

Effect of Piper Betle Nanospray 7% on Inflammation and IL-6 Levels in Postpartum Maternal Wounds : A Study in the Grobogan Regency Area, Central Java in 2025

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Piper betle nanospray, IL-6, REEDA scale, and postpartum mothers

ABSTRACT

Postpartum second-degree perineal lesions are common and trigger an inflammatory response with an increase in IL-6. Suboptimal treatment risks prolonging the inflammatory process and inhibiting wound healing. *Piper betle Linn* is recognized as an herbal ingredient with anti-inflammatory potential; its nanospray formulation is believed to penetrate deeper layers of the skin, thereby accelerating wound healing. This study evaluated the effectiveness of a 7% *betel* leaf extract nanospray on the healing of perineal wounds in postpartum care. The study employed a true experimental design with a pretest-posttest control group, involving 40 respondents selected through stratified random sampling. The variables examined were the use of 7% *betel* leaf extract nanospray and the healing of grade II perineal wounds. Data analysis was conducted using the Kruskal-Wallis test and the Mann Whitney, followed by the Wilcoxon test. The findings demonstrated that administration of *Piper betle Linn* 7% nanospray extract significantly accelerated perineal wound healing, as measured by the REEDA scale ($p < 0.05$), with the majority of the intervention group (65%) exhibiting good healing. However, there was no significant difference in IL-6 levels between the intervention and control groups ($p > 0.05$). *Piper betle Linn* 7% nanospray extract is effective in accelerating the healing of grade II perineal wounds in postpartum mothers, as indicated by a decrease in REEDA scores, but does not significantly affect the reduction of IL-6 levels.

INTRODUCTION

Vaginal labor is a natural process that often causes perineal injury in the mother. These injuries can vary from natural tears to the result of the use of medical devices, interventions, or episiotomy. The importance of postpartum perineal wound care cannot be underestimated, as it is essential to alleviate discomfort, maintain hygiene, prevent infection, and accelerate maternal postpartum recovery (Hasanah et al., 2021).

One of the most common types of perineal injuries is second-degree laceration, which involves tears in the lining of the vagina, skin, and muscles of the perineum. Although often considered a minor problem, these injuries can cause discomfort, limit daily activities and increase the risk of infection (Puissegur et al., 2023). Some of the complications that may arise include severe pain, postpartum infections, difficulty urinating and defecating, to long-term sexual

dysfunction. Therefore, it is important to find effective methods of treating perineal wounds to speed up the healing process and minimize the risk of complications (Choudhari et al., 2022).

The genital tract is particularly susceptible to postnatal infections, especially if treatment is inadequate. This infection is associated with several pathogenic bacteria such as *S. Epidermidis*, *S. Aureus*, *E. Coli*, *Streptococcus Haemolyticus Aerobic*, and *Clostridium Welchii* (Putri et al., 2020). The wound healing process itself involves a series of complex stages, from the inflammatory phase, proliferation, to remodeling. The inflammatory phase is the body's initial response to injury, which is characterized by redness, swelling, heat, and pain (Dewi & Assyaidah, 2025). In this phase, immune cells such as macrophages will produce pro-inflammatory cytokines, one of which is interleukin-6. IL-6 plays a central role in inducing the body's acute phase response to infection or injury. Although IL-6 plays an important role in initiating the immune response and clearing damaged tissue, excessive levels of IL-6 can cause oxidative stress that will inhibit the wound healing process optimally (Ekofitranto et al., 2025). However, when the active SOD enzyme works to reduce oxidative stress and suppress the release of IL-6, redness and swelling in the wound will be reduced. For this reason, REEDA scale measurement is an effective clinical way to objectively monitor the progress of wound recovery. This scale helps to see if inflammation has subsided and wounds are beginning to regenerate, which indirectly indicates a decrease in IL-6 levels and supports the healing process (Jus et al., 2024).

Global data show a high prevalence of perineal injuries. WHO (2020) reports that around 2.7 million mothers worldwide (about 80% of postpartum mothers) experience a perineal tear during childbirth. If wound care is not adequate, this number could rise to 6.3 million by 2050. Degree 2 laceration is the most common (73.4%), followed by degree 1 (17.7%), degree 3 (8.4%), and degree 4 (0.5%) (Lestari et al., 2024). In Asia, perineal rupture accounts for 50% of all global cases and is the second most common cause of bleeding after uterine atonia (Astuti & Marsita, 2024). In Indonesia, the 2018 Indonesian Demographic and Health Survey showed that about 75% of mothers who gave birth vaginally experienced perineal tears, with a prevalence of 24% (25-30 years) and 62% (32-39 years) (Fithri & Simamora, 2022).

