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Effect of Topical Noni (*Morinda citrifolia* L.) Extract Cream on Interleukin-1 and PDGF Expression in a Rat Incision Wound Model

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ABSTRACT

Wound healing involves complex biological processes influenced by inflammation and tissue regeneration, where excessive interleukin-1 (IL-1) activity can delay recovery, while platelet-derived growth factor (PDGF) plays a pivotal role in fibroblast proliferation and collagen deposition. This study aimed to evaluate the effect of topical Noni (Morinda citrifolia L.) extract cream on IL-1 levels and PDGF expression in incised skin tissue. A post-test only control group design was conducted using 30 male Wistar rats randomly allocated into five groups: healthy control, negative control with basic cream, positive control with povidone iodine, treatment with 15% Noni cream, and treatment with 30% Noni cream. Incised wounds were created on the dorsal skin and treated once daily for seven days, followed by analysis of IL-1 using ELISA and PDGF expression using RT-qPCR. Statistical analysis showed no significant differences among groups ($p=0.088$ for IL-1; $p=0.056$ for PDGF), yet descriptive results revealed lower IL-1 levels in the 30% Noni group and higher PDGF expression in the 15% group, while povidone iodine produced the least favorable outcomes. These findings suggest a dose-dependent dual action of Noni extract cream, with the 30% formulation tending to attenuate inflammation and the 15% formulation enhancing regenerative activity. These findings descriptively showed the lowest IL-1 levels, although the difference was not statistically significant. Within the limitations of this study, topical Noni extract cream demonstrates potential as a safe and natural adjunctive therapy for wound management, warranting further investigation with larger sample sizes, extended observation periods, and histopathological confirmation.

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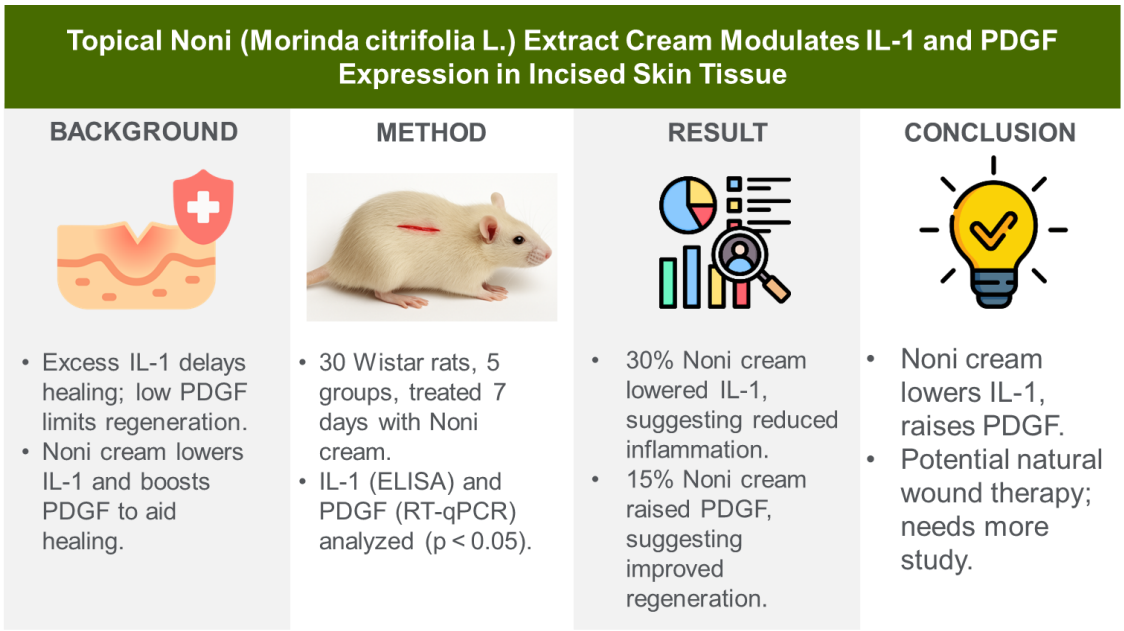
Key Messages:

- Topical Noni (*Morinda citrifolia L.*) extract cream demonstrates a potential dual role in wound healing by attenuating inflammation and promoting regenerative processes.
- The 30% formulation shows a tendency to reduce IL-1 levels, while the 15% formulation enhances PDGF expression, highlighting a dose-dependent therapeutic effect.
- This study supports the applicability of Noni extract cream as a safe and natural adjunctive option for wound management, warranting further clinical validation.

