JTL 15 (2): JULY-DECEMBER 2026
Page: 138-148

Contents list available at Jurnal Teknologi Laboratorium

JURNAL TEKNOLOGI LABORATORIUM

Journal Homepage: www.teknolabjournal.com
ISSN 2580-0191(Online) I ISSN 2338 – 5634(Print)

Original Research

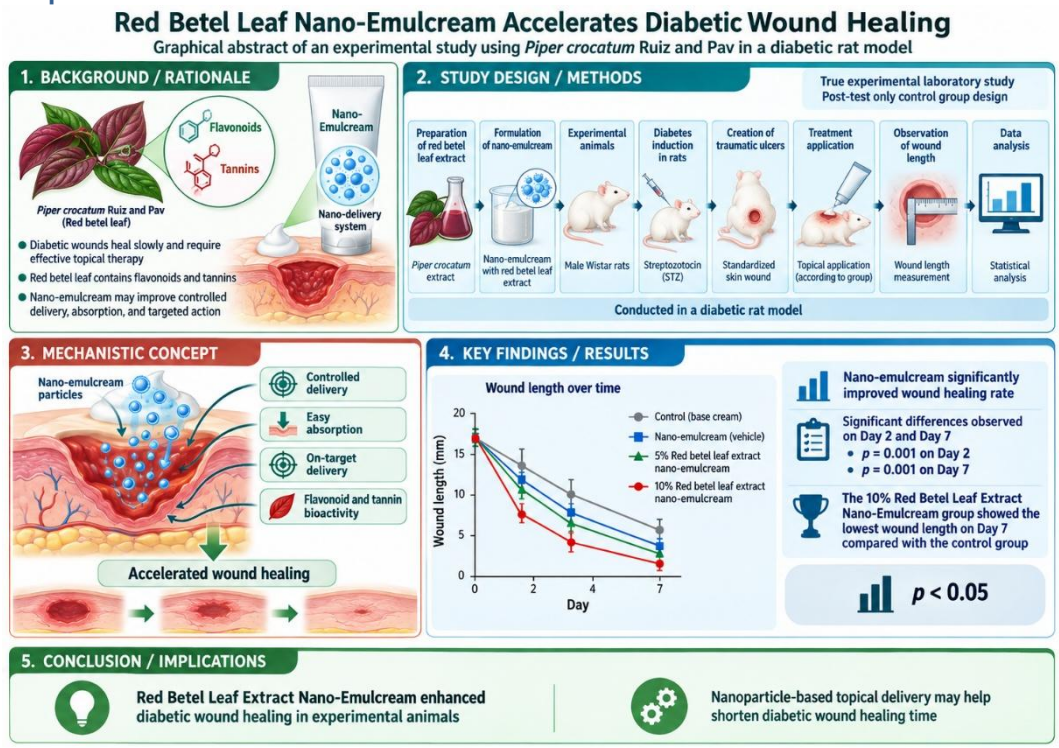
OPEN ACCESS

The Potential of red betel leaf extract nano-emulcream (Piper crocatum Ruiz and Pav) for diabetic wound healing

Gustiadi Saputra [1*], Egita Windrianatama Puspa [2], Intan Poespita Windiyani [1], Bella Selviana [1], Retno Titi Rahmania [1]

[1] Program Study of Medical Laboratory Technology, Politeknik Kesehatan Kesuma Bangsa, Lampung, Indonesia
[2] Program Study of Medical Laboratory Technology, Universitas Muhammadiyah Pringsewu, Lampung, Indonesia

Graphical Abstract



Abstract: This research is related to a drug delivery system to accelerate wound healing in patients with diabetes mellitus using bioactive compounds from red betel leaf (*Piper crocatum Ruiz and Pav*) made in Nano-emulcream form. Bioactive natural ingredients made with nanoparticle technology have the advantages of more controlled and easily targeted delivery, on-target delivery and easy absorption, resulting in accelerated diabetic wound healing due to the flavonoid and tannin content. The developed nanoparticle system is expected to shorten the healing time of diabetic wounds. This study observed the diabetic wound healing process using Red Betel Leaf Extract Nano-Emulcream (*Piper crocatum* Ruiz and Pav) in experimental animals. This study used a true experimental laboratory study with a post-test only control group design. The research stages included the preparation of red betel leaf extract, the preparation of red betel leaf extract nano-

Corresponding author.
E-mail address: gustiadisaputra51@gmail.com (Gustiadi Saputra)
DOI: 10.29238/teknolabjournal.v15i2.708
Received 25 November 2025; Received in revised form 11 May 2026; Accepted 15 June 2026

emulcream, the preparation of experimental animals, the induction of diabetes in the experimental animals, the creation of traumatic ulcers in the experimental animals, the application of treatment, the observation of wound length, and the data analysis. Overall, this study demonstrates that the synthesized Nano-emulcream significantly improve the wound healing rate in diabetic rat models. The results of this study showed a significant difference in the use of Red Betel Leaf Extract Nano-Emulcream on days 2 and 7 with significance values of 0.001 and 0.001, respectively (p-value <0.05). highlighted by the 10% Red Betel Leaf Extract Nano-Emulcream (*Piper crocatum* Ruiz and Pav) group which achieved the lowest wound length on day 7 compared to the control group.