This problem is also evident at the regional level. According to the Central Java pocketbook (2024), postpartum infections account for 6.4% of maternal deaths in the province, ranking third after hypertension and bleeding (Harrington, 2021). Specifically, as of June 2024, Grobogan Regency reported 10 cases of maternal death after childbirth, of which one case was referred to Purwodadi Islamic Hospital due to perineal wound infection. A report from the Purwodadi Islamic Hospital polyclinic in August 2024 also showed that 5 out of 20 postpartum mothers with perineal sutures experienced open wounds and puruation, a condition that is very susceptible to infection if not treated properly.

Treatment of perineal lesions can be done pharmacologically and non-pharmacologically (Gusnimar et al., 2021). A non-pharmacological method that attracts attention is the use of herbal ingredients such as betel leaves (*Piper betle Linn*). Betel leaves are known to be rich in chemical compounds such as flavonoids (quercetin) and kavicol that have hemostatic, anti-inflammatory, antioxidant, antibacterial, antidiabetic, and anticancer effects (Herdiana et al., 2024). Supported by the research of Christina (2014), who stated that boiling *Piper betle Linn* for 20 minutes produces high levels of kavicol, which is an antibacterial compound. The results of the T test showed a significant level of 0.000, which confirmed its effectiveness in accelerating the healing of perineal wounds in postpartum mothers (Christina & Kurniyanti, 2014).

Although several previous studies, such as Srirahandayani (2022), have shown the effectiveness of betel leaf extract in healing perineal wounds ($p = 0.001$) (15), specific studies on the use of *Piper betle Linn* 7% nanospray extract against grade II perineal wounds in postpartum mothers focused on decreasing IL-6 levels as an indicator of inflammatory processes and REEDA scale measurements to assess the healing process clinically, not much has been done.

Therefore, the researcher is interested in conducting this study. This nanospray formulation is expected to increase the effectiveness of the absorption of active substances from betel leaf extract into wound tissue, so that the drug will more easily enter the wound and work right on the inflamed

area. This increase in bioavailability has the potential to accelerate anti-inflammatory processes and cell regeneration which will ultimately support more optimal wound healing.

The research aims to evaluate the effectiveness of 7% *Piper Betle Linn* Nanospray extract in treating second-degree perineal wounds in postpartum mothers by focusing on the inflammatory process (IL-6 levels) and monitoring the healing process using the REEDA scale. This study is motivated by the high prevalence of perineal injuries, particularly second-degree lacerations, and the potential benefits of non-pharmacological treatments like herbal remedies. Given the role of IL-6 in the inflammatory response and the ability of betel leaf extract to reduce inflammation, this research investigates how the nanospray formulation can enhance the bioavailability of active compounds to accelerate wound healing. The findings of this research could provide new insights into non-invasive treatment options for perineal injuries, offering a potential solution to improve the healing process in postpartum mothers and reduce complications related to infections. The study not only contributes to understanding the benefits of Piper Betle Linn in wound care but also offers a promising alternative for more effective, natural, and accessible post-delivery care.

METHOD

This study is classified as experimental quantitative research and adopts a True Experimental design with a Pretest-Posttest Control Group Design (Srihandayani & Aliza, 2022), utilizing a stratified random sampling method (Adnan & Latief, 2020). According to the formula of *Lwangga* and *Lemeshow* (1997) (Roflin & Liberty, 2021), a total sample of 40 respondents was obtained. The subjects of this study were postpartum mothers with normal deliveries who experienced a second-degree perineal tear and were treated at Purwodadi Islamic Hospital from November 25, 2024, to February 31, 2025. The research instruments included questionnaires, REEDA scale observation sheets for one week, and laboratory results from the Human ELISA Kit IL-6 (Elabscience), which were measured on the first and seventh days postpartum. Statistical analysis was performed using IBM SPSS Statistics 23 software. For statistical testing, the Kruskal-Wallis test and the Mann Whitney were employed, followed by the Wilcoxon Signed-Rank Test.