GRAPHICAL ABSTRACT



INTRODUCTION

Wound healing is a complex and dynamic biological process that encompasses the sequential phases of hemostasis, inflammation, proliferation, and tissue remodeling (1,2). Minor injuries such as incised wounds that extend into the dermis are often underestimated and left to heal naturally, which increases the risk of delayed healing, infection, and suboptimal scar formation (3,4). Although topical antiseptics remain widely used, their potential to cause irritation and disrupt the skin microbiota underscores the need for safer and more effective alternatives (5,6).

In this context, natural compounds have gained increasing attention. Among them, *Morinda citrifolia* L. (commonly known as Noni) has been recognized for its broad pharmacological properties, including anti-inflammatory, antimicrobial, and antioxidant activities (7,8). Bioactive constituents of Noni such as flavonoids, alkaloids, and ascorbic acid have been reported to suppress the production of proinflammatory cytokines, particularly Interleukin-1 (IL-1), while enhancing the expression of Platelet-Derived Growth Factor (PDGF), which plays a crucial role in fibroblast recruitment, collagen synthesis, and tissue re-epithelialization (9–12).

IL-1, a key mediator in the inflammatory phase , can impair tissue repair when its activity is excessive, leading to prolonged inflammation (13,14). Conversely, PDGF released during the proliferative phase orchestrates fibroblast migration and extracellular matrix deposition, making it essential for effective tissue regeneration (15,16). Dysregulation of these mediators is strongly associated with delayed or pathological wound healing (17).

While these studies confirm the macroscopic benefits of Noni extract, the specific molecular pathways involving key inflammatory and proliferative mediators, such as IL-1 and PDGF, require further elucidation. Ethanolic extracts of Noni leaves and fruits have demonstrated the ability to accelerate fibroblast proliferation, reduce neutrophil infiltration, and enhance collagen deposition in animal models (7,9,18,19). Moreover, Noni-based topical formulations, including creams and hydrogels, have shown promising results in reducing infection risk while supporting tissue regeneration(20). However, despite these findings, the molecular effects of Noni extract on IL-1 modulation and PDGF expression in incised skin tissue remain insufficiently investigated.

This study was therefore designed to evaluate the effect of a topical *Morinda citrifolia* extract cream on IL-1 levels and PDGF expression in incised skin tissue. By addressing this gap, the present research aims to provide experimental evidence supporting the use of Noni extract as a safe, natural, and effective

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alternative in wound healing management.

METHODS

This study employed an experimental post-test only control group design to assess the effect of *Morinda citrifolia* L. (Noni) extract cream on IL-1 levels and PDGF expression in incised skin tissue. Five groups were established: a healthy control group (G1), a negative control group treated with basic cream (G2), a positive control group treated with povidone iodine (G3), treatment group 1 receiving topical Noni extract cream at 15% concentration (G4), and treatment group 2 receiving Noni extract cream at 30% concentration (G5). Concentrations of 15% and 30% were selected based on preliminary studies or findings from existing literature to assess for a dose-dependent effect. This design was chosen to minimize external confounding variables and to ensure that any differences observed between groups could be attributed to the administered interventions.

The sample size in this study was determined using Federer's formula $(n-1)(t-1) \geq 15$, where t represents the number of groups and n denotes the number of animals per group. Based on the experimental design involving five groups, the calculation indicated a minimum of five animals per group, yielding a total of 25 animals. To account for potential *drop-outs* due to mortality or animals not meeting inclusion criteria, an additional five animals were included, resulting in a total sample size of 30.