Keywords: Red Betel Leaf; Diabetes; Drug delivery system; Nano-emulcream; Piper crocatum Ruiz and Pav

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease characterized by elevated blood sugar levels due to insufficient insulin production and decreased insulin function [1,2], Diabetes mellitus is also a global challenge due to its high morbidity and mortality.

The International Diabetes Federation (IDF) stated in 2019 that diabetes is a global health problem, with approximately 463 million people worldwide suffering from diabetes, a figure expected to increase to 700 million by 2045[3]. One such condition is diabetic ulcers. Diabetic ulcers can lead to amputations, negatively impacting the patient's quality of life. In Indonesia, 15% of people with diabetes suffer from diabetic ulcers, which often lead to death[4]. The diabetic wound healing process is very complex, and several factors significantly influence the healing process (inflammation, proliferation, and wound closure)[5,6].

Current treatment for diabetic wounds uses topical antibiotics, which can cause side effects such as skin irritation, redness, allergies, and even edema. Furthermore, bacterial resistance to antibiotics increases mortality and treatment costs. This has certainly prompted researchers to find a method or method to ensure drug delivery systems are more targeted.

One potential natural ingredient is the Red Betel Leaf (*Piper crocatum* Ruiz and Pav), which contains flavonoids, alkaloids, tannins, and essential oils[7]. Phenolic compounds function as antiseptics. Red Betel Leaf also contains tannins, which are effective in hemostasis, vitamin A for epithelial cell formation and cell differentiation, and vitamin C for collagen formation[8].

These important compounds will be packaged into nanometer-sized particles (10–1000 nm), called nanoparticles, which can become an effective drug delivery system [9,10] so that important compounds can be distributed more efficiently and target specific pathologies quickly and precisely without causing any side effects. Biotoxicity[11,12].

The advantages of nanoparticles include their ability to penetrate intercellular spaces that can only be penetrated by colloidal particles, their ability to penetrate higher cell walls, either through diffusion or opsonification, and their flexibility to be combined with various other technologies and active compounds, thus opening up broad potential for development for various therapeutic target purposes[12].

Wound care techniques to accelerate the healing process of diabetic wounds by utilizing bioactive compounds from red betel leaves (*Piper crocatum* Ruiz and Pav) have been conducted by research[13]. The use of bioactive compounds for diabetic wound healing in the form of boiled red betel leaves maintained wound moisture with a moisture-retaining dressing, thus healing the wound. Another study[14] tested the effectiveness of red betel leaves on incision wounds in experimental animals in the form of an ointment, which was then applied to the resulting incision and observed the results of erythrocyte and hemoglobin counts.

Several studies also utilized bioactive compounds found in *Piper crocatum* Ruiz and Pav in the form of extracts [15,16,17] to observe wound healing through the p53, E-cadherin, and SOD1 pathways in hyperglycemic fibroblast cells. Blood sugar levels in patients with diabetes mellitus were also observed. The results showed that *P. crocatum* was able to increase collagen and wound closure through the expression of SOD1 and E-cadherin. Red betel leaf extract was also able to lower blood sugar levels in diabetes mellitus.

Another study [8] demonstrated antibacterial effects through the phytochemical profile of red betel leaves in inhibiting bacteria in teeth. And another study [18] demonstrated the anti-infective effects of oral microorganisms with herbal treatment of red betel leaves. These studies utilized red betel leaves in extract form.

While previous studies have explored *Piper crocatum* extract for wound care, these conventional formulations suffer from poor penetration into deep tissue and rapid degradation of bioactive compounds. To date, no study has investigated the dose-dependent efficacy of a nanoparticle-based delivery system for *Piper crocatum* extract specifically designed for diabetic wound models. Therefore, this study aims to evaluate the topical effects of formulation on diabetic wound healing, focusing on critical observational timepoints during early healing phases.

Although the effectiveness of utilizing bioactive compounds in red betel leaves (*Piper crocatum* Ruiz and Pav) in healing diabetic wounds has been demonstrated, the preparations applied are still in extract form, which has limitations in drug delivery systems for packaging the bioactive compounds and in distributing the drug to the infected area. Wound care methods with high humidity levels in the wound area are also susceptible to increasing bacterial infection.

MATERIAL AND METHOD

This study observed the healing process of diabetes mellitus wounds using Red Betel Leaf Extract Nano-Emulcream (*Piper crocatum* Ruiz and Pav) in experimental animals. This study used a true experimental laboratory research type with a Post-test only control group research design. This study has been approved by the Health Research Ethics Committee (KEPK) of the Faculty of Health Sciences at Universitas Muhammadiyah Pringsewu, with ethics certificate number: 007/KEPK/FKes/2025. All procedures involving laboratory animals were conducted in accordance with animal welfare standards to minimize pain and stress during the study. The sample calculation uses the Federer formula. This formula is used to determine the number of replicates (n) per group so that the research results have an adequate number of degrees of freedom : $(t - 1) \times (n - 1) \geq 15$ with 5 treatment groups. Based on this formula, the number of samples per group is 5 samples. Process diagram of the research on the potential of Red Betel Leaf Extract Nano-Emulcream (*Piper crocatum* Ruiz and Pav).

