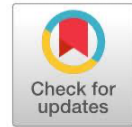


Comparative Effectiveness of Green Betel Leaf (*Piper betle* L.) Spray Gel and Conventional Gel on Perineal Wound Healing in Mice (*Mus musculus*)



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ABSTRACT

Perineal wounds following vaginal delivery are common and may lead to pain, infection, and delayed healing, reduced maternal quality of life. Green betel leaves (*Piper betle* L.) possess antibacterial, anti-inflammatory, and antioxidant that may promote wound healing, while spray gel formulations offer hygienic application and improved drug distribution. This study compared the effectiveness of green betel leaf spray gel and conventional gel in promoting perineal wound healing. A true experimental pretest-posttest study was conducted using 36 female *Mus musculus* with induced perineal wounds randomly allocated to spray or conventional gel groups (n =18 each). Perineal wound healing was assessed using REEDA scores on days 1, 3, 5, and 7. Data were analyzed using Friedman and Mann-Whitney U tests. Both formulations significantly improved wound healing over time. However, the spray gel demonstrated significantly greater improvement than the conventional gel, with a higher mean Δ REEDA score (5.28 ± 0.575 vs 4.67 ± 0.840 , $p = 0.020$), indicating greater reductions in wound severity. Green betel leaf spray gel was more effective than conventional gel in promoting perineal wound healing in mice. Its hygienic, non-contact application and superior healing performance support its potential as a topical intervention for postpartum perineal care, warranting further clinical evaluation.

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INTRODUCTION

Postpartum perineal wounds are common complications of vaginal delivery and result from either spontaneous perineal tears or episiotomy. These injuries involve the tissue between the vagina introitus and anus. These injuries often cause pain, discomfort, and difficulty performing daily activities, potentially interfering with breastfeeding and reducing maternal quality of life.(1) Beyond the immediate postpartum period, such wounds may result in long-term complications, including dyspareunia, delayed physical recovery, and increased risk of maternal anxiety or depressive symptoms, highlighting their broader clinical significance. According to the World Health Organization (WHO), approximately 85% of women undergoing vaginal birth experience perineal trauma, with an estimated incidence of 75%

in Indonesia.(2) Primiparous women are particularly vulnerable, and the moist perineal environment, combined with proximity to the anus, increases the risk of infection and complicates hygiene maintenance.(3)

Perineal wounds infection remains a major contributor to maternal morbidity and, in severe cases, maternal mortality. Conventional treatments, including antibiotics and povidone-iodine antiseptics, effectively reduce infection risk but may produce adverse effects, such as bacterial resistance, skin irritation, and impaired collagen synthesis.(4) Moreover, the cytotoxic effects of these agents on fibroblasts and other reparative cells may delay wound closure, revealing a gap between their effectiveness and safety in clinical practice.(5) This limitation highlights an urgent need for alternative interventions that can both prevent infection and support tissue repair without adverse effects.(6) Identifying safe, effective, and easy-to-apply non-pharmacological solutions, particularly those derived from natural materials with antibacterial, anti-inflammatory, and antioxidant properties, is therefore a critical step toward improving postpartum perineal care. (7)

Green betel leaf (*Piper betle* L.) has emerged as a promising medicinal plant because it contains chavicol, chavibetol, flavonoids, and eugenol, which possess antibacterial, antiseptic, antioxidant, and anti-inflammatory properties that promote tissue regeneration.(8) Previous experimental studies have primarily evaluated *Piper betle* extract in conventional dosage forms, such as decoctions, topical solutions, and ointments. Less studies evaluated practical for postpartum perineal care due to direct contact requirements, hygiene challenges, and higher risk of microbial contamination.(9) Additionally, comparative research on innovative dosage forms like spray gels versus conventional gels made from the same natural ingredients is lacking. Spray gel formulations offer advantages in terms of hygiene, ease of application, and faster absorption of active compounds without direct wound contact, suggesting a potentially safer and more effective option for postpartum perineal wound management.(10) Although numerous studies have demonstrated the wound-healing potential of *Piper betle*, evidence comparing different topical delivery systems remains scarce. In particular, no previous study has directly evaluated spray gel and conventional gel formulations using standardized REEDA assessments in a preclinical perineal wound model.