This calculation was performed under the assumption of a moderate effect size ($f = 0.4$), a significance level (α) of 0.05, and a statistical power ($1-\beta$) of 80%, parameters commonly applied in experimental animal studies to detect biologically meaningful differences. Based on these assumptions, the chosen sample size was deemed adequate to detect differences in IL-1 levels and PDGF expression across treatment groups with sufficient statistical reliability.

A total of 30 adult male Wistar rats were used as experimental subjects, determined based on Federer's formula for experimental design. Inclusion criteria were male rats aged 2–3 months, weighing between 200–220 grams, with no macroscopic abnormalities, and incised wounds measuring 1 cm in length and up to 2 mm in depth. Animals that became ill or died during the course of the study were considered as dropouts. The subjects were randomly assigned using a simple random sampling technique into five groups, each consisting of five rats with one additional rat per group as a reserve (six rats per cage). The incision wound model was applied uniformly across all animals. Several instruments were employed in this study, including an oven, incubator, microscope, analytical balance, blender, beakers, Petri dishes, cleaning cloths, surgical scissors, 70% alcohol, surgical needles and sutures, wound dressings, micropipettes, centrifuge, and a UV-Vis spectrophotometer. Tools and reagents for RNA extraction and PCR included Trizol reagent, RNase inhibitor, cDNA synthesis kits, PCR primers, and Taq polymerase enzyme. The materials used in the study included adult male Wistar rats, Noni (Morinda citrifolia L.) fruit extract, phosphate-buffered saline (PBS), formalin solution, and a combination of xylazine and ketamine for anesthesia. These tools and materials were used to support the assessment of interleukin-1 (IL-1) levels and platelet-derived growth factor (PDGF) expression in the skin tissue of incised wound models treated with topical Noni extract cream.

The Noni (*Morinda citrifolia* L.) extract was prepared by selecting approximately 2 kg of fresh, semi-ripe fruits exhibiting a yellowish-green hue. After thorough washing, the fruits were thinly sliced and dried in an oven at 50°C until fully dehydrated. The dried slices were then pulverized into a fine powder (simplisia) using a blender and stored in airtight containers in a dry environment. The extraction process involved macerating the simplisia in 70% ethanol at a 1:10 (w/v) ratio for 2–3 days in a dark setting with periodic stirring. The resulting mixture was filtered through muslin cloth or filter paper, and the clear filtrate was obtained through repeated filtration. The solvent was then removed using a rotary evaporator at 40–50°C to produce a concentrated extract, which was subsequently freeze-dried and stored in amber bottles or sealed containers in cool, dark conditions to preserve its bioactivity. For topical formulation, the extract was incorporated into creams at concentrations of 15% and 30%. The base cream was prepared by separately heating the oil phase, comprising 15 g of stearic acid, and the aqueous phase, containing 0.5 g of potassium hydroxide dissolved in distilled water, 5 g of glycerin, and 2 g of triethanolamine, each to 70°C. The two phases were then combined under continuous stirring until a uniform cream base was achieved

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and allowed to cool to approximately 40°C. The Noni extract was then added at the respective concentrations and blended thoroughly to ensure even dispersion. The final product was aseptically packaged into sterile containers and stored in a cool, dry location shielded from direct light until use.

