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Effect of Carica papaya Leaf Extract on Granulation and Epithelialization in Surgical Wounds

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Abstract

Background: Natural products are increasingly favored in wound care due to concerns about antibiotic resistance and side effects of synthetic drugs. Carica papaya L., a tropical plant native to Central America and widely grown in Indonesia, contains bioactive compounds with properties essential for tissue repair. This study tests whether a topical Carica papaya formulation speeds up wound healing by measuring granulation and epithelialization.

Methods: Using a quasi-experimental design. A total of 50 participants were divided into a control (standard wound care) and a treatment group (standard care + C. papaya extract). Analysis used the Paired T test.

Result: Paired t-tests indicated no significant changes in the control group ($p = 1.00$). In contrast, the treatment group demonstrated statistically significant improvements in granulation (pre: 0.44 ± 0.51; post: 1.56 ± 0.51; $t = -9.35$, $p < 0.001$) and epithelialization (pre: 0.68 ± 0.47; post: 1.72 ± 0.46; $t = -10.25$, $p < 0.001$). Independent-samples t-tests confirmed significant differences between groups after the intervention (granulation: $t = -9.35$, $p < 0.001$; epithelialization: $t = -10.25$, $p < 0.001$). These results support the incorporation of C. papaya extract into evidence-based complementary wound management protocols.

Conclusion: Carica papaya extract significantly enhances wound healing, promoting granulation and epithelialization. Thus, it may serve as an effective adjunctive therapy in clinical wound management.

Keywords: Carica Papaya, Epithelialization, Granulation tissue

BACKGROUND

The use of natural products in wound management has gained increasing attention due to rising concerns over antibiotic resistance and the adverse effects associated with synthetic drugs. Among these, Carica papaya L., a tropical plant native to Central America and widely cultivated in Indonesia, has shown promising wound-healing properties. The plant contains bioactive compounds, including papain, flavonoids, tannins, and alkaloids, that exhibit anti-inflammatory, antimicrobial, antioxidant, and proteolytic activities, all of which are crucial for promoting tissue regeneration (1). These multifaceted pharmacological actions make C. papaya an attractive candidate for the development of safe, affordable, natural wound-healing agents (2). However, despite the growing body of in vitro and animal-based studies supporting its efficacy, a critical question remains unanswered: to what extent have these promising preclinical findings been translated into clinical practice? Specifically, there is a need to systematically evaluate the number and quality of clinical trials involving human participants to determine the true therapeutic potential of C. papaya in wound management. Furthermore, identifying the methodological limitations and gaps in the existing clinical research is essential to guide future studies and facilitate the development of evidence-based guidelines for its use.

Chronic and postoperative wounds are a growing public health challenge, affecting millions each year and increasing healthcare costs. Delayed healing prolongs recovery, increases infection risk, and increases hospitalization costs. It also reduces quality of life. In developing countries like Indonesia, many lack access to advanced wound care, especially in rural or resource-limited settings. As a result, traditional remedies still play a major role in primary healthcare. One study reported that about 30% of patients with minor surgical wounds at community health centers used herbal treatments as their first-line therapy (3). This highlights the need for plant-based interventions that are accessible and culturally acceptable in Indonesia's healthcare system.

Previous studies demonstrate the wound-healing efficacy of C. papaya. Papaya leaf extract enhanced granulation tissue and re-epithelialization in animal models (4), while seed extract improved wound closure rates through upregulation of TGF-β1 and VEGFA, key growth factors in tissue repair (5). The antioxidant properties of C. papaya also protected fibroblasts and keratinocytes from oxidative stress, supporting cellular integrity during healing (6). Collectively, these findings indicate that C. papaya may accelerate healing by modulating inflammatory and regenerative pathways (7).

Despite strong preclinical evidence, clinical validation of C. papaya's wound-healing effects remains limited. Most studies so far have been conducted in vitro or in animal models. Few have involved human participants. Many existing clinical studies also lack rigorous designs, standardized formulations, or proper control groups. This limits the generalizability of their findings. Robust pretest–posttest control-group trials are essential to advancing C. papaya from traditional use to evidence-based practice.