Stage 1: Preparation of red betel leaf extract (*Piper crocatum* Ruiz and Pav)
The research process into the potential of Red Betel Leaf Extract Nano-Emulcream (*Piper crocatum* Ruiz and Pav) in healing diabetic wounds began with the preparation of red betel leaf extract. A 500-gram sample of dried red betel leaf was weighed and soaked in 5 liters of analyzed ethanol at a 1:10 ratio to facilitate the extraction of the compounds. The extraction process was carried out for 3 days, with stirring every 24 hours. The sample was filtered, then the filtrate was evaporated using a rotary evaporator to produce a thick red betel leaf extract [19].

Stage 2: Production of Red Betel Leaf Extract Nano-Emulcream (*Piper crocatum* Ruiz and Pav) (Characterization and Particle Size Analyzer/PSA)
The preparation of red betel (*Piper crocatum*) leaf extract nano-emulcream was initiated by formulating the oil phase in a mortar, where the red betel leaf extract

was ground until homogeneous with propylene glycol, followed by the sequential addition and constant blending of VCO, Span 80, Tween 80, nipasol, and 96% ethanol to ensure uniformity. Concurrently, the aqueous phase was prepared by dissolving nipagin in half of the total volume of distilled water, which was subsequently combined with the oil phase using a magnetic stirrer at 1,000 rpm and 50°C for 10 minutes to yield the nanoemulsion. Meanwhile, the gel base was fabricated by dispersing Carbomer 940 evenly over the remaining half of the preheated distilled water, allowed to swell for 15 minutes, ground into a gel matrix, and homogenized with glycerin. In the final stage, the pre-formed nanoemulsion was incorporated into the gel base, followed by the addition of triethanolamine (TEA) with continuous stirring until thickening occurred. The particle size was subsequently reduced using an Ultra-Turrax homogenizer at 15,500 rpm for 10 minutes to obtain a homogeneous[20]. The mixture was then stirred using a magnetic stirrer at 250 rpm for 30 minutes. The nanoparticles were then characterized using a UV-Vis spectrophotometer to determine the maximum wavelength indicating the formation. This was followed by characterization using a Particle Size Analyzer to determine the size and distribution of the formed particles.

Stage 3: Preparation of Wistar rats (*Rattus norvegicus*)
This stage involved acclimatizing the animals to the testing room to adjust or adapt to the conditions and temperature of the testing room for 7 days before the next stage.

Stage 4: Induction of Diabetes in the Experimental Animals
In this stage, the animals were induced intraperitoneally with alloxan monohydrate A7413, Sigma Aldrich, at a dose of 100 mg/kg body weight, to stimulate diabetes. Alloxan was prepared by dissolving 0.9 g of alloxan monohydrate in 6 ml of phosphate-buffered saline to obtain a concentration of 150 mg/ml [21]. The rats were deprived of food or water for more than 12 hours overnight before alloxan induction. The development of diabetes mellitus in these animals was confirmed 72 hours after alloxan induction and was confirmed by an average blood glucose level exceeding 200 mg/dL using a GlucoDR device.

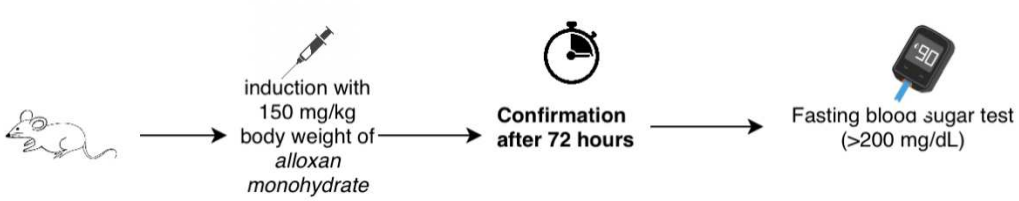


Figure 1. Induction of diabetes in experimental animals

Stage 5: Traumatic ulcer in diabetic Wistar rats
In this stage, a traumatic ulcer or wound is created in the diabetic test animal. After the test animal is confirmed to have diabetes mellitus (fasting glucose >200 mg/dL), a 2 cm and 2 mm deep traumatic ulcer is created along the back using a stainless steel blade/scalpel. Prior to the traumatic ulcer, the test animal is anesthetized with ketamine/xylazine. A traumatic ulcer is confirmed after 24 hours, with the clinical appearance of a yellowish-white ulcer with a reddish border[22].

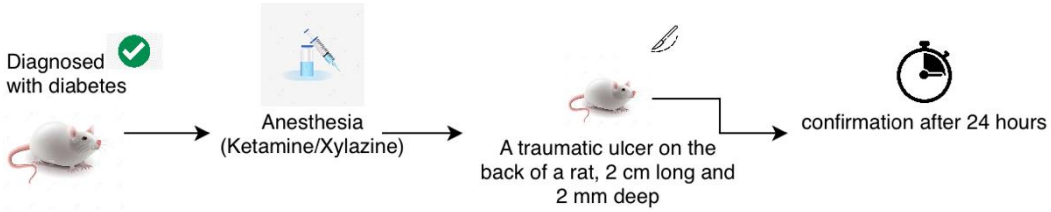


Figure 2. Creation of a traumatic ulcer in a diabetic Wistar

Stage 6: Treatment Application
At this stage, after the traumatic wound or ulcer condition in the diabetic experimental animals has been established, the experimental application will be carried out on five groups of experimental animals. Group 1 (negative control) was given 0.9% NaCl, group 2 (positive control) was given povidone iodine, and groups 3, 4, and 5 were given Red Betel Leaf Extract Nano-Emulcream at concentrations of 5%, 10%, and 15%, respectively.