RESULTS AND DISCUSSION

The results of phytochemical screening using the TLC method, Piper betle Linn extract 7% showed positive for flavonoids (5.56% b/b) and kavicol. In the organoleptic test, a liquid form was obtained, with a distinctive smell of betel nut, bitter, spicy, blackish-green color with a thick texture. The pH stability test was obtained at 4.20 and the extract was homogeneous. The viscosity test showed the preparation was equivalent to water, with the dispersion test of the preparation sprayed on mica plastic from 10 cm resulting in a spray area of 10 x 10 cm, and an irritation test was conducted on three volunteers showing no allergic reactions, such as redness, itching, soreness, or swelling. The results of the assessment of respondent characteristics were obtained mostly from 40 respondents aged 20-35 years (low risk), as many as 15 people (75%) in the intervention group and 13 people (65%) in the control group. Most respondents were second-educated (SMA/MA/SMK) with the same number of parity (primary and multi), namely 10 people (50%) in both the intervention and control groups, and all respondents had good personal hygiene (100%) with a frequency of 2-3 times a day. Based on the Body Period Index, the majority had normal nutritional status (18.5-25) as many as 15 people (75%) in the intervention group, and 17 people (85%) in the control group. Meanwhile, based on Hb levels, most respondents showed normal results (11-15 gr/dl), of which 16 people (80%) were in the intervention group, and 17 people (85%) in the control group. The healing process of perineal wounds based on the REEDA scale indicator can be seen in Table 1 below:

Table 1. REEDA scale frequency distribution

REEDA Scale	Intervention Group		Control Group	
Category	N	%	N	%

REEDA Scale	Intervention Group		Control Group	
Poor	6	30	11	55
Good	13	65	7	35
Very Poor	1	5	2	10
Total	20	100	20	100

Source: Processed primary data, 2025

Meanwhile, laboratory results of IL-6 levels as an inflammatory marker can be seen in Table 2 below:

Table 2. Frequency distribution of IL-6 levels

IL-6 Level	Intervention Group – Day 1		Intervention Group – Day 7		Control Group – Day 1		Control Group – Day 7	
	N	%	N	%	N	%	N	%
Normal (0–43.5 pg/ml)	19	95	19	95	18	90	18	90
Elevated (>43.5 pg/ml)	1	5	1	5	2	10	2	10
Total	20	100	20	100	20	100	20	100

Source: Processed primary data, 2025

Discussion

Judging from the effectiveness of using Piper betle Linn 7% nanospray extract in accelerating the healing process of grade II perineal wounds in postpartum mothers, the results of the Kruskal Wallis test found a significant difference ($p < 0.05$) on the REEDA scale score from the first to the seventh day between the treatment and control groups. This shows that the administration of Piper betle Linn 7% nanospray extract is effective in accelerating the healing of perineal wounds. Green betel leaves are widely known as an herb for speeding up wound healing, including postpartum perineal wounds. The flavonoid content acts as an anti-inflammatory, antioxidant, and antiseptic that supports optimal tissue regeneration and reduces the risk of complications (Sari et al., 2021). Meanwhile, kavicol has antimicrobial and analgesic properties, important for preventing infection and relieving pain in open wounds (Laksmidara et al., 2024). According to Dwianggraini (Biswas et al., 2022), kavicol compounds show antibacterial properties five times stronger than phenols.

Nanotechnology is being developed for drug delivery because its particle shape and size can affect the solubility, absorption, and distribution of drugs in the body (Noval & Malahayati, 2021). The spray technique in this topical formulation offers advantages such as wide coverage of the skin without direct contact, quick drying, non-stick, easy to use, safe, hygienic, and easy to clean (Karlina et al., 2024). A study conducted by Lutviandhitrani G, Harjanti D W, and Wahyono F (2015) showed that green betel leaves have an effectiveness equivalent to the antibiotic penicillin dihydrostreptomycin. It should be noted that penicillin works as a bactericidal agent by interfering with the synthesis of bacterial cell walls (Lutviandhitarani et al., 2015). Also supported by research by Wulandari & Rahayuningsih (2022) shows that the use of betel leaf decoction for 20 minutes, administration twice a day (morning and evening) for seven days effectively reduces the risk of infection in perineal wounds (Wulandari & Rahayuningsih, 2022). The assessment of the REEDA scale as a clinical indicator to measure the healing process of perineal wounds during the administration of 7% *piper betle linn* nanospray extract can be seen in Figure 1 below:

