p = 0.001, 95% CI: 20.88–75.38), while differences with K1 were not significant (p = 0.129). On day 14, P1 remained the highest, significantly differing from K1 (-47.47, p = 0.001, 95% CI: 23.35–71.59), P2 (-56.8, p = 0.000, 95% CI: 34.47–79.13), and K2 (-82.3, p = 0.000, 95% CI: 58.18–106.42). K1 vs. P2 was not significant (p = 0.65), but K1 vs. K2 (-34.82, p = 0.009) and P2 vs. K2 (-25.49, p = 0.038) were.

P1 significantly enhanced epithelialization at both time points. Sutures in K1 did not consistently improve healing, as differences with K2 were only significant on day 14. P2 showed better healing than K2 but was less effective than P1.

Table 3. One-Way ANOVA dan Tukey HSD Test to Epithelization

Group I	**Group II**	***Mean Difference***	***p-value***	***95% CI Lower Bound***	***95% CI Upper Bound***	***ANOVA p-value***
Epithelization day 3						
P1	K1	21.85	0.129	-5.4	49.1	0,001
P1	P2	40.57	0.003	15.34	65.79	
P1	K2	48.13	0.001	20.88	75.38	
K1	P2	18.72	0.217	-8.53	45.97	
K1	K2	26.28	0.08	-2.85	55.41	
P2	K2	7.56	0.83	-19.69	34.81	
Epithelization day 14						
P1	K1	47.47	0.001	23.35	71.59	0,000
P1	P2	56.8	0.000	34.47	79.13	
P1	K2	82.3	0.000	58.18	106.42	
K1	P2	9.33	0.65	-14.79	33.45	
K1	K2	34.82	0.009	9.04	60.61	
P2	K2	25.49	0.038	1.37	49.62	

Source: Primary data processed, 2025

Table 4 analysis showed a significant increase in VEGF levels in the treatment groups compared to controls on day 3 (p = 0.009) and day 14 (p = 0.000), indicating enhanced angiogenesis and tissue regeneration. On day 3, P1 had significantly higher VEGF than K2 (+15.82, p = 0.033, 95% CI: 1.26–30.38), while differences with K1 (p = 0.13) and P2 (p = 0.962) were not significant. P2 also had higher VEGF than K2 (+17.92, p = 0.016). On day

14, P1 had significantly higher VEGF than K1 (+35.47, p = 0.000, 95% CI: 23.61–47.33) and K2 (+23.08, p = 0.001, 95% CI: 11.22–34.94), while the difference with P2 was not significant (p = 0.469). P2 also had significantly higher VEGF than K1 (-40.88, p = 0.000) and K2 (+28.49, p = 0.000), but K1 vs. K2 was not significant (p = 0.056). These results confirm that P1 consistently enhances VEGF expression, particularly on day 14, supporting its role in promoting angiogenesis and tissue repair. The effect was more pronounced in sutured wounds, suggesting an optimal environment for VEGF activation.

Tabel 4. One-Way ANOVA and Turkey HSD Tests in VEGF

Group I	Group II	*Mean Difference*	*p-value*	*95% CI Lower Bound*	*95% CI Upper Bound*	*ANOVA p-value*
VEGF Day 3						
P1	K1	11.65	0.13	-2.92	26.21	0,009
P1	P2	-2.1	0.962	-15.59	11.38	
P1	K2	15.82	0.033	1.26	30.38	
K1	P2	-13.75	0.066	-28.31	0.81	
K1	K2	4.17	0.844	-11.4	19.74	
P2	K2	17.92	0.016	3.36	32.49	
VEGF day 14						
P1	K1	35.47	0.000	23.61	47.33	0,000
P1	P2	-5.41	0.469	-16.39	5.57	
P1	K2	23.08	0.001	11.22	34.94	
K1	P2	-40.88	0.000	-52.74	-29.02	
K1	K2	-12.39	0.056	-25.07	0.28	
P2	K2	28.49	0.000	16.63	40.34	

Source: Primary data processed, 2025

The analysis in Table 5 indicates that the combination gel significantly reduces IL-16 levels, a pro-inflammatory cytokine, during wound healing (p = 0.000 for both day 3 and day 14). On day 3, P1 had significantly lower IL-16 than K1 (-10.28, p = 0.000, 95% CI: -14.17 to -6.40) and K2 (-11.09, p = 0.000, 95% CI: -14.98 to -7.21), indicating reduced inflammation. However, P1 had higher IL-16 than P2 (+8.09, p = 0.000). Among controls, K1 and K2 showed no significant difference (p = 0.931), but P2 had significantly higher IL-16 than K2 (+19.19, p = 0.000). On day 14, P1 maintained lower IL-16 than K1 (-23.54, p = 0.000, 95% CI: -28.01 to -19.06) and K2 (-5.06, p = 0.027, 95% CI: -9.53 to -0.58). No significant difference was observed between P1 and P2 (p = 0.325). K1 had significantly higher IL-16 than P2 (+25.98, p = 0.000), and K1 vs. K2 also showed a significant difference (+18.48, p = 0.000).These findings confirm that P1 consistently reduces IL-16 levels, with a more pronounced effect in sutured wounds (Irfan-Maqsood, 2016).