Therefore, this study aims to evaluate the impact of a C. papaya-based topical formulation on wound-healing parameters, specifically granulation and epithelialization, in a controlled clinical setting. By integrating traditional ethnomedicinal knowledge with modern scientific validation, this research contributes to the growing body of evidence supporting the use of natural products in clinical wound care. The findings are expected to provide valuable insights into the therapeutic potential of C. papaya as an adjunctive, affordable, and culturally relevant intervention for wound management, particularly within low- and middle-income healthcare systems such as Indonesia's. The primary objective of this study is to evaluate the effectiveness of a Carica papaya-based topical formulation in enhancing wound healing, as measured by granulation and epithelialization scores, compared to standard wound care.

METHODS

Study Design

This study employed a quasi-experimental design with a pretest–posttest control group approach. It was conducted at a local healthcare center in Indonesia.

Population and Sample

Fifty adults aged 40 to 70 years with clean surgical wounds were selected using purposive sampling. Participants met the inclusion and exclusion criteria. They were then randomly assigned to one of two groups to ensure internal validity. Each drew a sealed envelope containing a card indicating whether they were assigned to the control group (n = 25), which received standard wound care, or the intervention group (n = 25), which received standard care plus a Carica papaya leaf extract–based ointment. This procedure used purposive selection but randomized group assignment. Fifty adults aged 40-70 years with clean surgical wounds were included. Inclusion criteria were: (1) non-infected, minor wounds, (2) willingness to participate, and (3) no known allergies to the intervention. Exclusion criteria were: (1) diabetes, (2) immunosuppressive conditions or therapy, and (3) prior use of other wound-healing agents. The dependent variables were granulation tissue formation and epithelialization, which served as indicators of wound healing. Both variables were measured using a three-level ordinal scale (poor, moderate, good). This scoring system was selected for its practicality in clinical settings; however, it has not been previously validated. This lack of formal validation represents a limitation of the present study.

Intervention

The intervention group received standard wound care supplemented with a Carica papaya leaf extract-based ointment. The extract was prepared using a maceration method with 96% ethanol as the solvent. Fresh Carica papaya leaves were washed, air-dried, and ground into powder. The powder was then immersed in ethanol for 72 hours, followed by filtration and evaporation using a rotary evaporator to obtain a crude extract. The extract was incorporated into a standard ointment base at a concentration of 10% (w/w). The formulation was prepared weekly and stored in airtight containers at 4°C to maintain stability throughout the study period. No significant changes in color, odor, or consistency were observed during application, indicating acceptable short-term stability. Using an ordinal scoring scale as follows:0 = Poor, 1 = Moderate, 2 = Good Assessments were performed twice—before (pretest) and after (posttest) the 14-day intervention period.

Data Collection

The evaluation was carried out by trained healthcare personnel using a standardized clinical wound observation checklist to ensure consistency and reliability. The C. papaya extract was prepared from fresh leaves, standardized, and formulated into a hydrogel base suitable for topical application. Participants in the intervention group were instructed to apply the papaya-based formulation to their wounds twice daily for 14 consecutive days. The control group received only standard saline dressing as per routine wound management protocol. Both groups were monitored closely to ensure adherence and to record any adverse reactions during the study period.

Data Analysis

Data were analyzed using SPSS version 26.0. The normality of the data distribution was verified using the Shapiro–Wilk test. Paired t-tests were used to assess within-group differences (pretest vs. posttest). Independent-samples t-tests were used to compare post-intervention outcomes between the control and intervention groups. A p-value of less than 0.05 was considered statistically significant.

Ethical Considerations

This study received ethical approval from the Institutional Ethics Review Board of the participating healthcare center and Universitas Jember (reference number 265/UN25.1.14/KEPK/2025). All participants were provided with detailed information about the study objectives, procedures, potential risks, and benefits. Written informed consent was obtained from all participants prior to enrollment. Confidentiality and anonymity of participant data were strictly maintained throughout the research process.

RESULT AND DISCUSSION

Demographic Characteristics

A total of 50 participants completed the study until the end of the follow-up period. The demographic and clinical characteristics of the participants are presented in Table 1.