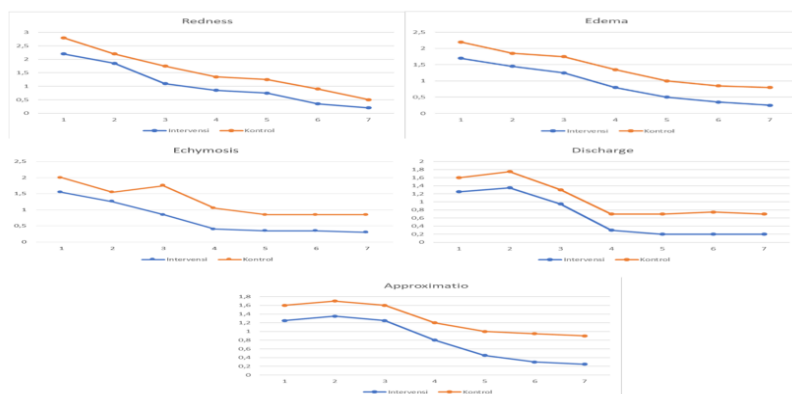


Figure 1. Comparison of REEDA Scale

The intervention group showed a significant reduction in REEDA scores to 0 (complete healing) on the fifth postpartum day, which was statistically faster compared to the control group with lower average REEDA scores for redness (0.75), edema (0.50), echymosis (0.35), discharge (0.20), and approximation (0.45) compared to the control group.

This study ensured that the assessment of injuries was objectively using the REEDA scale by the blinded and equalized assessors, although there were differences in the initial REEDA scores. Detailed observations were made over seven days to assess the progression of the wound and signs of abnormalities which not only provided a picture on a daily basis but also allowed for the drawing of more valid and representative conclusions regarding the speed and quality of the wound healing as a whole. Standardized therapy administered 2 times a day (morning and night) is designed to keep drug concentrations stable, ensure adherence to therapy, and support optimal healing (Robles-Piedras et al., 2024).

This study is in line with Laksmidara, et.al., (2022), that wounds on the perineum are declared to heal quickly if < 7 days and how long it takes to heal if > 7 days. Optimal wound healing is characterized by the absence of redness, swelling and pain during activity, as well as fused tissue and dry wounds.

These results are also supported by the findings of Amini et al. (2022) who show that the administration of betel leaf treatment significantly reduces the severity of perineal lesions. In the betel leaf treatment group, the mean REEDA scores for redness (3.79), edema (3.79), ecchymosis (2.68), secretion (2.79), and approximation (3.74) were lower compared to the control group (redness 5.37, edema 5.21, eczemosis 4.21, secretion 4.42, approximation 5.47), indicating better wound condition during the treatment period. Furthermore, Siagian's (2020) study also supported these results by reporting a faster average healing of perineal wounds in the betel leaf intervention group of 3.00, SD 1,372 with Min-Max (2-5) days and an average total score of REEDA=0 on the seventh day compared to the control group that showed no change in wound healing until the seventh day (Amini & Suwondo, 2022).

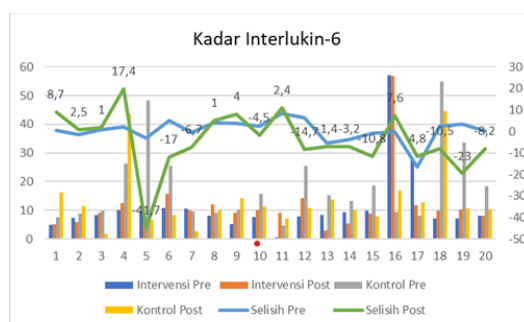


Figure 2. Comparison of IL-6 Levels

The effect of 7% Piper betle Linn nanospray extract on decreased levels of IL-6 as an inflammatory marker in perineal lesions based on Figure 2 showed a different pattern between the intervention and control groups, but statistically no significant difference. In the intervention group, although the majority of respondents (95%) had normal IL-6 levels (0-43.5 pg/ml), there was a tendency to increase IL-6 levels on the seventh day postpartum compared to the first day. In contrast, in the control group, there was a decrease in IL-6 levels from the first day to the seventh day, although in this group, 5% of respondents showed an increase in IL-6 levels at different times. These results suggest that perineal wound healing likely does not depend solely on IL-6 regulation but rather involves more complex mechanisms.