The incised wound model in Wistar rats was established following ethical guidelines for animal research. After a 7-day acclimatization period under controlled laboratory conditions (temperature 22–25°C, 12-hour light/dark cycle, with ad libitum access to food and water), the animals were anesthetized intraperitoneally using a combination of ketamine (50–80 mg/kg) and xylazine (5–10 mg/kg) to ensure the absence of pain perception during the procedure. Adequate anesthesia was confirmed by the absence of response to mild nociceptive stimuli. The dorsal skin was shaved using an electric clipper to expose a 3 cm diameter area and subsequently cleansed with antiseptic and 70% ethanol to prevent infection. A linear incision measuring 1 cm in length and up to 2 mm in depth was made perpendicular to the skin surface using a sterile No. 11 surgical scalpel, involving both the epidermis and upper dermis layers. After the procedure, animals were placed in a warm recovery chamber and monitored until full consciousness was regained. Topical application of Noni (Morinda citrifolia L.) extract cream, either at 15% or 30% concentration depending on the assigned group, was administered directly onto the wound site once daily throughout the intervention period according to the study design.

On day 8 following the final treatment, skin tissue samples were collected from the wound area for subsequent analysis using the ELISA method. Euthanasia was performed using diethyl ether vapor to induce loss of consciousness followed by death. A precise excision was made at the site of the incised wound using sterile scissors and forceps. The excised tissue was weighed and then immediately immersed in phosphate-buffered saline (PBS, pH 7.4). Tissue homogenization was conducted under cold conditions (4°C) to preserve protein integrity, followed by centrifugation at 2000–3000 rpm for 20 minutes. The resulting supernatant, containing soluble proteins and cytokines, was carefully collected as the test sample. All samples were stored at −20°C until further analysis.

IL-1 concentrations were measured using a Mouse IL-1 ELISA Kit (Thermo Fisher Scientific) according to the manufacturer's protocol. Absorbance was read using a microplate reader at a wavelength of 450 nm. The assay procedure began with the preparation of IL-1 standards in ten wells of a microplate. Capture antibodies were added to each well and incubated for 30 minutes at 37°C or overnight at 4°C. A washing solution was prepared by diluting the 30× concentrate with distilled water (1 mL concentrate in 29 mL aquadest), and wells were washed five times with this buffer after incubation. Blocking buffer was then applied to promote antigen binding to the plate surface, followed by incubation for 60 minutes at 37°C or overnight at 4°C. Next, 10 µL of sample and 40 µL of sample diluent were added to each well and mixed thoroughly to ensure homogeneity. The plate was incubated for 120 minutes at room temperature. Afterward, 100 µL of biotinylated antibody was added to each well and incubated for 60 minutes at 37°C or overnight at 4°C. Wells were again washed five times before adding 100 µL of ABC solution, followed by a 30-minute incubation at 37°C. After a final wash cycle, 90 µL of HRP-conjugate and 90 µL of TMB substrate were added to each well. The plate was incubated for 30 minutes at 37°C. Finally, 100 µL of stop solution was added, changing the color from blue to yellow, and optical density (OD) values were measured at 450 nm using an ELISA reader. The resulting OD readings were used to determine IL-1 concentrations in the samples.

For the analysis of PDGF gene expression, skin tissue samples were collected from the central dorsal wound area using a 6 mm biopsy punch, preserved in RNAlater solution, and stored at −80°C to maintain RNA integrity. Approximately 10–30 mg of frozen tissue from each sample was then homogenized under liquid nitrogen using a tissue grinder and transferred into RNase-free microcentrifuge tubes. For every 10 mg of tissue, 0.3 mL of Binding Buffer 4 (pre-mixed with β-mercaptoethanol) and 15 µL of proteinase K were added to promote cell lysis, followed by vortexing and incubation at 56°C for 10–20 minutes. The lysate was centrifuged at 12,000 × g for 5 minutes at room temperature, and the resulting supernatant was collected for further analysis. Gene expression was assessed using one-step quantitative reverse transcription PCR (qRT-PCR), with β-actin as the housekeeping gene. Each 20 µL reaction mixture contained 10 µL of 2× PerfectStart Green One-Step qRT-PCR SuperMix, 0.4 µL each of 10 µM forward and reverse primers, 0.4 µL of TransScript® RT/RI Enzyme Mix, 0.4 µL of Passive Reference Dye (50×), 5 µL of