Animal models, particularly mice (*Mus musculus*), are widely used in preclinical wound-healing research due to their physiological and immunological similarities to humans, ease of handling, and well-characterized wound repair mechanisms. This preclinical study was designed following the ARRIVE guidelines to ensure rigorous reporting of animal experiments. Based on these considerations, this study was conducted to compare the effectiveness of spray gel and gel formulations of green betel leaf extract on perineal wound healing in mice. The findings are expected to serve as a foundation for developing innovative, safe, and practical herbal-based non-pharmacological therapies for perineal care in postpartum women.

METHOD

This study employed a true experimental, two-group pretest–posttest design to compare the effectiveness of spray gel and gel formulations of green betel leaf extract (*Piper betle* L.) on perineal wound healing in mice, based on changes in REEDA scores. The experiment was conducted from 03 to 09 June 2025. A total of 36 healthy female mice (*Mus musculus*), aged 2 months and weighing 25–30 grams, were included. Inclusion criteria comprised clinically healthy, non-pregnant mice aged 2 months and weighing 25-30 gram, with no evidence of previous wounds or infections. Exclusion criteria included signs of illness, severe allergic reactions, or death during the experimental period. Missing observations were handled using the last observation carried forward (LOCF) approach. Female mice were selected because their anatomical and physiological characteristics more closely resemble postpartum perineal conditions. To minimize assessment bias, REEDA

evaluations were performed by blinded assessors who were not informed of the intervention groups.

The mice were randomly assigned to two groups ($n = 18$ per group) using a computer-generated simple randomization method. Perineal wounds were created under general anesthesia using ketamine-xylazine, a standardized perineal incision measuring approximately 1 cm was created using a sterile surgical blade under aseptic conditions. Treatments were administered twice daily for seven days by the same investigator, using a standardized dose of 0.1 mL per application. Both formulations contained 10% (w/v) green betel leaf extract using Carbopol 940 as the gelling agent to ensure uniform consistency and optimal absorption.

Wound healing was evaluated on days 1, 3, 5, and 7 using the REEDA scale (Redness, Edema, Ecchymosis, Discharge, Approximation). The scale consists of five indicators scored from 0 to 3, yielding a total score range of 0–15, where lower scores indicate better wound healing. The REEDA instrument was adapted for animal use by modifying observational descriptors to suit murine skin characteristics while maintaining the original scoring structure. The observation sheet had been validated in previous wound-healing studies, and intra-rater reliability was assessed prior to the experiment (intraclass correlation coefficient = 0.92) to ensure consistent scoring.(9)

Data were analyzed using IBM SPSS Statistics version 25. Within-group changes in REEDA scores were evaluated using the Friedman test for repeated measures, while between-group differences were assessed using the Mann–Whitney U test. The effectiveness of the intervention was further evaluated using the normalized gain (N-Gain), which was calculated by comparing the improvement in REEDA scores after treatment with the maximum possible improvement for each participant. Higher N-Gain values indicated greater improvement in wound healing and were classified as low (<0.30), moderate ($0.30–0.69$), or high (≥ 0.70). Statistical significance was set at $p < 0.05$, and all tests were two-tailed. The study received ethical approval from the Health Research Ethics Committee of Poltekkes Kemenkes Semarang (Approval No. 932/EA/F.XXIII.38/2025). This study was reported in accordance with the ARRIVE 2.0 guidelines and followed the 3R principles (Replacement, Reduction, and Refinement) to ensure animal welfare. Animals were monitored daily for signs of pain or distress throughout the study.

RESULTS

Perineal wound healing was evaluated using REEDA scores to compare the effectiveness of green betel leaf spray gel and conventional gel in mice (*Mus musculus*) over a seven-day treatment period.

Baseline Characteristics

Baseline characteristics of the experimental animals were compared to ensure the equivalence of both treatment groups before intervention.

Table 1. Baseline characteristics of experimental animals in the spray gel and gel groups.