Based on the results of the Mann Whitney test, the significance value ($p = 0.358 > 0.05$) indicates that statistically, this result is not significant. Although there was a Z-value difference of (-0.920) in IL-6 levels between the two groups observed, this does not provide strong evidence that the intervention given had a substantial effect on IL-6 levels. Good wound healing is a complex process that is influenced by various factors beyond IL-6 modulation, such as age, nutrition, vascularization conditions, the presence or absence of infection, and the activity of other growth factors in triggering the proliferation phase (Purnama et al., 2017). In addition, it is a fact that the given intervention can have other beneficial mechanisms in wound healing (see Figure 1), such as antimicrobial or antioxidant effects, which may contribute to the acceleration of the healing process without significant IL-6 modulation (Nayaka et al., 2021).

The inflammatory phase is an initial and essential response to injury (Aprilia, 2023). Although often considered negative, controlled inflammation plays an important role in clearing pathogens and damaged cells, as well as preparing the wound area for new tissue regeneration. When an injury occurs, damaged cells and microorganisms at the site of injury will release various inflammatory mediators, such as histamine, bradykinin, and prostaglandins. These mediators cause vasodilation and increase vascular permeability. This allows immune cells and plasma proteins to move to the wound area. The first immune cells to respond are neutrophils, which play a role in bacterial phagocytosis as well as cellular debris. After a few days, macrophages will become the dominant cells. Macrophages have a dual role, in addition to cleaning the wound area, they also release various growth factors (such as TGF- β , EGF, and VEGF) and cytokines (such as IL-1, IL-6, IL-8, and TNF- α). These cytokines and growth factors are crucial in triggering and supporting the inflammatory phase with the goal of initiating the repair process, but if this response is excessive, it can become detrimental and lead to chronic inflammation (Tyavambiza et al., 2022).

Interleukin-6 is a cytokine that plays an important role as a marker of inflammation or serious infections such as sepsis (Megarani, 2023). Along with TNF- α and IL-1, IL-6 is known to be a powerful trigger of the pro-inflammatory response, which is induced by lipopolysaccharides (LPS) of bacteria, making it an indicator of systemic activation of pro-inflammatory cytokines. According to Hirano, IL-6 plays a central role in inducing the body's acute phase response to infection or injury, including stimulation of acute phase protein production in the liver. Its longer half-life compared to TNF- α , and IL-1 makes it a more stable marker of inflammation (Hirano, 2021). However, interestingly IL-6 has complex properties and can be anti-inflammatory as well. This suggests that IL-6's role in inflammation is not always detrimental but also has dual properties that regulate the body's response (Darmawan, 2021).

The REEDA scale is used as a highly relevant clinical observation tool for monitoring external manifestations of inflammatory reactions and wound healing progress by providing a visual and quantitative picture of the severity and resolution of inflammatory processes in perineal lesions (Pebolo et al., 2020). Various studies have shown that green betel leaves have great potential as a safe and effective natural alternative in postpartum care, but in contrast to this study where there is a tendency to increase IL-6 levels in the intervention group where the inflammatory phase should have subsided, this can be explained by the following mechanisms:

First, there are side effects of DMSO use. Dimethyl Sulfoxide (DMSO) is a versatile solvent that is widely used in pharmaceuticals and laboratories, mainly due to its ability to increase the penetration of substances through biological membranes such as the skin. One of the unique side

effects of DMSO is the appearance of a garlic-like taste in the mouth after contact with the skin. DMSO can disrupt the structure of the stratum corneum which then triggers inflammatory responses such as irritation, redness, burning, or itching (Karim et al., 2023). Individual skin sensitivity varies, some people may experience irritation even at low concentrations, while others are more tolerant. This irritation is an initial response from the immune system that can trigger an increase in pro-inflammatory cytokines such as IL-6, TNF- α , IL-1 β , and IL-8 as a form of the body's defence against compounds that are considered foreign or irritating. An increase in IL-6 in the normal range and in conjunction with better clinical improvement in the intervention group (Table 1) suggests that this increase is likely part of an orderly and controlled healing process, rather than an indication of adverse inflammation (Tiwari & Pathak, 2023).