Table 5. One-Way ANOVA and Turkey HSD Tests on IL-16

Group I	Group II	*Mean Difference*	*p-value*	*95% CI Lower Bound*	*95% CI Upper Bound*	*ANOVA p-value*
IL-16 day 3						
P1	K1	-10.28	0.000	-14.17	-6.40	0,000
P1	P2	8.09	0.000	4.50	11.69	
P1	K2	-11.09	0.000	-14.98	-7.21	
K1	P2	18.38	0.000	14.50	22.26	
K1	K2	-8.09	0.931	-4.96	3.34	
P2	K2	19.19	0.000	15.30	23.07	
IL-16 day 14						
P1	K1	-23.54	0.000	-28.01	-19.06	0,000
P1	P2	2.45	0.325	-1.70	6.59	
P1	K2	-5.06	0.027	-9.53	-0.58	
K1	P2	25.98	0.000	21.51	30.46	
K1	K2	18.48	0.000	13.7	23.26	
P2	K2	-7.5	0.002	-11.98	-3.03	

Source: Primary data processed, 2025

The analysis in Table 6 reveals significant changes in fibroblast count, epithelial length, VEGF, and IL-16 levels in group P1 between days 3 and 14 ($p < 0.05$, Paired T-Test), reflecting gingival wound healing dynamics. Fibroblast count significantly decreased by -12.25±4.79 ($p = 0.014$, 95% CI: -19.87 to -4.63), indicating a transition from the proliferative to the maturation/remodeling phase as collagen synthesis demand declines. Epithelial length decreased by -45.62±8.82 ($p = 0.002$, 95% CI: -59.66 to -31.57), suggesting rapid epithelialization peaking at day 3 and stabilizing by day 14, marking near-complete tissue regeneration. VEGF dropped by -12.96±5.16 ($p = 0.015$, 95% CI: -21.16 to -4.76), indicating reduced angiogenesis demand as vascularization stabilizes, highlighting the gel's role in early wound healing. IL-16 increased by +14.41±1.31 ($p = 0.000$, 95% CI: 12.32 to 16.5), possibly reflecting residual inflammation during ongoing healing, warranting further investigation.

Table 6. Paired T-Test P1 Group at day 3 and day 14

Pair variable	*Mean ± SD*	*95% CI Lower Bound*	*95% CI Upper Bound*	*p-value*
Fibroblast	−12.25±4.79	-19.87	-4.63	0.014
Epithel	−45.62±8.82	-59.66	-31.57	0.002
VEGF	−12.96±5.16	-21.16	-4.76	0.015

Pair variable	*Mean ± SD*	*95% CI Lower Bound*	*95% CI Upper Bound*	*p-value*
IL-16	14.41±1.31	12.32	16.5	0.000

Source: Primary data processed, 2025

The analysis in Table 7 reveals significant changes in fibroblast count, epithelial length, VEGF, and IL-16 levels in the control group (K1) between days 3 and 14 ($p < 0.05$, Paired T-Test), reflecting natural wound healing without active intervention. Fibroblast count decreased by -11.00±2.65 ($p = 0.019$, 95% CI: -17.57 to -4.43), indicating a transition from proliferation to maturation. Compared to the treatment group (P1), fibroblast regeneration was slower, highlighting the gel's role in accelerating this phase. Epithelial length decreased by -19.99±2.27 ($p = 0.004$, 95% CI: -25.62 to -14.36), suggesting slower epithelialization than the treatment group, indicating that the placebo had minimal effect in enhancing tissue regeneration. VEGF increased by 10.87±2.54 ($p = 0.018$, 95% CI: 4.55 to 17.18), reflecting ongoing angiogenesis in the control group.