Stage 7: Observation of the length and width of the traumatic ulcer measurements were explicitly performed on designated timepoints, specifically on day 2 and day 7 post-injury.

Stage 8: Data Analysis
Data were expressed as Mean ± Standard Deviation (SD). The normality of data distribution and homogeneity of variances were assessed using the Shapiro-Wilk test and Levene's test, respectively. Statistical significance among the experimental groups was analyzed using Welch's ANOVA. And Post-Hoc Games-Howell to comparisons were subsequently to determine specific pairwise differences between groups. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant. All statistical analyses were executed using SPSS version 26.

RESULTS AND DISCUSSION

The results of the characterization test were carried out with 2 types of FTIR spectrum tests, namely the characterization test on Red Betel Leaf Extract (*Piper crocatum* Ruiz and Pav) and the characterization test on the Red Betel Leaf Extract Nano-emulcream (*Piper crocatum* Ruiz and Pav) preparation. The results of the characterization test on the extract and the Red Betel Leaf Nano-Emulcream preparation obtained 9 points and 13 peak points/Peaks which indicate the results of the FTIR analysis on the red betel leaf extract containing various functional groups which indicate the diversity of chemical components and bioactive compounds. Thus, this FTIR spectrum provides an illustration that red betel leaves contain complex compounds including hydrocarbons, phenolic compounds, and nitrogen-containing compounds[18,14], which can support the bioactive potential of Red Betel Leaves. It can be concluded that flavonoids, tannins, and essential oils are present in the chemical composition of red betel leaves. These results align with previous research [23] that examined flavonoids, tannins, and essential oils using the FTIR method[24]. Each identified spectral peaks indicating the characteristic functional groups of each compound. Two characterization tests of the RBL Nano-Emulcream preparation revealed no changes in the compound content of the prepared preparations.

The results of the Particle Size Analyzer (PSA) test (**Table 1**) using the NanoTrac II instrument with the Dynamic Light Scattering (DLS) method indicate that the particle size of red betel leaf (*Piper crocatum* Ruiz & Pav) nanoparticle extract is in the range of 176.35–361.8 nm, with a Polydispersity Index (PDI) value between 1.055–1.132. At a RBL-NEC concentration of 5%, an average particle size of 176.35 nm (PDI 1.055) was obtained, indicating a heterogeneous particle size distribution. This suggests a potential tendency for particle aggregation within the emulcream matrix, which represents a limitation of the current formulation design. At RBL-NEC 10%, the particle size increased to 266.8 nm (PDI 1.127), and at RBL-NEC 15%, the particle size reached 361.8 nm (PDI 1.132) with a more heterogeneous distribution.

Table 1. PSA test results for three concentrations of Red Betel Leaf Extract Nano-Emulcream

No	Sample	PSA Parameters		Average Parameters (x̄)	
		Mean Intensity (MI)	Polydispersity Index (PDI)	MI	PDI
1	RBL-NEC 5%	164.7 nm	1.008	176.35	1.055
	RBL-NEC 5%	188 nm	1.102		
2	RBL-NEC 10%	274.2 nm	1.108	266.8	1.127
	RBL-NEC 10%	259.4 nm	1.146		
3	RBL-NEC 15%	349.1 nm	1.114	361.8	1.132
	RBL-NEC 15%	374.5 nm	1.151		

The high PDI value (>1.0) is likely due to the diversity of bioactive components in *Piper crocatum* extract that have different affinities to the carrier polymer, thus forming a heterogeneous particle size population. Although the PSA results show a high PDI due to the sensitivity of the instrument to particle aggregates, microscopic observations indicate that most individual particles are still in the nanometer range[25,26].

The increase in particle size with increasing concentration is due to particle aggregation and size growth due to the greater number of precursors, so that the particles tend to combine to form larger particles. All results are still within the nanoparticle size range (10–1000 nm), making them suitable for use in drug delivery systems. These results align with previous research [27] which reported a red betel leaf extract nanoemulsion size of 514.4 nm, and are supported by research explaining that the higher the concentration of the active ingredient, the larger the resulting particle size due to a decrease in the zeta potential value, which causes the molecules to easily attract each other and aggregate[28,29,30].

Table 2. Effect of Treatment on Wound Length on Day 2 and Day 7

Treatment Group	Day 2 (Mean ± SD)	Day 7 (Mean ± SD)
C – (Negative Control)	1.95 ± 0.05	1.57 ± 0.08
C + (Positive Control)	1.60 ± 0.12	0.88 ± 0.19
RBL-NEC 5%	1.83 ± 0.08	0.82 ± 0.16
RBL-NEC 10%	1.71 ± 0.07	0.22 ± 0.08
RBL-NEC 15%	1.69 ± 0.12	0.34 ± 0.20
P Value (*Welch*)	0.001	0.001

On Day 2, the negative control group (C-) exhibited the largest mean wound length at 1.95±0.05. The Games-Howell post hoc test demonstrated that the C- group was significantly different from the positive control group (C+; 1.60±0.12), the 10% extract dose group (RBL-NEC 10%; 1.71±0.07), and the 15% extract dose group (RBL-NEC 15%; 1.69±0.12). This indicates that from the early phase of healing (Day 2), administration of the extract at a minimum concentration of 10% successfully stimulated a statistically significant reduction in wound length. Conversely, the low-dose group (RBL-NEC 5%; 1.83±0.08) did not show a significant difference in mean wound length compared to the negative control group. Interestingly, all extract-treated groups (RBL-NEC5%, RBL-NEC10%, and RBL-NEC15%) demonstrated a therapeutic efficacy comparable to that of the positive control group (C+), with no statistically significant differences observed among these groups ($p>0.05$).

