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*Modulation of Interleukin-6 and Vascular Endothelial Growth Factor by topical Noni leaf (*Morinda citrifolia *L.) extract cream in a rat incision wound model*

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Abstract: Noni leaf (*Morinda citrifolia* L.) extract (NLE) has been reported to possess anti-inflammatory and pro-angiogenic properties that may support wound healing. This study evaluated the effects of topical NLE cream on interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF) expression in male Wistar rats with standardized full-thickness incision wounds. Thirty rats were randomly assigned into five groups: normal control, negative control (cream base), positive control (povidone-iodine), and two treatment groups receiving 20% or 40% NLE cream. All topical treatments were applied once daily for three consecutive days. Wound tissue was collected and analyzed on day four. IL-6 levels were lowest in the normal control group (9.34 ± 6.01 pg/mL) and were significantly reduced in the 20% NLE group compared with the negative control (19.80 ± 15.95 vs. 100.8 ± 26.99 pg/mL; $p = 0.002$). In contrast, VEGF levels were highest in the 40% NLE group (59.76 ± 9.39 pg/mL; $p < 0.01$), indicating enhanced angiogenic activity. These findings suggest that topical NLE cream, particularly at higher concentrations, may promote wound healing by modulating inflammatory responses and stimulating angiogenesis, supporting its potential use as a complementary topical therapeutic agent.

Keywords: IL-6; incisional wounds; *Morinda citrifolia*; topical cream; VEGF.

INTRODUCTION

The pursuit of rapid wound healing with optimal aesthetic outcomes remains a critical concern in healthcare, driven by patient demand and the limitations of conventional therapies[1]. Synthetic wound care materials, while widely used, often pose risks such as microbial resistance, irritation, and high costs, necessitating safer, cost-effective alternatives[2].

Natural products derived from medicinal plants, have gained attention for their biocompatibility and multifunctional therapeutic properties[3,4]. Among these natural remedies, Noni (*Morinda citrifolia* L.) leaf extract (NLE) has emerged as a promising candidate due to its rich phytochemical profile, including alkaloids, flavonoids, and triterpenes, which exhibit antioxidant, anti-inflammatory, and pro-healing activities[5–7]. Topical formulations of NLE cream have demonstrated efficacy in enhancing wound contraction and tissue regeneration in preclinical models, offering localized therapeutic benefits with minimal systemic effects[8,9].

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However, current studies on Noni-based wound treatments have predominantly focused on macroscopic healing parameters such as wound closure, fibroblast proliferation, and histological changes[10,11]. For instance, a study reported that 70% ethanol extract of Noni leaves achieved 92.45% wound closure in rats within 11 days, outperforming conventional treatments[9]. Similarly, NLE creams at varying concentrations have shown dose-dependent improvements in fibroblast proliferation and antioxidant capacity[8,12]. Quantitative analyses also indicate that Noni leaf extract at 20%, 25%, and 30% concentrations modulates TNF-α, IL-1, PDGF, and TGF-β levels, with 20% identified as the most effective dose[6]. Although Noni leaf extract shows promise in wound healing, its specific effects on pro-inflammatory and pro-angiogenic biomarkers, especially IL-6 and VEGF remain underexplored, unlike Sapodilla leaf extract which has been studied for its impact on IL-6 and TGF-β[3]. Furthermore, comparative analyses between NLE and standard treatments like povidone-iodine are scarce, hindering the assessment of its relative efficacy[13]. Addressing these gaps will not only elucidate Noni's mechanism of action but also strengthen its credibility as a viable alternative in wound management.

Recent advancements in wound care research underscore the role of molecular mediators, such as interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), in regulating inflammation and tissue repair. IL-6, a pro-inflammatory cytokine, is pivotal in the early inflammatory phase, while VEGF drives angiogenesis during the proliferative stage[14,15]. Dysregulation of these biomarkers can prolong inflammation or impede healing, particularly in acute wounds like incisions, which are characterized by clean yet deep tissue damage[16]. The application of NLE cream, which possesses antioxidant properties, has been shown to modulate these critical phases by inhibiting NF-κB activation, thereby reducing IL-6 production and accelerating the transition from inflammation to proliferation. Moreover, its antioxidant activity supports angiogenesis by preserving nitric oxide (NO) availability and preventing HIF-1α degradation, ultimately enhancing VEGF expression and promoting neovascularization essential for tissue regeneration[17,18].