Table 7. Paired T-Test K1 Group at day 3 and day 14

Variable pair	*Mean ± SD*	*95% CI Lower Bound*	*95% CI Upper Bound*	*p-value*
Fibroblast	−11.00±2.65	-17.57	-4.43	0.019
Epithel	−19.99±2.27	-25.62	-14.36	0.004
VEGF	10.87±2.54	4.55	17.18	0.018
IL-16	−1.16±0.14	-1.50	-0.81	0.005

Source: Primary data processed, 2025

The analysis in Table 8 demonstrates the gel's effectiveness in wound healing without sutures, though healing was slower than in P1. Fibroblast count decreased by -16.75±9.57 ($p = 0.039$), indicating transition to maturation, with a greater decline than in P1, suggesting mechanical stabilization enhances fibroblast activity. Epithelial length decreased by -29.38±13.53 ($p = 0.023$), reflecting slowed epithelialization after day 3, confirming sutures create a more favorable healing environment. VEGF declined by -16.26±4.09 ($p = 0.004$), suggesting reduced angiogenesis as vascular stabilization occurs, with a sharper decline than P1, implying sutures aid gel distribution. IL-16 increased by 8.68±1.96 ($p = 0.003$), indicating persistent inflammation at day 14, suggesting the gel is less effective in controlling inflammation without sutures. Overall, P2 showed significant wound healing, but at a slower rate than P1, highlighting the role of mechanical stabilization in optimizing regeneration and reducing inflammation.

Table 8. Paired T-Test P2 Group at Day 3 and at Day 14

Variable pair	*Mean ± SD*	*95% CI Lower Bound*	*95% CI Upper Bound*	*p-value*
Fibroblast	−16.75±9.57	-31.98	-1.52	0.039
Epithel	−29.38±13.53	-50.90	-7.85	0.023
VEGF	−16.26±4.09	-22.77	-9.76	0.004
IL-16	8.68±1.96	5.57	11.80	0.003

Source: Primary data processed, 2025

The analysis in Table 9 illustrates natural wound healing without treatment or mechanical stabilization. Fibroblast count decreased by -4.00±1.00 (p = 0.02), indicating a transition to maturation, but with minimal support for fibroblast activity. Epithelial length decreased by -11.45±3.23 (p = 0.026), reflecting slower epithelialization compared to treated and sutured groups, confirming that both mechanical stabilization and active treatment accelerate healing. VEGF declined by -5.37±1.82 (p = 0.036), showing reduced angiogenesis, with a smaller decline than active treatment groups, suggesting prolonged vascular maturation. IL-16 increased by 20.45±4.94 (p = 0.019), indicating prolonged inflammation at day 14, delaying the transition to proliferation.

Table 9. Paired T-Test K2 Group at Day 3 and Day 14

Variable Pair	*Mean ± SD*	*95% CI Lower Bound*	*95% CI Upper Bound*	*p-value*
Fibroblast	−4.00±1.00	-6.48	-1.52	0.02
Epithel	−11.45±3.23	-19.47	-3.43	0.026
VEGF	−5.37±1.82	-9.9	-0.84	0.036
IL-16	20.45±4.94	8.17	32.73	0.019

Source: Primary data processed, 2025

Figure 1 shows histological analysis of rabbit gingival mucosa on day 3 post-treatment with guava leaf ethanol gel and polyvinylpyrrolidone hydrogel. The treatment group (P1) exhibited greater epithelial thickness (128.61–129.98 µm) than controls (69–97 µm), indicating enhanced epithelialization. Flavonoids, tannins, and saponins in guava extract stimulated keratinocyte migration and collagen synthesis, while hydrogel maintained wound moisture, promoting regeneration. Reduced IL-16 levels accelerated the transition to the proliferative phase, with improved tissue organization and angiogenesis marked by increased VEGF expression

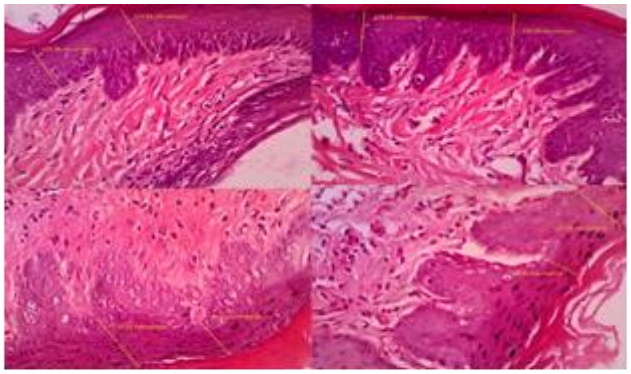

Figure 1 Histology Results from Gingiva Mucous Epithelization of Rabbit at Day 3 after Combination of Guava Leaf Ethanol Gel (Psidium guajava Linn) and Polyvinylpyrrolidone Hydrogel

Source: Primary data processed, 2025

Figure 2 histological analysis on day 14 post-treatment showed near-complete healing in the treatment group (P1), with thicker, well-organized epithelium (161.74–173.22 µm) compared to controls (128.53–136.82 µm). Fibroblast activity declined, marking the transition to the maturation phase with stabilized collagen synthesis and ECM organization. VEGF levels decreased, indicating sufficient vascularization, while IL-16 levels were significantly lower, suggesting reduced inflammation. Unlike the untreated control (K2), which still showed inflammation, P1 exhibited optimal regeneration, confirming the gel's effectiveness in accelerating wound healing.