And by day 7, a distinct and more pronounced pattern of efficacy emerged across the treatment groups. The negative control group (C-) maintained the largest mean wound length (1.57±0.08) and remained highly significantly different ($p\leq0.003$) compared to all other intervention groups. The administration of the moderate extract dose (RBL-NEC10%) and high extract dose (RBL-NEC15%) yielded the most optimal healing outcomes, with mean wound lengths of 0.22±0.08 and 0.34±0.20, respectively. Both groups were found to be significantly more effective in reducing wound length compared to the positive control group (C+; 0.88±0.19). The RBL-NEC10% and RBL-NEC15% groups also

outperformed the low-dose RBL-NEC5% group (0.82±0.16). However, increasing the extract concentration from 10% (RBL-NEC10%) to 15% (RBL-NEC15%) did not result in a statistically significant difference in wound healing acceleration. Meanwhile, the low-dose RBL-NEC5% group (0.82±0.16) exhibited a healing efficacy that was statistically equivalent and not significantly different from the positive control group at this stage of observation.

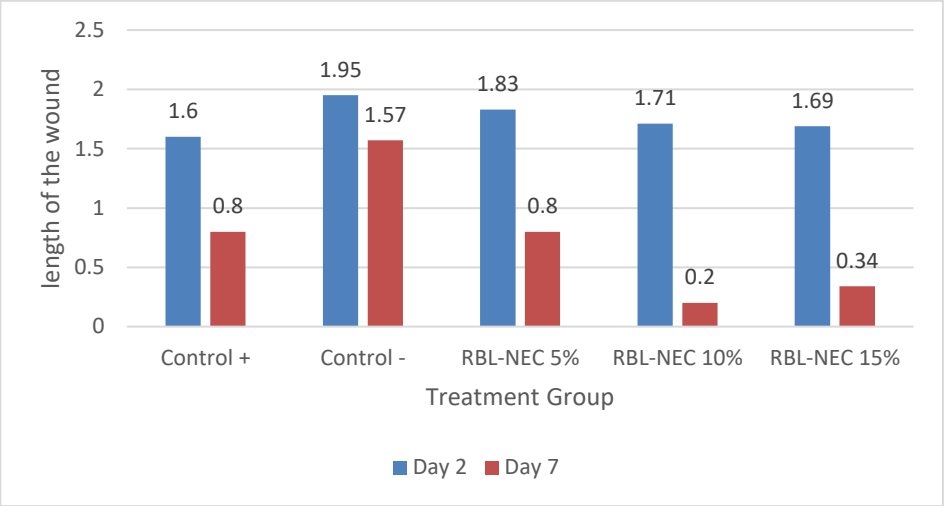


Figure 3. Graph of average reduction in wound length , wounds (cm) in experimental animals on day 2 and day 7

Figure 3. shows that increasing the concentration from 5% to 10% resulted in a sharp increase in healing effectiveness on Day 7 (down from 0.80 to 0.20). However, further dose increases to 15% no longer showed an increase in the acceleration effect, but rather tended to stabilize (at 0.34). Thus, it can be visually concluded that RBL-NEC 10% is the most optimal concentration in accelerating wound healing efficiency in this test animal model.

On day 2, wound healing effects began to appear in the 10% and 15% RBL-NEC groups, which showed faster anti-inflammatory and antimicrobial activity than the other groups. This phase is still included in the early inflammatory phase where hemostasis and clearance of tissue debris by inflammatory cells occur. Healing activity at this stage is related to the ability of nano-emulcream to suppress inflammatory mediators. These results are in line with research by Sukmawati et al. who reported that white turmeric extract nanoparticles were able to suppress inflammation in excision wounds in mice in the first 48 hours through antioxidant and antibacterial activity that reduced neutrophil infiltration[31]. Several studies have shown that nanoparticles derived from herbal ingredients with high phenolic compound content can inhibit the formation of inflammatory mediators, thereby helping to accelerate the transition from the inflammatory phase to the proliferation phase in the wound healing process[32,33,34]. Furthermore, Wulandari's research reported that Rhaphidophora pinnata leaf nanoparticle gel accelerated wound closure starting on day 3 compared to the control, through mechanisms such as increased fibroblast activity and reduced tissue edema[35].

On day 7, all treatment groups showed a greater reduction in wound size, particularly in the 10% RBL groups, indicating a potentially enhanced progression into the proliferative phase. This phase is characteristically associated with granulation tissue formation, fibroblast proliferation, collagen deposition, and re-epithelialization. While these underlying cellular mechanisms were not directly evaluated in the present study, the macroscopic acceleration of wound closure aligns with studies by Yuliani et al. and Che et al., which demonstrated that chitosan-based nanoparticles can enhance fibroblast migration and type I collagen production[36,37]. However, increasing the concentration to 15% did not improve

results, likely due to particle saturation or local tissue irritation, as also found by Afshar et al. and Medic et al[38,39]. Overall, the RBL-NEC 105 formulation proved to be the most effective in accelerating macroscopic wound healing. These outcomes may be associated with the potential antimicrobial, anti-inflammatory, and fibroblast proliferation stimulation effects reported in previous literature; however, further histological and biomolecular analyses are required to definitively confirm these specific mechanisms in this model.