This study aims to investigate the effects of NLE cream on IL-6 and VEGF levels in male *Wistar* rats with incision wounds, bridging the current knowledge gap. Specific objectives include quantifying these biomarkers across experimental groups: non-wounded controls, placebo cream, povidone-iodine, and NLE at 20% and 40% concentrations. By analyzing differential cytokine expression, the research seeks to correlate NLE's phytochemical properties with its anti-inflammatory and pro-angiogenic activities. However, one limitation of this study is the absence of macroscopic wound evaluations, such as wound area measurements, histological analysis, or standardized scoring, which would have strengthened the correlation between biochemical findings and actual wound healing outcomes. Findings from this study will expand the theoretical framework of herbal wound therapies, providing mechanistic insights into Noni's role in modulating critical healing pathways. Practically, the results could guide the development of standardized NLE formulations, offering a cost-effective, natural adjunct to synthetic wound care regimens. Ultimately, this work aligns with global trends in integrating traditional medicine into evidence-based healthcare, emphasizing safety, efficacy, and accessibility.

MATERIAL AND METHOD

Study Design

This study employed a laboratory-based experimental design with a post-test-only control group model to evaluate the effect of NLE cream on wound healing by assessing IL-6 and VEGF levels. Thirty male Wistar rats were randomly assigned to five groups (n = 6 per group): a normal control group (G1), a negative

control group receiving base cream (G2), a positive control group treated with povidone-iodine (G3), and two treatment groups receiving 20% (G4) and 40% (G5) NLE cream. Randomization was performed using a computer-generated sequence, and group allocation was concealed until the intervention. Each rat was treated as one experimental unit.

Ethical clearance

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Sultan Agung Islamic University (No.396/X/2024/Komisi Bioetik) and complied with ARRIVE guidelines. Anesthesia was induced using an intraperitoneal injection of ketamine (80 mg/kg) combined with xylazine (10 mg/kg). At the end of the study (day four), rats were humanely euthanized by CO_2 inhalation followed by cervical dislocation to ensure death. Outcome assessment (ELISA and data analysis) was conducted in a blinded manner.

Study Location and Duration

The study was conducted at the Stem Cell and Cancer Research (SCCR) Laboratory, Semarang, Indonesia. The research was carried out over a four-week period, from December 2024 to January 2025, encompassing animal acclimatization, intervention, and biochemical analyses.

Population and Samples

The study used male Wistar rats (*Rattus norvegicus*) aged 2–3 months, weighing 180–220 grams, and obtained from the SCCR Laboratory animal facility. Prior to experimentation, rats were acclimatized for seven days under controlled environmental conditions (temperature 20–25°C, humidity 40–60%, and a 12-hour light/dark cycle). Rats were fed a standard chow diet and given water ad libitum. Inclusion criteria required the animals to be healthy and free of anatomical abnormalities, while exclusion criteria eliminated any rat displaying illness or abnormal behavior during the acclimatization period. A total of 30 rats were used, divided into five groups with six rats each.