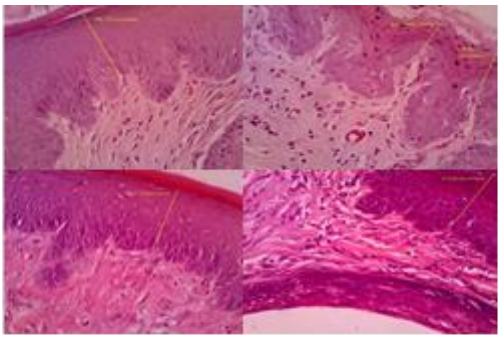

Figure 2 Histological Evaluation of Mandibular Gingival Mucosal Wound Healing in Rabbits on Day 14 Post-Treatment with a Combination of Ethanol Extract of Guava Leaves and Polyvinylpyrrolidone Hydrogel

Source: Primary data processed, 2025

Wound healing involves inflammation, proliferation, and remodeling, with fibroblasts playing a crucial role in ECM production, collagen synthesis, and immune regulation [15]. This study demonstrated that a combination of ethanol extract of guava leaves (*Psidium guajava* Linn) and polyvinylpyrrolidone (PVP) hydrogel significantly enhances fibroblast proliferation, VEGF expression, and epithelialization while reducing inflammation. On day 3, fibroblast counts in the treatment group (P1) were 64.50 ± 4.43, significantly higher than controls (p =

0.041), with further increases by day 14 (76.75 ± 7.68 vs. 66.67 ± 1.53) [16]. The hydrogel sustained fibroblast activity into the remodeling phase, minimizing fibrosis [20]. VEGF, a key angiogenic factor, was also significantly elevated in P1 (68.99 ± 4.77 vs. 57.34 ± 1.54 on day 3; 81.95 ± 5.23 vs. 58.87 ± 6.02 on day 14), suggesting enhanced vascularization and oxygen supply [21, 27]. The gel also modulated inflammation by reducing IL-6 (38.28 ± 0.95 on day 3 to 23.87 ± 1.88 on day 14, $p < 0.000$), expediting the transition to proliferation [25]. Additionally, IL-16, an inflammatory marker, decreased by 45% in P1 by day 3, reaching 27.34 ± 1.21 pg/mL on day 14 compared to 41.78 ± 2.87 pg/mL in controls, fostering a favorable environment for regeneration [34]. The hydrogel's moisture-retaining properties supported keratinocyte migration and gradual bioactive release, further enhancing healing efficiency [23]. Histological analysis confirmed superior epithelialization in P1, with epithelial thickness reaching 176.95 ± 11.99 µm by day 14 compared to 129.48 ± 7.29 µm in controls [24]. Guava leaf extract's flavonoids and tannins played essential roles in reducing oxidative stress, forming a protective barrier, and enhancing collagen deposition [22, 26]. The antibacterial effects against *Staphylococcus aureus* and *Pseudomonas aeruginosa* further reduced infection risks, crucial for chronic wound management [34]. These findings suggest that integrating herbal bioactive compounds with biomaterials like PVP hydrogel provides a promising therapeutic strategy for enhancing wound healing, optimizing fibroblast activity, angiogenesis, and inflammation control [21, 29, 36].

CONCLUSION

The combination of guava leaf ethanol extract and PVP hydrogel demonstrates significant potential in enhancing gingival wound healing in rabbits, with the treatment group showing increased fibroblast count, accelerated epithelialization, elevated VEGF levels, and markedly reduced IL-6 levels, indicating effective inflammation control and a favorable wound microenvironment. The synergy between the bioactive compounds present in guava leaf extract — namely flavonoids, tannins, and terpenoids — and the moisture-retaining, biocompatible properties of PVP hydrogel collectively improves bioavailability, promotes angiogenesis, and minimizes excessive inflammation and scarring, with suture-assisted application further enhancing wound stabilization and uniform gel distribution. These findings position this combination therapy as a promising topical agent for postoperative oral and maxillofacial wound care and the management of chronic or non-healing wounds such as diabetic ulcers; however, future research should focus on elucidating the molecular mechanisms and signaling pathways underlying these synergistic effects, evaluating clinical translation in human subjects with respect to optimal dosage, application frequency, and safety profile, and fostering collaboration between researchers, clinicians, and the pharmaceutical industry to develop commercially viable products that can benefit patients with impaired wound healing.

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