CONCLUSION

Red Betel Leaf Extract Nano-Emulcream (*Piper crocatum* Ruiz & Pav) showed potential to accelerate wound healing in an alloxan-induced diabetic rat model. A formulation with a particle size of 176–361 nm enhances the effectiveness of bioactive compounds such as flavonoids and tannins through anti-inflammatory, antibacterial, and antioxidant activities. In vivo testing results showed that a 10% concentration significantly reduced wound length ($p < 0.05$) compared to the control group. In conclusion, the developed red betel leaf extract nano-emulcream showed potential effectiveness as a topical wound-healing agent. However, further toxicity, skin irritation, and systemic safety evaluations are strictly required before clinical translation as an alternative topical therapy to accelerate tissue regeneration in diabetic wounds.

AUTHORS' CONTRIBUTIONS

Gustiadi Saputra: Conceptualization, methodology, supervision, and manuscript writing. **Egita Windrianatama Puspa**: Extract preparation, nano-emulcream synthesis, and induction of diabetes in experimental animals. **Intan Poespita Windiyani**: Nano-emulcream formulation and research data analysis. **Bella Selviana**: Animal care and traumatic ulcer formation. **Retno Titi Rahmania**: Application of nano-emulcream preparations and wound healing measurements.

ACKNOWLEDGEMENT

The Authors would like to express their gratitude to:

- The Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia for its financial support through the Early Career Faculty Research (PDP) scheme in the BIMA (Research and Community Service Information Base) program for the 2025 fiscal year. This research was conducted based on Decree [Number SK 0070/C3/AL.04/2025 and Contract Number 119/LL2/DT.05.00/PL/2025], which served as the main pillar for the implementation of all research activities.
- The Director of Politeknik Kesehatan Kesuma Bangsa and the Research and Community Service Institute (LPPM) for the facilities, permits, and administrative support provided during the research period.
- Universitas Airlangga for granting permission and facilitating the laboratory for the implementation of this research.

FUNDING INFORMATION

This research was funded by the Ministry of Education, Culture, Research, and Technology of the Republic of Indonesia through its financial support under the Young Lecturer Research Scheme (PDP) within the BIMA (Research and Community Service Database) program for the 2025 fiscal year. This research is conducted based on Decision Number SK 0070/C3/AL.04/2025 and Contract Number 119/LL2/DT.05.00/PL/2025, which serve as the main basis for the implementation of all research activities.

DATA AVAILABILITY STATEMENT

This study obtained data on the reduction in wound size in experimental animals with a diabetes mellitus model induced by alloxan monohydrate. The data that

support the findings of this study are available from the corresponding author upon reasonable request. The datasets are currently maintained in secure institutional records to ensure data integrity, and interested researchers may contact the corresponding author to obtain the relevant spreadsheets and statistical charts.

DISCLOSURE STATEMENT

The undersigned authors hereby declare that there are no potential conflicts of interest, whether financial, personal, or professional, related to the research, data, interpretation of results, or writing of this manuscript. There are no affiliations with parties that may benefit or be harmed by the publication of these research results. All scientific decisions and conclusions presented are based solely on the empirical data collected. We guarantee that all findings, data, and conclusions in this manuscript are presented honestly, transparently, and objectively, in full accordance with the principles of scientific publication ethics, and without influence from commercial relationships, personal pressure, or other third parties.