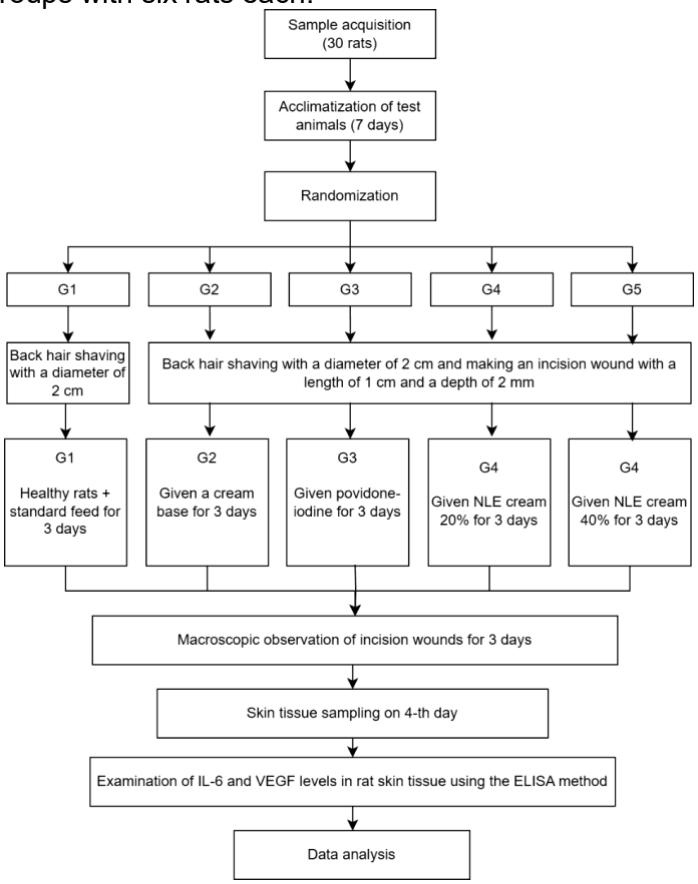

Figure 1. Experimental design of this study, involving 5 different groups.

Induction of Incised Wound Model

The dorsal area of each rat was shaved and disinfected with 70% ethanol. A standardized full-thickness linear incision measuring 1 cm in length and 2 mm in depth was made using a sterile scalpel under aseptic conditions. Surgical instruments were sterilized by autoclaving before use and disinfected with 70% ethanol between animals. To prevent infection, the wound area was cleansed daily with sterile saline prior to treatment application. The assigned interventions were applied topically once daily for three consecutive days (0.1 g per wound area per day).

Preparation of NLE Cream

Noni leaves (*Morinda citrifolia* L.) were dried, pulverized, and macerated in 70% ethanol for 72 hours, filtered, and concentrated using a rotary evaporator at 40 °C. The crude extract was formulated into creams containing 20% or 40% extract. The base consisted of stearic acid (10–15%), cetyl alcohol (2–3%), medium-chain triglycerides (5–10%), glycerin (5%), methylparaben (0.2–0.5%), and demineralized water to volume. The vehicle control consisted of the same base without extract. The final cream underwent pH measurement at 25 °C using a calibrated pH meter (target 5.5–6.5), viscosity determination with a Brookfield viscometer (spindle no. 64, 25 °C, 10 rpm), and stability testing for 30 days at 25 °C and 40 °C, monitoring for phase separation, pH drift, and color/odor changes. The creams were homogenized and stored in sterile airtight containers at 4–8 °C until use.

Tissue Sampling and Biochemical Analysis

On day four post-wounding, rats were anesthetized using an intraperitoneal injection of a ketamine-xylazine combination, following the institutionally approved ethical protocol. Subsequently, skin samples from the wound area were collected. Tissue homogenization was performed using RIPA buffer (Sigma-Aldrich) supplemented with protease inhibitors (Roche) at 4°C. Supernatants were obtained via centrifugation at 12,000 rpm for 20 minutes. IL-6 and VEGF levels were quantified using ELISA (Rat IL-6 ELISA kit and Rat VEGF ELISA kit, Elabscience, Catalog No. E-EL-R0015 and E-EL-R0031). Optical density readings were taken at 450 nm using a microplate reader (Shimadzu UV-1900, Shimadzu Corporation, Japan). Each sample was analyzed in duplicate.

Data Analysis

Normality of residuals was assessed using the Shapiro–Wilk test, followed by Levene's test for homogeneity of variances. When both assumptions were met, data were analyzed using one-way ANOVA followed by LSD post hoc tests. If data were normally distributed but variances were unequal, ANOVA was followed by Tamhane's T2 post hoc test. If data were non-normally distributed, the Kruskal–Wallis test was used, followed by Mann–Whitney U tests with Bonferroni correction for multiple comparisons. Results were reported as mean ± standard deviation, and $p < 0.05$ was considered statistically significant. Statistical analysis were conducted using SPSS version 27.0.