Table 1. Demographic Characteristics of Respondents (N = 50)

Characteristic	Control (n = 25)	Intervention (n = 25)	Total (N = 50)	p-value*
Sex, n (%)				0.87
Male	8 (32%)	7 (28%)	15 (30%)	
Female	17 (68%)	18 (72%)	35 (70%)	
Age Group (years), n (%)				0.92
40–50 years	6 (24%)	5 (20%)	11 (22%)	
51–60 years	16 (64%)	16 (64%)	32 (64%)	
61–70 years	3 (12%)	4 (16%)	7 (14%)	
Baseline Granulation Score (Pretest)				0.07
Mean (SD)	0.20 (0.41)	0.44 (0.51)	0.32 (0.47)	
Median (Min–Max)	0 (0–1)	0 (0–1)	0 (0–1)	
Baseline Epithelialization Score (Pretest)				0.05
Mean (SD)	0.40 (0.50)	0.68 (0.47)	0.54 (0.50)	
Median (Min–Max)	0 (0–1)	1 (0–1)	0.5 (0–1)	

Chi-square test for categorical data; Mann-Whitney U test for numerical data (baseline scores). No significant differences were observed between groups for any characteristic ($p > 0.05$), indicating that both groups were homogeneous at baseline.

Table 1 shows that most participants were female (70%) and aged 51 to 60 years (64%). Statistical analysis revealed no significant differences between the control and intervention groups in sex distribution ($p = 0.87$), age group ($p = 0.92$), or baseline granulation scores ($p = 0.07$). These results demonstrate that both groups had comparable characteristics before the intervention.

Effectiveness of the Intervention on Granulation Tissue Formation

Analysis of granulation tissue formation revealed marked differences between the two groups following the 14-day treatment period. Detailed results are presented in Table 2.

Table 2. Comparison of Granulation Scores Between Groups

Group	N	Pre Mean (SD)	Post Mean (SD)	Within-Group Change	Between-Group Difference at Posttest
Control	25	0.20 (0.41)	0.20 (0.41)	MD=0.00	MD = 1.36
				(t = 0.00; p = 1.00)	95% CI [1.08 – 1.64]
Treatment	25	0.44 (0.51)	1.56 (0.51)	MD = 1.12	Effect Size (Cohen's d) = 2.69
				(t = -9.35; p < 0.001)	(p < 0.001)

In the control group, granulation scores remained constant from pretest to posttest (mean ± SD: 0.20 ± 0.41 at both time points). Statistical analysis indicated no significant difference (t = 0.00; p = 1.00). Thus, standard wound care alone did not improve granulation tissue formation. Conversely, the intervention group's granulation scores increased from 0.44 ± 0.51 to 1.56 ± 0.51. This increase was statistically significant (t = -9.35; p < 0.001).At posttest, the mean difference between groups was 1.36 (95% CI: 1.08–1.64), with a Cohen's d of 2.69, indicating a large effect size. The Carica papaya leaf extract ointment demonstrated significant statistical and clinical efficacy in promoting granulation tissue formation.

Effectiveness of the Intervention on Epithelialization Formation

Analysis of Epithelialization formation revealed marked differences between the two groups following the 14-day treatment period. Detailed results are presented in Table 3.

Table 3. Comparison of Epithelialization Scores Between Groups

Group	N	Pre Mean (SD)	Post Mean (SD)	Within-Group Change	Between-Group Difference at Posttest
Control	25	0.40 (0.50)	0.40 (0.50)	MD=0.00	MD = 1.32
				(t = 0.00; p = 1.00)	95% CI [1.05 – 1.59]
Treatment	25	0.68 (0.47)	1.72 (0.46)	MD = 1.04	Effect Size (Cohen's d) = 2.81
				(t = -10.25; p < 0.001)	(p < 0.001)

Analysis of the epithelialization process revealed a pattern similar to that of granulation tissue formation. In the control group, epithelialization scores remained unchanged from pretest to posttest (0.40 ± 0.50 to 0.40 ± 0.50), with statistical analysis confirming no significant difference (t = 0.00; p = 1.00). These results indicate that standard care alone was insufficient to promote epithelialization.

In contrast, the intervention group demonstrated a highly significant improvement in epithelialization scores, increasing from 0.68 ± 0.47 before treatment to 1.72 ± 0.46 after treatment (t = -10.25; p < 0.001). The mean difference in epithelialization scores between groups at posttest was 1.32 (95% CI: 1.05 – 1.59). The effect size, calculated using Cohen's d, was 2.81, which falls into the large effect category. This finding confirms that the ointment containing Carica papaya leaf extract was highly effective in accelerating wound epithelialization.