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RNA template, and 3.4 µL of RNase-free water. After mixing and removing air bubbles, the master mix was loaded into PCR strip tubes, vortexed, spun down, and run in a qRT-PCR machine. The amplification program consisted of reverse transcription at 50°C for 5–15 minutes, initial denaturation at 94°C for 30 seconds, followed by 45 amplification cycles (94°C for 5 seconds and 58°C for 30 seconds). SYBR Green fluorescence was detected during the annealing/extension phase. After completion, amplification curves were examined for exponential patterns, and relative gene expression levels were calculated using the 2^−ΔΔCt method, normalizing PDGF expression to β-actin and comparing between experimental groups.

Data were analyzed with SPSS version 26. Normality was assessed using the Shapiro–Wilk test, and homogeneity was assessed using Levene's test. For normally distributed and homogeneous data ($p>0.05$), one-way ANOVA was applied followed by LSD post hoc analysis. For normal but non-homogeneous data, ANOVA with Tamhane's post hoc test was performed. Non-normally distributed data were analyzed using the Kruskal–Wallis test, with Mann–Whitney tests for pairwise comparisons. A p-value < 0.05 was considered statistically significant.

CODE OF HEALTH ETHICS

This study received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University, Semarang, Indonesia, under approval number 280/VI/2025/Komisi Bioetik, dated June 1, 2025.

RESULTS

Table 1 presents interleukin-1 (IL-1) levels in skin tissue across five distinct treatment groups following a 7-day intervention in a rat incision wound model. Preliminary statistical evaluations confirmed that the dataset satisfied the necessary assumptions for parametric testing, demonstrating a normal distribution via the Shapiro-Wilk test and homogeneity of variances through Levene's test (both $p > 0.05$). Subsequent comparative analysis utilizing a One-way ANOVA yielded a p-value of 0.088. Because this value exceeds the conventional 0.05 threshold for statistical significance, it indicates that there is no statistically significant difference in IL-1 expression among the evaluated groups. Consequently, while observational variances in mean IL-1 concentrations are present—with the Povidone Iodine group (G3) exhibiting the highest levels (10.49 ± 1.44) and the 30% Noni extract cream group (G5) demonstrating the lowest (8.17 ± 1.01), which closely approximates the healthy baseline group (G1, 8.50 ± 1.24)—the application of topical Noni (Morinda citrifolia L.) extract cream did not result in a statistically significant modulation of IL-1 levels compared to the other treatments or controls at this specific 7-day healing milestone.

Table 1. Interleukin-1 (IL-1) Levels in Skin Tissue Following 7-Day Treatment

Group	G1 Healthy Group	G2 *Basic Cream*	G3 *Povidone Iodine*	G4 EBM 15% Cream	G5 EBM 30% Cream	*p-value*
Mean	8.50	8.65	10.49	9.27	8.17	
SD	1.24	1.60	1.44	1.29	1.01	
Shapiro-Wilk	0.204*	0,764*	0,808*	0,564*	0,699*	
Leuvene Test						0.839*
One way anova						0,088

Description: Values are presented as Mean ± SD. Data distribution was assessed using the Shapiro–Wilk(*) test for normality ($p > 0.05$) and Levene's test (*) for homogeneity ($p > 0.05$). Group comparisons were performed using one-way ANOVA (*) ($p < 0.05$ considered statistically significant).

Table 2 presents the descriptive statistics and comparative analysis of Platelet-Derived Growth Factor (PDGF) expression, measured as fold change, across five experimental groups following a 7-day treatment period. Initial assessments confirmed that the dataset satisfied the necessary assumptions for parametric testing, exhibiting both a normal distribution across all groups via the Shapiro-Wilk test and homogeneity of variances through Levene's test (both $p > 0.05$). The subsequent one-way ANOVA analysis yielded a p-value of 0.056; because this value sits marginally above the conventional threshold for statistical significance ($p < 0.05$), it dictates that there is no statistically significant difference in overarching