RESULTS AND DISCUSSION

Macroscopic examination of the incision sites was performed daily and representative images are shown in Figure 2. Progressive wound contraction and early granulation tissue formation were visible from day 1 to day 3 in all treatment groups. The wounds treated with NLE cream, particularly at 40%, appeared narrower with better epithelial alignment by day 3 compared with the negative control group, suggesting accelerated wound contraction and earlier progression to the proliferative phase, consistent with previous studies[8,19]. The three-day treatment was based on the early phases of wound healing: IL-6 peaks within 1–3 days post-injury to mediate inflammation, while VEGF expression begins around day two to three, initiating angiogenesis as the wound enters the proliferative phase[15,17].

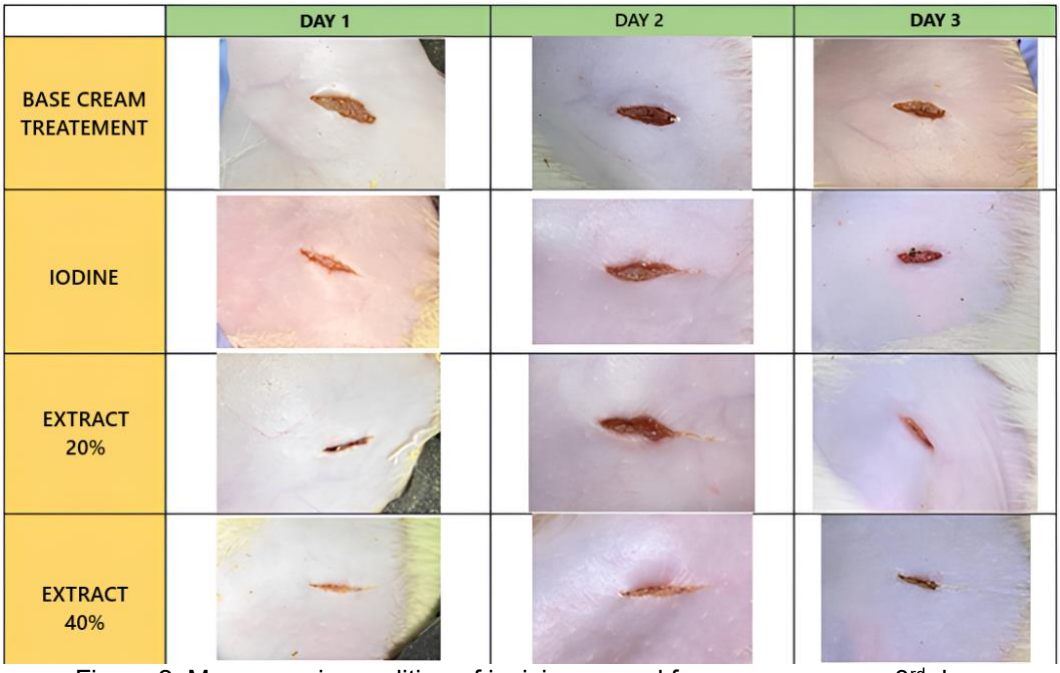

Figure 2. Macroscopic condition of incision wound for every group on 3rd day.