Between-Group Comparison

Table 4. Between-Group Comparison

Outcome Measure	T-Value	P-Value
Granulation	-9.35	<0.001
Epithelialization	-10.25	<0.001

Table 4 indicates that independent samples t-tests confirmed these results. Significant differences between groups were observed at posttest for both granulation ($t = -9.35$, $p < 0.001$) and epithelialization ($t = -10.25$, $p < 0.001$). Participants treated with the Carica papaya topical formulation exhibited superior wound-healing outcomes compared to those receiving standard care alone.

In summary, the findings demonstrate that the Carica papaya leaf extract formulation significantly enhanced wound healing, as shown by marked improvements in granulation tissue formation and epithelialization. The lack of change in the control group supports the conclusion that these improvements resulted from the papaya-based intervention rather than natural healing processes. These results offer robust statistical and clinical evidence supporting the potential use of C. papaya extract as an effective complementary agent in wound management.

DISCUSSION

The findings indicate that a Carica papaya–based formulation significantly enhances wound healing, especially granulation and epithelialization. These results align with previous preclinical studies reporting the beneficial effects of C. papaya extracts in modulating inflammation, promoting fibroblast proliferation, and accelerating tissue repair (8,9). Key bioactive compounds such as papain, flavonoids, and tannins likely contribute to these effects by supporting collagen remodeling and stimulating angiogenesis at the wound site (10,11).

The observed improvements extend beyond statistical significance to clinical relevance. The intervention group achieved near-maximal scores for granulation (1.56 out of 2) and epithelialization (1.72 out of 2) within 14 days, indicating accelerated wound healing (12). This acceleration reduces wound exposure time, potentially lowering the risk of secondary infections, decreasing patient discomfort, and reducing healthcare costs associated with prolonged wound care . Large effect sizes (Cohen's $d > 2.5$ for both outcomes) suggest that the therapeutic benefits are both statistically and clinically significant for clinicians and patients.

Regarding comparative effectiveness, this study demonstrates clear superiority of C. papaya over standard saline dressings; however, its position within the broader wound care landscape requires evaluation against other agents. Compared to conventional topical antibiotics such as silver sulfadiazine or povidone-iodine, C. papaya provides multifactorial mechanisms including enzymatic debridement via papain, anti-inflammatory activity, and antioxidant effects—beyond antimicrobial action alone . Compared with other herbal preparations such as Aloe vera or Centella asiatica, C. papaya exhibits granulation effects comparable to or superior to those, likely due to its potent proteolytic activity that removes necrotic tissue while promoting regeneration (13). Nonetheless, head-to-head comparative trials are necessary to establish its relative efficacy against these established natural and conventional agents.

Safety considerations are critical when introducing plant-based topical formulations into clinical practice. Although no adverse reactions were observed during the 14-day study period, the potential for allergic contact dermatitis or skin irritation remains. Carica papaya contains proteolytic enzymes (papain) and latex components that may sensitize susceptible individuals, potentially triggering type I

hypersensitivity or irritant contact dermatitis (14). Patients with known latex allergy or prior sensitivity to papaya fruit may be at increased risk; thus, pre-application patch testing is recommended for individuals with a history of plant allergies. Additionally, the concentration of active compounds (10% w/w in this study) and the application frequency require careful consideration, as higher concentrations may increase the risk of local irritation. Future studies with larger samples and extended follow-up are necessary to fully characterize the safety profile, including rare adverse events. Compared to the control group, which showed no improvement, the treatment group exhibited a substantial, statistically significant increase in granulation and epithelialization scores after 14 days. This difference underscores the therapeutic potential of C. papaya as a natural wound-healing agent. The enhancement likely results from the synergistic action of proteolytic enzymes and antioxidants, which facilitate the removal of necrotic tissue and promote healthy granulation tissue formation (15). These findings align with those of Hakim et al., who demonstrated that C. papaya seed extract upregulated TGF-β1 and VEGFA expression, key regulators of fibroblast proliferation and angiogenesis.