Characteristic	Group						p-value
	Spray gel			Conventional gel			
	n	%	Mean $\pm$ SD	n	%	Mean $\pm$ SD	
Age (days)	18	100	62.78 $\pm$ 3.91	18	100	62.22 $\pm$ 3.91	0.777*
Body weight (grams)	18	100	26.78 $\pm$ 1.73	18	100	26.39 $\pm$ 1.69	0.534*

Based on Table 1, there were no significant differences in age or body weight between groups. Therefore, it could be concluded that the sample characteristics in the spray gel and conventional gel groups had homogeneous variances, indicating no significant difference between the two groups.

Changes in REEDA Scores

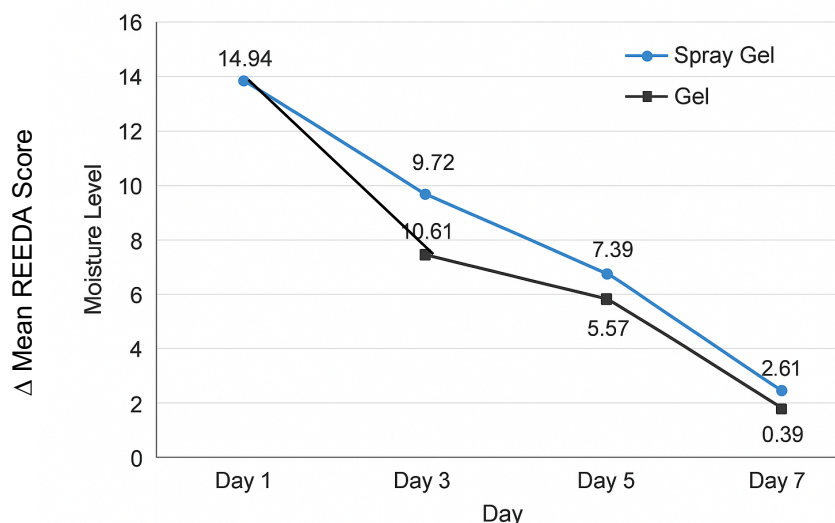
To determine the effectiveness of the spray gel and conventional gel treatments, bivariate statistical tests were performed to compare REEDA scores between the intervention and control groups. Normality testing indicated a non-normal distribution of REEDA scores at all observation points ($p < 0.05$). Therefore, non-parametric tests were applied, specifically the Friedman test for within-group comparisons and the Mann–Whitney U test for between-group comparisons, with a 5% significance level or a 95% confidence interval.

Table 2. Comparison of REEDA score between the spray gel group and the conventional gel groups during the observation period

REEDA Scores Measurement	Groups		P-Value	U	Z
	Spray gel	Conventional Gel			
	Mean Rank	Mean Rank			
Pre-Observation (Day 1)	18.50	18.50	0.000**	162.0	0.000
Post-Observation (Day 3)	22.36	14.64	0.023**	92.5	-2.270
Post-Observation (Day 5)	21.97	15.03	0.033**	99.5	-2.127
Post-Observation (Day 7)	22.28	14.72	0.020**	94.0	-2.335
P-value	0.000*	0.000*			
χ^2	52.867	54.00			
df	3	3			

*Friedman **Uji Mann Whitney

The REEDA scores were compared between the spray gel and conventional gel groups at each observation point using the Mann–Whitney U test, while within-group changes over time were analysed using the Friedman test. At baseline (Day 1), both groups had identical mean ranks (18.50 vs. 18.50), indicating no significant difference between groups ($U = 162.0$, $Z = 0.000$, $p = 1.000$), confirming comparable baseline wound conditions before treatment. On subsequent days, the Spray Gel group consistently showed lower REEDA scores observed in from Day 3 onward reflected faster wound healing than in the conventional gel group (22.36 vs. 14.64, $U = 92.5$, $Z = -2.270$, $p = 0.023^{**}$), Day 5 (21.97 vs. 15.03, $U = 99.5$, $Z = -2.127$, $p = 0.033^{**}$), and Day 7 (22.28 vs. 14.72, $U = 94.0$, $Z = -2.335$, $p = 0.020^{**}$), indicating significantly better wound healing in the Spray Gel group. Within-group analysis using the Friedman test showed significant changes over time for both groups (Spray Gel: $\chi^2 = 52.867$, $df = 3$, $p = 0.000^*$; Gel: $\chi^2 = 54.00$, $df = 3$, $p = 0.000^*$), demonstrating that wound healing progressed significantly from Day 1 to Day 7 in both groups.