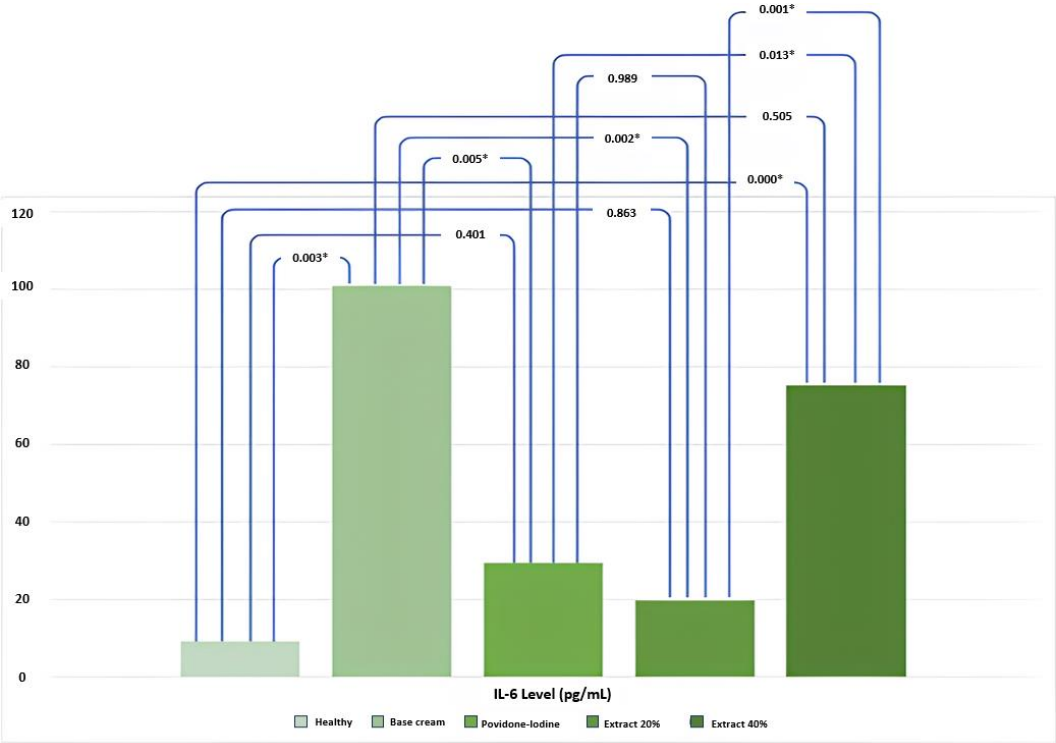

Figure 3. Average IL-6 level for each group.

The ELISA analysis of IL-6 levels in wound tissue samples showed significant differences among the groups (Figure 3 and Table 1). The lowest IL-6 concentration was observed in the healthy control group (G1) at 9.34 ± 6.01 pg/mL, whereas the highest concentration was found in the negative control group (G2) at 100.8 ± 26.99 pg/mL. The application of 20% NLE cream significantly reduced IL-6 levels to 19.80 ± 15.95 pg/mL (G4), while 40% NLE cream resulted in an IL-6 concentration of 75.18 ± 6.99 pg/mL (G5). Statistical analysis using one-way ANOVA yielded a p-value of <0.001 ($p<0.05$), indicating significant differences among the treatment groups.

Table 1. Average IL-6 expression for each group and One way Anova

Group	Healthy (G1)	Base Cream (G2)	Povidone-Iodine (G3)	Extract 20% (G4)	Extract 40% (G5)	*P value*
Mean ± SD	9.34 ± 6.01	100.8 ± 26.99	29.54 ± 19.26	19.80 ± 15.95	75.18 ± 6.99	
Shapiro-Wilk	0.899#	0.606#	0.273#	0.152#	0.987#	
Lavene's test						0.011‡
One way Anova						<0.001*

Note: #Normal p>0.05 ##Not Normal p<0.05 †Homogen p>0.05
‡Non-Homogen p<0.05 *Significant p<0.05

Table 2. IL-6 expression post hoc Tamhane test result

Group	Healthy (G1)	Base Cream (G2)	Povidone-Iodine (G3)	Extract 20% (G4)	Extract 40% (G5)	Healthy (G1)
Healthy (G1)	-	*0.003	0.401		0.863	*<0.001
Base Cream (G2)	*0.003	-	*0.005		*0.002	0.505
Povidone-Iodine (G3)	0.401	*0.005	-		0.989	*0.013
Extract 20% (G4)	0.863	*0.002	0.989		-	*0.001
Extract 40% (G5)	*<0.001	0.505	*0.013		*0.001	-