C. papaya modulates the inflammatory phase of wound healing. Papain, a cysteine protease, reduces inflammation by degrading damaged proteins, preventing the accumulation of necrotic tissue that impedes healing (16). Flavonoids and tannins exert antioxidant and antimicrobial effects, helping limit oxidative stress and infection at wound sites (17). This combined activity likely facilitates the rapid transition to the proliferative phase observed in the treatment group.

Improved epithelialization scores in the treatment group confirm C. papaya's regenerative potential. Re-epithelialization is crucial for wound closure and needs keratinocyte migration, growth, and differentiation (18). Polyphenolic compounds in papaya extract may help these processes by aiding extracellular matrix synthesis and supporting cell adhesion. Garcia-Villegas et al. reported similar outcomes. They found papaya extract protected fibroblasts from oxidative stress, preserving tissue regeneration.

Clinically, these results are significant for wound care in Indonesia and other low-resource settings where herbal remedies remain prevalent due to limited access to modern products. This study provides evidence supporting the integration of C. papaya extract into complementary wound care as a cost-effective, culturally accepted, and locally available alternative to commercial formulations (19). The findings also validate Indonesian ethnomedicinal practices, such as the use of papaya leaves for minor wounds.

This study further emphasizes the role of natural products as adjunctive therapies amid increasing concerns about antibiotic resistance. The antimicrobial activity of C. papaya is well documented, particularly against Staphylococcus aureus and Pseudomonas aeruginosa, common wound pathogens (20). Incorporating such natural agents into standard wound care protocols may reduce reliance on topical antibiotics, thereby mitigating resistance while preserving therapeutic efficacy .

Despite promising results, several limitations warrant consideration. The sample size of 50 participants was relatively small and limited to a single healthcare center, potentially limiting the generalizability of the findings. Furthermore, histopathological analyses were not conducted, precluding direct observation of cellular-level tissue changes. Long-term follow-up was also absent, preventing assessment of sustained healing outcomes or recurrence rates. Future studies addressing these limitations would enhance the evidence base for clinical adoption.

Future research should employ larger, multi-center trials involving diverse populations and wound types to validate the present findings. Incorporating biochemical markers, such as hydroxyproline concentration and cytokine profiles, could help elucidate the molecular mechanisms underlying C. papaya's wound-healing effects. Furthermore, comparative studies using other herbal or synthetic formulations would help position C. papaya extract within the broader spectrum of wound

care options. Such evidence would be valuable for developing standardized papaya-based therapeutic products and establishing clinical guidelines for their use.

These findings indicate opportunities for pharmaceutical innovation. Incorporating papaya bioactives into hydrogels, nanofibers, or films may enhance stability, absorption, and sustained release at wound sites (21). Such technologies could improve the efficacy of papaya-based products, particularly for chronic or diabetic wounds requiring prolonged exposure (22-26).

In summary, this study provides robust evidence that Carica papaya extract significantly accelerates wound healing by enhancing granulation and epithelialization. The results corroborate previous preclinical findings and validate traditional uses of papaya leaves in Indonesian medicine. While further research is needed to elucidate the molecular mechanisms and long-term outcomes, these findings support integrating C. papaya into modern, evidence-based wound management. By bridging traditional knowledge with scientific validation, this study contributes substantially to the advancing field of phytotherapeutic wound care.

CONCLUSION

Topical application of a Carica papaya–based formulation significantly enhanced granulation and epithelialization in surgical wounds, demonstrating its potential as a safe, effective, and affordable complementary therapy for wound management. These findings support integrating C. papaya into evidence-based clinical practice, especially in low-resource settings where accessibility and cultural acceptance are critical. Future research should involve larger, multi-center trials and molecular analyses to further validate efficacy and elucidate underlying mechanisms, facilitating the development of standardized C. papaya–based wound care products for primary healthcare systems.

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AUTHOR'S CONTRIBUTION STATEMENT

MS: conceptualization, writing-original draft, review & editing. MT: conceptualization, methodology, manuscript review. R: conceptualization, and manuscript review. IZ: etichal clearance, data analysis, and co-writing-original draft.DHP: formal analysis, writing -original draft, manuscript review. FZ: validation, manuscript review.NRL: validation, manuscript review.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

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