Based on a systematic review by Madsen, et al., local burning was the most reported skin reaction in 13 studies, with one study even mentioning all participants experiencing it. Although it is generally temporary, there are also serious cases that require discontinuation of treatment. In addition to burning, other reported skin reactions include transient peripheral edema accompanied by itching and erythema, exfoliative erythroderma in psoriasis patients, and prominent bump areas in patients with dermatographia (Madsen et al., 2019). Acute allergic reactions due to DMSO use were also reported in the study of Cordoba et al., in which 63 out of 144 patients experienced allergic reactions. Further univariate analysis showed that through the volume instilled ($P=0.005$), the amount of DMSO ($P=0.008$), total nucleated cells ($P=0.002$), total number of granulocytes ($P=0.000001$), and clotting ($P=0.000001$) was significantly associated with the occurrence of these side effects (Cordoba et al., 2007).

Second, the blood sampling area. The increase in IL-6 detected in the blood through the duct media vein does not directly reflect a specific inflammatory condition in the wound area, but rather a broader inflammatory response throughout the body due to several factors or it could also be a pleiotropic response of IL-6 that functions in tissue repair elsewhere that is not directly related to the specific wound healing observed on the REEDA scale. The increase does not always mean bad (Widyaningtiyas et al., 2014). These results are supported by Said et al.'s research through his meta-analysis of 57 studies, covering 3,166 normal IL-6 values in healthy adult blood with a measured range between 0 and 43.5 pg/ml (Said et al., 2021). With different areas, Del Barco E. et al. (2023) examined interleukin 6 levels in amniotic fluid, noting that the average gestational age at amniocentesis was 21.8 weeks (range 15.0–38.7) and at delivery was 38.6 weeks (range 30.9–41.4) (Del Barco et al., 2023).

Third, nutritional status is over or obese. Obesity is a group with high levels of free radicals and low degrees of chronic inflammation. This is supported by increased production of pro-inflammatory adipositoquins such as IL-6, IL-8, leptin, CRP, haptoglobin, and TNF- α , as well as increased immune cell activity in obese individuals (Susantiningsih & Mustofa, 2018). This is because adipose tissue not only serves as a store of energy but is also an active endocrine organ that produces various cytokines and inflammatory mediators, which ultimately trigger the formation of free radicals. Pregnancy and childbirth in obese women can exacerbate this chronic inflammatory condition and lead to higher levels of IL-6 after childbirth (Rahmawati, 2014).

Based on this study, the characteristics of respondents showing obesity were confirmed as risk factors for increased IL-6 in both groups, in line with clinical evidence of poor wound healing disorders in respondents with obesity. This study is supported by the results of the analysis in Medellu's research, et.al it was found that IL-6 levels in obesity conditions with a correlation value of $p = 0.359$; $p < 0.05$. This means that the greater the degree of obesity (BMI >30), the higher the interleukin 6 level (Medellu et al., 2023).

Thus, based on the increased levels of IL-6 that occurred in some of the intervention group study subjects, it showed greater complexity in the postpartum wound healing process than assumed by standard wound healing algorithms. There are two main possibilities to consider explaining this phenomenon, namely that the increase in IL-6 may not be solely related to the healing process of local perineal wounds but rather is influenced by systemic factors such as obesity or other common

inflammations that were not specifically the focus of this study. The existence of findings that are in line with the REEDA scale suggests a correlation but is not necessarily directly related to local wound healing algorithms. Furthermore, the difference between the application of topical herbal ingredients to the perineum and the measurement of IL-6 through venous blood collection creates a gap. This raises the question of whether the increase in IL-6 is a local response to perineal wound healing or a broader indicator of systemic inflammation.

CONCLUSION

The results of this study demonstrate that 7% *Piper betle Linn* nanospray extract effectively accelerates the healing of grade II perineal wounds in postpartum mothers, as indicated by a significant reduction in REEDA scores in the intervention group compared to the control. However, the nanospray did not produce a statistically significant decrease in IL-6 levels, suggesting that while it may enhance physical wound healing, its impact on biochemical markers of inflammation remains unclear. This highlights the potential of herbal treatments such as *Piper betle Linn* nanospray for postpartum wound recovery but also underscores the need for further research. Future studies should involve larger sample sizes, incorporate additional inflammatory biomarkers, utilize longer follow-up periods, and consider alternative wound healing assessments such as histological analysis to better elucidate the therapeutic mechanisms and long-term effects of *Piper betle Linn* extract. Exploring the synergistic potential of combining nanospray formulations with other wound healing strategies is also recommended to achieve more comprehensive results.

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