Note: * p<0,05

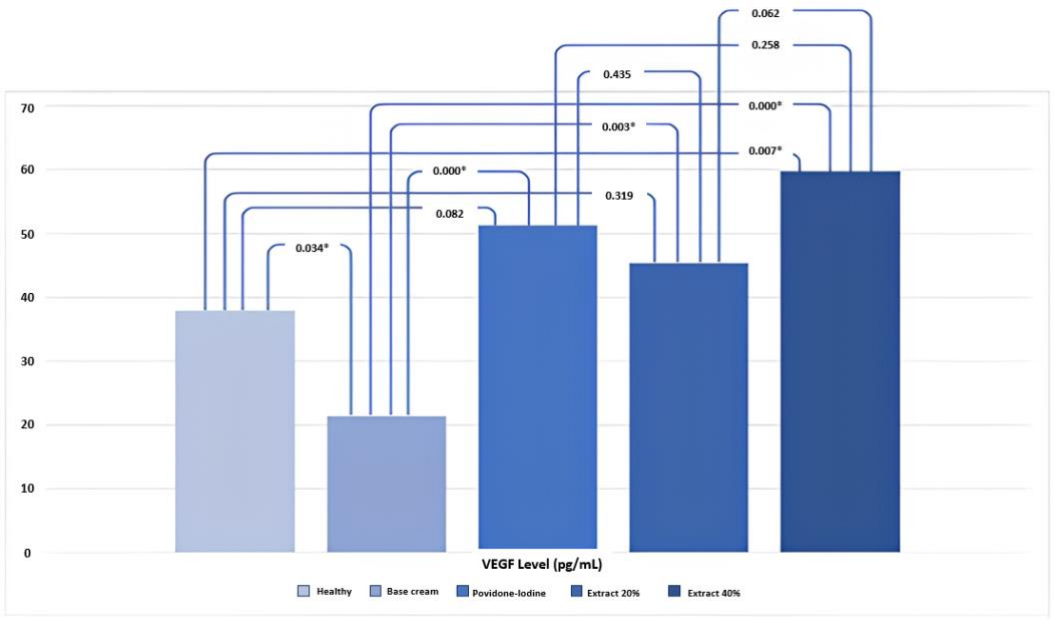

Figure 4. Average VEGF level for each group.

Post hoc Tamhane analysis confirmed that IL-6 levels in the NLE-treated groups (G4 and G5) were significantly lower than those in the negative control group (G2) (Table 2). Additionally, the IL-6 concentration in the 20% NLE cream group was significantly lower than in the 40% NLE cream group, suggesting that the lower dose provided an optimal anti-inflammatory effect[6].

The VEGF levels varied significantly among the groups, with the lowest concentration recorded in the negative control group (G2) at 21.43 ± 10.59 pg/mL and the highest in the 40% NLE cream group (G5) at 59.76 ± 9.39 pg/mL (Figure 4 and Table 3). The 20% NLE cream group (G4) exhibited a VEGF concentration

of 45.41 ± 8.37 pg/mL. One-way ANOVA analysis confirmed a statistically significant difference among the groups ($p<0.05$).

Post hoc Tamhane analysis indicated that VEGF levels in the 40% NLE group were significantly higher than in all other groups, highlighting the role of NLE in promoting angiogenesis and tissue regeneration (Table 4)[8]. The increase in VEGF expression suggests that NLE cream enhances vascularization, supporting rapid tissue recovery.

Table 3. Average VEGF expression for each group and One way Anova

Group	Healthy (G1)	Base Cream (G2)	Povidone-Iodine (G3)	Extract 20% (G4)	Extract 40% (G5)	*P value*
Mean ± SD	37.92 ± 9.18	21.43 ± 10.59	51.24 ± 21.36	45.41 ± 8.37	59.76 ± 9.39	
Shapiro-Wilk	0.159#	0.608#	0.221#	0.584#	0.282#	
Lavene's test						0.012‡
One way Anova						<0.001*

Note: #Normal p>0.05 ##Not Normal p<0.05 †Homogen p>0.05
‡Non-Homogen p<0.05 *Significant p<0.05

Table 4. VEGF expression post hoc Tamhane test result

Group	Healthy (G1)	Base Cream (G2)	Povidone-Iodine (G3)	Extract 20% (G4)	Extract 40% (G5)	Healthy (G1)
Healthy (G1)	-	*0.034	0.082		0.319	*0.007
Base Cream (G2)	*0.034	-	*<0.001		*0.003	*<0.001
Povidone-Iodine (G3)	0.082	*<0.001	-		0.435	0.258
Extract 20% (G4)	0.319	*0.003	0.435		-	0.062
Extract 40% (G5)	*0.007	*<0.001	0.258		0.062	-