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PDGF expression among the various interventions. Nevertheless, from a purely descriptive standpoint, a trending peak in mean PDGF expression was observed in the 15% Noni extract cream group (G4, 1.11 ± 0.08), followed closely by the 30% cream group (G5, 1.01 ± 0.09). In contrast, the Povidone Iodine treated group (G3) demonstrated the lowest expression profile (0.94 ± 0.09), which closely mirrored the baseline physiological levels seen in both the healthy control (G1, 0.95 ± 0.70) and the basic cream control (G2, 0.97 ± 0.11) groups, suggesting that while the Noni extract treatments showed a slight observational trend toward elevated PDGF, they did not induce a statistically definitive alteration at the 7-day healing milestone

Table 2. Results of descriptive tests of PDGF expression averages (fold change) and one-way ANOVA after 7 days of treatment

Group	G1 Healthy Group	G2 *Basic Cream*	G3 *Povidone Iodine*	G4 EBM 15% Cream	G5 EBM 30% Cream	*p-value*
Mean	0.95	0.97	0.94	1.11	1.01	
SD	0.70	0.11	0.09	0,08	0.09	
Shapiro-Wilk	0,727*	0,783*	0,910*	0,082*	0,740*	
Leuvene Test						0,671*
One way anova						0,056

Description: * *Shapiro-Wilk* = Normal (p>0,05), * *Leuvene Test* = Normal (p>0,05), * *One way anova* = Significant (p<0,05)

DISCUSSION

The present study evaluated the effect of topical *Morinda citrifolia* (Noni) extract cream on IL-1 levels and PDGF expression in incised skin tissue. Although statistical analysis revealed no significant differences among the groups, descriptive data indicated biologically relevant trends. The group treated with povidone iodine exhibited the highest IL-1 levels, while the group treated with 30% Noni extract cream showed the lowe G1 ues. C G2 sely, P G3 xpres G4 as hi G5 n the 15% Noni extract group, suggesting a dose-dependent dual effect of the extract in modulating inflammatory and proliferative phases of wound healing.

The finding that povidone iodine was associated with elevated IL-1 aligns with prior literature indicating that although it is a potent antiseptic, povidone iodine may prolong inflammation due to local irritation (21). In contrast, the reduction of IL-1 in the 30% Noni group supports the hypothesis that phenolic and flavonoid compounds in Noni exert anti-inflammatory effects through suppression of the NF-κB signaling pathway, a central regulator of IL-1 production (22,23). Sinambela et al. (2022) similarly reported that high-concentration Noni extract reduced IL-1 in a rat wound model, facilitating transition from the inflammatory to proliferative phase. These results suggest that Noni extract cream may attenuate excessive inflammation, thereby accelerating wound healing (18).

An intriguing aspect of this study is the apparent dual, dose-dependent effect, with the 30% formulation favoring inflammation suppression and the 15% formulation enhancing tissue proliferation. This pattern raises the possibility of a biphasic dose–response relationship, where different concentrations of the extract elicit distinct biological effects. Higher doses may deliver stronger anti-inflammatory actions by suppressing cytokine signaling, while moderate doses might optimize growth factor expression by avoiding receptor saturation or negative feedback mechanisms. Such biphasic effects have been described for several plant-derived bioactive compounds, where dose determines whether the net effect is anti-inflammatory, proliferative, or even cytotoxic (24). Future mechanistic studies examining cytokine and growth factor receptor interactions across a broader range of Noni extract concentrations would be valuable in clarifying this phenomenon.

The phytochemical composition of the Noni extract further supports these observations. The notable phenolic content provides a plausible explanation for the reduction in IL-1 levels, as phenolic compounds are well-documented to exert anti-inflammatory effects via NF-κB inhibition and free radical scavenging (20). Meanwhile, the relatively lower flavonoid content may explain why proliferative responses were most pronounced at the intermediate concentration (15%), suggesting that distinct phytochemical

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constituents may act synergistically yet exhibit concentration-dependent functional differences.