REFERENCE

1. Rismayanti, i., Sundayana, I., Pratama P. Penyembuhan Luka Grade 2 pada Pasien Diabetes Mellitus Dengan Modern Dressing Wound Care.*Jurnal Keperawatan Silampari* 2020;2507(February):1-9.
2. Mariadoss AVA, Sivakumar AS, Lee CH, Kim SJ. Diabetes mellitus and diabetic foot ulcer: Etiology, biochemical and molecular based treatment strategies via gene and nanotherapy. *Biomed Pharmacother*. 2022;151(May):113134. doi:10.1016/j.biopha.2022.113134
3. Ong KL, Stafford LK, McLaughlin SA, et al. Global, regional, and national burden of diabetes from 1990 to 2021, with projections of prevalence to 2050: a systematic analysis for the Global Burden of Disease Study 2021. *Lancet*. 2023;402(10397):203-234. doi:10.1016/S0140-6736(23)01301-6
4. Khumaidi K, Fitra L, Isnayati I. Perawatan Luka dengan Madu dalam Penyembuhan Luka Diabetikum pada Pasien Diabetes Melitus. *J Nurs Innov*. 2022;1(1):1-4. doi:10.61923/jni.v1i1.1
5. Safitri AI, Saidah Q, Nurhayati C. Literatur Review; Pengaruh Pemberian Olahan Ikan Gabus Terhadap Proses Penyembuhan Luka DM. *Jurnal Ilmu Keperawatan Stikes Hang Tuah Surbaya*. 2022;17(1):55-56. doi:10.30643/jiksht.v17i1.169
6. Sun Y, Tao Q, Wu X, Zhang L, Liu Q, Wang L. The Utility of Exosomes in Diagnosis and Therapy of Diabetes Mellitus and Associated Complications. *Front Endocrinology (Lausanne)*. 2021;12(October):1-15. doi:10.3389/fendo.2021.756581
7. Natilla B, Rohama, Mukti YA. Penetapan kadar flavonoid total dari tingkatan fraksi ekstrak daun sirih merah metode spektrofotometri UV-Vis. *Jurnal Farmasi dan Sains Indonesia.* 2023;3(2):2019-2024.
8. Heliawati L, Lestari S, Hasanah U, Ajiati D, Kurnia D. Phytochemical Profile of Antibacterial Agents from Red Betel Leaf (Piper crocatum Ruiz and Pav) against Bacteria in Dental Caries. *Molecules*. 2022;27(9). doi:10.3390/molecules27092861
9. J N, E K, S R. “Green Synthesis of Zinc Oxide Nanoparticles: Eco-Friendly Advancements for Biomedical Marvels.” *Resource Chem Mater*. 2024;3(4):294-316. doi:10.1016/j.recm.2024.05.001
10. Chen M, Quan G, Sun Y, Yang D, Pan X, Wu C. Nanoparticles-Encapsulated Polymeric Microneedles for Transdermal Drug Delivery. *J Control Release*. 2020;325:163-175. doi:10.1016/j.jconrel.2020.06.039
11. Ruan S, Guo X, Ren Y, Cao G, Xing H, Zhang X. Nanomedicines Based On Trace Elements for Intervention of Diabetes Mellitus. *Biomed Pharmacother*. 2023;168:115684. doi:10.1016/j.biopha.2023.115684
12. Ningrum WA, Wirasti W, Permadi YW, Himmah FF. Uji Sediaan Lotion

Nanopartikel Ekstrak Terong Belanda Sebagai Antioksidan. *J Ilmu Kesehaant*. 2021;14(1):99. doi:10.48144/jiks.v14i1.539
13. Hariani Mustari N, Ardi M. Efektifitas Rendam Air Rebus Daun Sirih dan Moist Wound Healing terhadap Penyembuhan Luka pada Pasien Diabetes Mellitus Tipe 2.*Jurnal Ilmiah Kesehatan Diagnosis*. 2021;16:81-86.
14. Widyawati R, Kasy F, Yunani R, Pratama JWA. Efektivitas Salep Ekstrak Daun Sirih Merah (Pipercrocatum) terhadap luka insisi pada tikus putih (Rattus norvegicus). *VITEK Bid Kedokt Hewan*. 2021;11(2):39-46. doi:10.30742/jv.v11i2.82
15. Setyawati A, Wahyuningsih MSH, Nugrahaningsih DAA, Effendy C, Fneish F, Fortwengel G. Piper crocatum Ruiz & Pav. ameliorates wound healing through p53, E-cadherin and SOD1 pathways on wounded hyperglycemia fibroblasts. *Saudi Journal Biology Sci*. 2021;28(12):7257-7268. doi:10.1016/j.sjbs.2021.08.039
16. Sari EK. Pengaruh Ekstrak Daun Sirih Merah Terhadap Gula Darah Sewaktu Penderita Diabetes Melitus di UPT Puskesmas Branti Raya Lampung Selatan. *Jurnal Ilmu Keperawatan Indonesia*. 2022;3(2):97-103.
17. Intami E, Girsang E, Napiah A.Manfaat Ekstrak Daun Sirih Merah (Piper crocatum) Sebagai Obat Tradisional Diabetes Melitus. *Journal Kesehatan Saintika Meditory*. 2022;4(4657):78-84.
18. Kurnia D, Lestari S, Mayanti T, Gartika M, Nurdin D. Anti-Infection of Oral Microorganisms from Herbal Medicine of Piper crocatum Ruiz & Pav. *Drug Desain Development and Therapy*. 2024;18(May):2531-2553. doi:10.2147/DDDT.S453375
19. Apriliani A, Supriyanta J, Badriah L. L Arini Aprilliani, Jaka Supriyanta, Lailatul Badriah. Formulation and Antioxidant Efectivity Test of Handbody Lotion of 70% Ethanol Extract Cucumber (Cucumis sativus L.) Fruit Using DPPH Method *Jurnal Farmagazine*. 2022;IX(1):20-28.
20. Karim F, Tungadi R, Thomas NA. Biosinstesis Nanopartikel Perak Ekstrak Etanol 96% Daun Kelor (Moringa oleifera) dan Uji Aktivitasnya sebagai Antioksidan. *Indones J Pharm Educ*. 2021;2(1):32-41. doi:10.37311/ijpe.v2i1.11725
21. Ulfa AM, Primadiamanti A, Alim FN. Uji Efektivitas Formulasi Salep Ekstrak Kulit Jeruk Nipis (Citrus Aurantifolia) Sebagai Penyembuhan Luka Diabetes Tipe I Pada Tikus Jantan. *Jurnal Farmasi Malahayati*. 2022;4(2):126-137. doi:10.33024/jfm.v4i2.5246
22. Ayu Henny Achjar K, Made Candra Dinata I, Ayu Henny Achjar K, Ketut Gama I, Sudiantara K. Gambaran Pemberian Terapi Senam Kaki Diabetes Pada Lansia Dengan Diabetes Melitus Tipe Ii. *J Gema Keperawatan*. 2022;15(2):305-319.
23. Noordan, E R, Rahmat D, Sandhiutami, N, M D, Yuliana, N D. Quality Parameter Analysis , Antioxidant Activity , and FTIR Profile of Turmeric (Curcuma longa L .) from Medan , Sumba , and Papua. *Indonesian Journal Pharm Educ*. 2025;5(1):119-131. doi:10.37311/ijpe.v5i1.30494
24. Wahyuni, Abdul A, Qonitah F. Identifikasi Senyawa Hasil Ekstrak Etanol Daun Adas (Foeniculum Vulgare Mill) Dengan Skrining Fitokimia. *J Pharm Sci Med Res*. 2021;4(2):55-64.
25. Dzakwan M, Priyanto W. Formulasi, Karakterisasi Dan Aktivitas Antioksidan Nanosuspensi Morin dengan Metode Sonopresipitasi. *Jurnal Ilmiah Farmasi Farmasyifa*. 2020;3(2):121-131.
26. Xie Y, Xiao H, Zheng D, Mahai G, Li Y, Xia W. Associations of prenatal metal exposure with child neurodevelopment and mediation by perturbation of metabolic pathways. *Nature Communication*. Published online 2025. doi:10.1038/s41467-025-57253-3
27. Karlina DW, Noval, Yuwindry I. Formulasi dan Evaluasi Nano Spray Gel dengan Ekstrak Daun Sirih Merah (piper crocatum Ruiz & Pav) Sebagai