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Figure 1. Δ Mean REEDA score reduction during the seven-day observation period

The mean REEDA scores in both groups decreased progressively from Day 1 to Day 7. Both groups started with identical baseline scores (14.94). From Day 3 onward, the spray gel group consistently showed a greater decline in mean REEDA scores than the conventional gel group. By Day 7, the spray gel group reached a mean score of 0.39, compared with 2.61 in the conventional gel group, indicating that perineal wound healing in *Mus musculus* was faster and more complete with the spray gel formulation than with the conventional gel.

Table 3. Effect size and treatment effectiveness based on changes in REEDA score

Measurement Instrument	Groups	N	Δ Mean ± SD	Effectiveness (%)	Effect Size
REEDA Score	Spray gel	18	5,28 ± 0,575	98.4 **	0.55
	Conventional gel	18	4,67 ± 0,840	83.1**	0.38

N-Gain Score *Cohen's d

The results in Table 3 show that on day 7, the spray gel group had a mean REEDA score of 5.28 ± 0.575 , while the conventional gel group had a mean score of 4.67 ± 0.840 . The effectiveness of the spray gel in accelerating perineal wound healing reached 98.4%, compared with 83.1% in the conventional gel group. Additionally, the effect size on Day 7 was 0.55 for the Spray Gel group, indicating a moderate treatment effect, whereas the Gel group showed an effect size of 0.38, indicating a small treatment effect. These findings suggest that green betel leaf spray gel produced a greater treatment effect and superior clinical effectiveness than the conventional gel in reducing REEDA scores in *Mus musculus*.

DISCUSSION

The present study demonstrated that both spray gel and conventional gel formulations of green betel leaf (*Piper betle L.*) significantly accelerated perineal wound healing in mice (*Mus musculus*), as measured by reductions in REEDA scores. From day 1 through day 7, both groups exhibited progressive decreases, with the spray gel group consistently demonstrating greater improvement. On day 7, the mean Δ REEDA score was 5.28 ± 0.575 for the spray gel group, compared with 4.67 ± 0.840 for the gel group ($p = 0.020$). The N-

Gain score reflected an effectiveness of 98.4% for the spray gel versus 83.1% for the gel, and the effect size (Cohen's $d = 0.55$) indicated a moderate treatment effect and greater clinical effectiveness of the spray gel on wound healing.

The superior performance of the spray gel is primarily attributed to the essential oil content of green betel leaf, which contains chavicol, eugenol, caryophyllene, and estragole. (9) These compounds exhibit antibacterial, anti-inflammatory, antifungal, and antiseptic properties. (11) Chavicol has bactericidal activity approximately five times stronger than phenol, acting through protein denaturation and disruption of bacterial cell membranes to inhibit pathogenic growth. (12) These anti-inflammatory compounds reduce redness and oedema by suppressing prostaglandins synthesis and inflammatory cytokines production, while flavonoids and polyphenols provide antioxidant protection, promoting transition from the inflammatory phase to the proliferative phase. (13) Tannins act as natural astringents, strengthening capillary walls, reducing exudation, and supporting micro-haemostasis. Collectively, these mechanisms facilitate tissue approximation, re-epithelialization, and collagen deposition. (14)

The spray gel formulation enhances the biological activity of green betel leaf by producing fine droplets that distribute the active compounds uniformly across the wound surface. This delivery system improves bioavailability, while minimizing mechanical trauma, pain, and cross-contamination. (15) Maintaining a moist, clean, and bacteria-free environment supports angiogenesis, fibroblast proliferation, and collagen formation, accelerating tissue repair. (16) In contrast, conventional gel requires manual topical application, which may cause discomfort and localized microbial entry, although it still promotes healing by maintaining moisture and gradual release of active compounds. (17)