Despite these biologically meaningful trends, the absence of statistical significance warrants further consideration. Several factors may account for this outcome. The no significant p-value (0.088 for IL-1; 0.056 for PDGF) indicates a trend toward biological relevance, though statistical confirmation was limited by the small sample size (n=5 per group). Limited sample size reduces statistical power, increasing the risk of type II error, where real differences remain undetected (25). Additionally, the timing of tissue sampling on day 7 may have influenced the findings. IL-1 typically peaks in the early phase of wound healing (24–72 hours) and declines by day 7 (26,27). This timing may explain why intergroup differences were less pronounced. Future studies employing multiple sampling time points would better characterize the dynamic expression of IL-1 during healing. Moreover, the concentrations of Noni extract evaluated in this study (15% and 30%) may not represent the optimal therapeutic range required to achieve maximal anti-inflammatory and regenerative effects simultaneously. Future investigations incorporating larger cohorts, multiple observation time points, and a broader dose–response assessment are therefore warranted to more accurately delineate the temporal and concentration-dependent effects of *Morinda citrifolia* extract on wound healing dynamics.

The observation that 15% Noni extract cream produced the highest PDGF expression is noteworthy. PDGF is critical for fibroblast proliferation, angiogenesis, and extracellular matrix deposition (10,15). Flavonoids and phenolics are known to enhance PDGF expression via PI3K/Akt and MAPK/ERK pathways, supporting the observed findings (24). In contrast, povidone iodine showed the lowest PDGF expression, likely due to prolonged inflammation interfering with proliferative signaling. Similar findings were reported by Nirwana et al. (2017), who demonstrated that natural extracts rich in antioxidants and phenolics could enhance PDGF levels and improve wound healing outcomes (28).

Taken together, the findings indicate that Noni extract cream has potential as a dual-action topical therapy: the 30% formulation effectively reduces inflammation by lowering IL-1 levels, while the 15% formulation optimally enhances PDGF expression and tissue regeneration. This dose-response relationship suggests the importance of determining the most effective balance between anti-inflammatory and regenerative properties.

Nevertheless, this study has several limitations. The small sample size may have limited statistical power. The use of a single endpoint (day 7) may not fully capture the temporal dynamics of cytokine and growth factor expression. Additionally, histopathological analysis was not performed, which could have provided morphological confirmation of molecular findings. Future research should address these limitations by including larger cohorts, multiple observation time points, and histological validation. One notable limitation of this study concerns the measurement of IL-1 levels using a commercial Mouse IL-1 ELISA Kit (Thermo Fisher Scientific) on Wistar rat tissue samples. As this kit was primarily validated for mouse antigens, the degree of cross-reactivity with rat IL-1 cannot be guaranteed and may vary depending on the specific antibody clone used. The absence of validation data for rat samples introduces the possibility of reduced assay accuracy, which could influence the interpretation of IL-1 results. Ideally, a rat-specific ELISA kit or additional validation experiments confirming cross-reactivity should have been employed to ensure the reliability of these findings.

CONCLUSION

This study demonstrated that topical *Morinda citrifolia* (Noni) extract cream at concentrations of 15% and 30% did not produce statistically significant changes in IL-1 levels or PDGF expression by day 7 following wounding. Although statistical significance was not achieved, this study suggests that topical Morinda citrifolia extract cream has potential dual function in wound healing: the 30% formulation showed a trend toward reducing inflammatory IL-1 levels, while the 15% formulation was associated with increased expression of the regenerative marker PDGF. Nevertheless, these trends lacked statistical confirmation; they may reflect biologically relevant effects that were not fully captured due to the limited sample size, single endpoint assessment, and variability inherent in wound healing processes. Further investigations incorporating larger sample populations, multiple time points across the healing continuum, and histopathological evaluation are recommended to better define the therapeutic potential and optimal

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dosing parameters of *Morinda citrifolia* extract cream as a natural topical agent for wound repair.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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