Antioksidan dengan Variasi Konsentrasi Carbopol 940.*Jurnal Surya Med*. 2024;10(2):288-301.
28. Oktaviani . Z., M. J. Arief A, Sastyarina Y. Phytochemical Screening, Characterization of Bawang Dayak Extract Nanoparticles, and Literature Review of Nanoparticles as Antihyperglycemia. . *Pharmasci. Journal Pharm Sci*. Published online 2024:115-119. doi:10.53342/pharmasci.vi.410.
29. Kusumo, G G, Dipahayu D. Effect of Nano Extract Formulation on Antioxidant Activity of 70 % Ethanolic Extract of Purple Sweet Potato ' s Leaves.*Journal Pharm Sci*. 2022;7(1):43-47.
30. Khofifah N, Putri Y, Munandar H, Miswanda D. Determination of minimum inhibitory concentration and minimum bactericidal concentration of papaya leaf extract (Carica papaya L .) and its nanoparticles against Cutibacterium acnes bacteria Penentuan konsentrasi hambat minimum dan konse. *Journal Pharm Science*. 2025;8(1):51-66.
31. Sukmawati L D. Wound healing using white turmeric extract nanoparticles in rats .*Journal Veteriner*. 2022;23(2):183-190. doi:DOI:10.19087/jveteriner.2022.23.4.441
32. Jayusman PA, Nasruddin NS, Inaas N, Apandi M. Therapeutic Potential of Polyphenol and Nanoparticles Mediated Delivery in Periodontal In fl ammation : A Review of Current Trends and Future Perspectives. *Pharmacology*. 2022;13(July):1-17. doi:10.3389/fphar.2022.847702
33. Puja AM, Rupa EJ, Kim YJ, Yang D chun. Medicinal Plant Enriched Metal Nanoparticles and Nanoemulsion for Inflammation Treatment : A Narrative Review on Current Status and Future Perspective UV-Vis focus Nanoparticles. *Immuno*. 2023;3:182-194.
34. Elhabal SF, Abdelaal N, Abdul S, et al. Green Synthesis of Zinc Oxide Nanoparticles from Althaea officinalis Flower Extract Coated with Chitosan for Potential Healing Effects on Diabetic Wounds by Inhibiting TNF- α and IL-6 / IL-1 β Signaling Pathways. *International Journal Nanomedicine*. 2024;19(March):3045-3070.
35. Kasmadi, F S, Rahman, A O, Rahman H, Yuliawati, Samudra, A G. Wound Healing Activity of Gel Nanoparticles of Rhaphidophora pinnnata Leaves Extract in Male Rats. *Borneo J Pharm*. 2025;8(2):135-148. doi:10.33084/bjop.v8i2.7525
36. Lestari NRD, Cahyaningrum SE, Herdyastuti N, Setyarini W, Arizandy RY. Antibacterial and Wound Healing Effects of Chitosan-Silver Nanoparticle and Binahong (Anredera cordifolia) Gel Modified with Cinnamon Essential Oil. *Tropical Journal of Natural Product Research*. 2024;8(January):5936-5945.
37. Che X, Zhao T, Hu J, et al. Application of Chitosan-Based Hydrogel in Promoting Wound Healing : A Review. *Polymers (Basel)*. 2024;16(1):1-20.
38. Afshar M, Rezaei A, Eghbali S. Nanomaterial strategies in wound healing : A comprehensive review of nanoparticles , nanofibres and nanosheets. *Int Wound J*. 2024;21(December 2023):1-13. doi:10.1111/iwj.14953
39. Medic BS, Tomic N, Lagopati N, Gazouli M. Advances in Metal and Metal Oxide Nanomaterials for Topical Antimicrobial Applications : Insights and Future Perspectives. *Molecules*. 2024;29(11):1-17.