Compared with previous studies, the Spray Gel demonstrated faster and more effective wound healing. The improved outcome may also be attributable to increased residence time, enhanced penetration of active compounds, and reduced manipulation of the wound surface. While prior murine studies using *Piper betle* ointments or gels typically required 9–10 days for significant wound closure, the Spray Gel in this study achieved substantial reductions in REEDA scores within 7 days as presented in Table 3. This accelerated effect may be attributed to the spray formulation, which allows more uniform coverage, better absorption, and less disruption of the wound surface compared with conventional ointments or gels. (18) Additionally, differences in wound models and assessment methods may contribute; for example, this study used a standardized perineal wound model with repeated REEDA scoring, providing sensitive detection of early healing changes. (19) Unlike topical antibiotics or povidone iodine, which primarily act through antimicrobial mechanisms, the spray gel may combine anti-inflammatory, antimicrobial, and antioxidant effects of *Piper betle* extract, leading to faster tissue repair. (20) The high N-Gain effectiveness of 98.4% further supports its superior performance over conventional treatments. Collectively, these findings strengthen previous evidence while providing new quantitative evidence regarding the superiority of spray gel delivery systems for postpartum wound care highlighted by Novita et al., but also provide quantitative preclinical evidence that Spray Gel is a promising, potentially novel intervention specifically for perineal wound healing. (21)

The study has important theoretical and practical implications. Theoretically, it reinforces the understanding that bioactive compounds such as chavicol, eugenol, flavonoids, and tannins accelerate wound healing in moist tissue environments like the perineum by modulating inflammation, oxidative stress, and tissue regeneration. (8,9) Practically, the spray gel's hygienic and convenient application provides a strong basis for potential clinical translation after adequate safety evaluation, offering midwives a safe and effective topical intervention that may improve patient compliance, reduce healing time, and minimize infection risk. (22)

However, limitations include the use of healthy female mice without comorbidities, which may not fully replicate postpartum conditions in humans. Long-term outcomes, pain scores, and functional recovery were not assessed. The study also did not include histopathological assessment, bacterial load quantification, or biochemical markers of inflammation, which could have provided mechanistic evidence supporting the observed clinical improvement. Therefore, caution is required when extrapolating these findings to postpartum women.

Future randomized controlled clinical trials involving postpartum women are required to determine clinical effectiveness, safety, patient acceptability, and cost-effectiveness before implementation into routine obstetric care. Comparative studies with standard antiseptics or antibiotic creams could further establish its relative efficacy, while investigations into optimal dosing, frequency, and long-term outcomes would strengthen the evidence base for translational application.

Overall, these findings provide preliminary preclinical evidence supporting the development of green betel leaf spray gel as an innovative topical therapy for postpartum perineal wound management, providing both mechanistic insight and practical advantages. This study lays the foundation for future development of herbal-based, safe, and effective topical formulations for postpartum wound management, potentially improving midwifery practice and patient outcomes.

CONCLUSION

Both spray gel and conventional gel formulations of green betel leaf (*Piper betle* L.), applied twice daily for 7 days, effectively accelerated perineal wound healing in mice (*Mus musculus*), with the spray gel demonstrating significantly greater efficacy than the conventional gel (mean Δ REEDA 5.28 ± 0.575 vs 4.67 ± 0.840 ; $p = 0.020$). The superior performance of the spray gel may be associated with improved delivery of the plant's bioactive compounds, including chavicol, eugenol, flavonoids, and tannins, which are known to possess antibacterial, anti-inflammatory, and antioxidant effects. These findings provide preclinical evidence supporting the potential of *Piper betle* spray gel as a topical intervention for perineal wound management. Nevertheless, because this study was conducted in an animal model, further well-designed clinical trials are required to establish its safety, efficacy, and clinical applicability in postpartum women.

AUTHOR CREDIT STATEMENT

All authors contributed significantly to this study. Conceptualized the research, designed the study protocol, and coordinated data collection. Author 2 and 3 assisted in drafting and critically revising the manuscript. All authors reviewed and approved the final manuscript and take responsibility for the accuracy and integrity of the work.

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DECLARATION OF COMPETING INTEREST

There is no conflict of interest.

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