Note: * p<0,05

Wound healing involves a series of complex physiological processes, including inflammation, proliferation, and tissue remodeling[20,21]. IL-6 is a pro-inflammatory cytokine that plays a crucial role in the early inflammatory phase of wound healings[22–24]. However, excessive IL-6 expression can prolong inflammation and delay healing[15,25]. The significant reduction in IL-6 levels in the NLE-treated groups suggests that the bioactive compounds in NLE, including flavonoids and alkaloids, inhibit NF-κB activation, thereby reducing pro-inflammatory cytokine production[3,26]. This suppression is critical during the inflammatory phase of wound healing, particularly within the first 1–3 days, when IL-6 expression peaks[15]. In parallel, flavonoids support angiogenesis by stabilizing HIF-1α, promoting VEGF expression, and enhancing endothelial cell proliferation and migration[17,27].

VEGF, on the other hand, is a key regulator of angiogenesis and tissue regeneration[28]. Increased VEGF expression in the NLE-treated groups indicates that NLE cream facilitates the formation of new blood vessels, improving oxygen and nutrient delivery to the wound site[17,29]. The observed elevation in VEGF following 40% NLE application suggests that higher doses of the extract may more effectively stimulate neovascularization. VEGF expression typically begins around day two post-injury and marks the transition from the inflammatory to the proliferative phase of healing[17,30]. Increased VEGF enhances oxygen and nutrient

delivery to regenerating tissues, a critical requirement for efficient wound closure[1,31].

This dose-dependent pattern suggests a biphasic response: 20% NLE more effectively suppresses inflammation, while 40% NLE enhances angiogenesis. This may reflect a threshold beyond which higher concentrations shift the healing dynamic from immunomodulation to vascular regeneration. Such biphasic actions are consistent with the dual roles of flavonoids in modulating both NF-κB-mediated inflammation and PI3K/AKT-dependent angiogenesis[19].

The findings of this study align with previous research demonstrating the wound-healing potential of NLE. Topical application of NLE significantly increased fibroblast proliferation and collagen deposition in wound sites[32,33]. Additionally, the role of phenolic compounds in Noni leaf accelerates re-epithelialization and reduces oxidative stress in wound healing[10].

The results of this study suggest that NLE cream, particularly at a 20% concentration, provides an optimal balance between anti-inflammatory and pro-angiogenic effects, promoting effective wound healing. These findings highlight the potential of NLE as a therapeutic agent for wound care, particularly in reducing inflammation while enhancing vascularization.

One limitation of this study is the focus on only two concentrations of NLE cream. Future studies should explore a broader range of concentrations to determine the optimal formulation for clinical application. Additionally, further investigation into the molecular mechanisms underlying NLE's effects on IL-6 and VEGF expression is warranted. Long-term studies evaluating the histological changes in wound tissue following NLE treatment would also provide valuable insights into its regenerative potential.

CONCLUSION

This study demonstrated that NLE cream effectively modulates both inflammatory and angiogenic responses in incisional wound healing. The 20% concentration yielded optimal anti-inflammatory effects by significantly reducing IL-6 levels, while the 40% concentration promoted higher VEGF expression, suggesting a role in vascular regeneration. These findings indicate a dose-dependent dual mechanism. However, due to the short study duration and lack of histological evaluation, future research should explore longer treatment periods, broader concentration ranges, and mechanistic insights to validate NLE's clinical potential in wound care.

AUTHORS' CONTRIBUTIONS

Enike Putri Ananto: Conceptualization, Methodology, Software, Data curation, Writing-Original draft preparation, Visualization **Setyo Trisnadi**: Supervision, Validation, Writing-Reviewing and Editing **Danis Pertiwi**: Supervision, Validation, Writing-Reviewing and Editing

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DATA AVAILABILITY STATEMENT

The data supporting this study are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the

authors. The data is the result of the author's research and has never been published in other journals.

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