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Characterization and Effectiveness Testing of a Transdermal Patch Combining Red Betel Leaf Extract and Tapak Liman Extract for the Healing of Diabetic Gangrene Wounds

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Abstract: This study aimed to develop and evaluate three nanogel-based transdermal patch formulations combining red betel leaf (*Piper crocatum*) and tapak liman (*Elephantopus scaber L.*) extracts to accelerate diabetic gangrene wound healing. The extracts were obtained by maceration using 70% ethanol and qualitatively indicated flavonoid-like compounds through color reactions and TLC profiles. The nanogel was prepared from a nanoemulsion containing Tween 80, PEG 400, olive oil, and distilled water, then incorporated into a carbopol-based gel matrix with propylene glycol, triethanolamine, and nipagin. The mixture was dried in an oven at 50 °C and stored in a desiccator for 24 hours to form a stable patch. Physical evaluation showed a pH of 6.0–6.7, patch thickness of 0.106–0.113 mm, and nanoparticle sizes of 74.46, 108.2, and 118.7 nm for Formulas 1–3, respectively. In vivo testing used diabetic rats divided into five groups: positive control (iodine plaster), negative control (untreated), and Formulas 1–3 with extract ratios of 3:1, 1:1, and 1:3. Formula 3, with a particle size of 118.7 nm, achieved complete wound closure by day 7. These findings highlight the potential of this nanogel-based transdermal system as a promising foundation for developing effective topical therapies for diabetic gangrene wounds.

Keywords: Diabetic gangrene; *Elephantopus scaber L.*; Flavonoids; *Piper crocatum*; Transdermal patch; Wound healing

Introduction

Diabetes mellitus is a chronic increase in blood sugar due to insulin deficiency, which can cause tissue damage and gangrene (Elisabet et al., 2023). Gangrene is severe damage to the skin and underlying tissues, including tendons, muscles, bones, and joints, which often occurs in people with Diabetes Mellitus (DM) (Carolina et al., 2024). In Indonesia, the incidence of gangrene wounds in diabetic patients remains very high, with an amputation rate of around 30% (Andini et al., 2024). Diabetes patients even have a 15–46% higher risk of amputation compared to non-diabetic individuals, and this complication accounts for nearly 80% of diabetes-related hospitalizations, with a mortality rate of 32% (Nadilla et al., 2023). These data indicate that diabetic gangrene is not only a medical problem but also a serious social issue, as it can cause permanent disability, reduced quality of life, and economic burden for patients and their families. This condition underscores the need for more effective, safe, and affordable treatment approaches, one of which is through the use of traditional medicinal plants containing active compounds with potential as alternative therapies to accelerate the healing of gangrene wounds (Susila, 2022).

Red betel leaves contain tannins, flavonoids, polyphenols, and saponins, all of which act as

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antibacterial agents on wounds. Red betel leaves are used in herbal treatments for gangrene because they are believed to promote wound healing (Amlia et al., 2025). Besides red betel leaves, there are also tapak liman leaves (*Elephantopus scaber L.*)., which have antibacterial and antioxidant potential through their flavonoid content, such as luteolin-7-glucoside, and terpenoids, such as epipriedelinol, lupeol, monoterpenoid linalool, phytol, and triterpenoid glycoside (Gunarti & Hidayah, 2022).

To improve the effectiveness of active ingredient delivery, a nanocomposite-based transdermal patch delivery system was chosen because it has several advantages, such as ease of use, minimal side effects, and the ability to accelerate the absorption of active ingredients directly into the wound area (Al-fira et al., 2024). In addition, the nano-scale particle size can increase flavonoid solubility, skin penetration, and drug release control, thereby improving the effectiveness of gangrene wound therapy (Sindhu et al., 2022). Therefore, this study aims to develop an innovative transdermal patch based on a nanocomposite combination of red betel leaf extract and tapak liman extract as an effort to accelerate the healing of gangrene wounds caused by diabetes.

Method

This study used extracts of red betel leaf (*Piper crocatum*) and tapak liman (*Elephantopus scaber L.*) obtained through maceration in 70% ethanol. The nanogel formulation was prepared in two stages. First, nanoemulsions were prepared using concentrated extracts from both plants as active components, olive oil as the oil phase, Tween 80 as a surfactant, PEG 400 as a co-surfactant, and distilled water as the water phase. Then, the nanoemulsion was incorporated into a gel matrix containing carbopol as a thickening agent, propylene glycol as a humectant, triethanolamine as a pH stabilizer, nipagin as a preservative, and distilled water as a solvent. The mixture of the two extracts was then added to the base and homogenized to create a stable nanogel formulation. It was then oven-dried at 50°C, and after drying, it was placed in a desiccator for approximately 24 hours. The patch was removed from the mold, cut, and attached to the plaster as a base adhesive, and then stored in a closed container.

Tool

The tools used in this study included a closed glass jar for maceration, a rotary evaporator for solvent removal, and a vortex mixer and magnetic stirrer with a temperature controller for homogenization. Flavonoid analysis was performed using a UV-Vis spectrophotometer along with measuring equipment such as pipettes, volumetric flasks, and an analytical balance. The preparation of nanoemulsions and nanogels utilized a sonicator, while particle size was measured using a Malvern ZEN169 Particle Size Analyzer (PSA). Evaluation of the gel's physical properties involved tools such as glass slides and spherical glass for homogeneity and spreadability, an adhesive strength tester with a 250 g load, a pH meter, and a viscometer with a beaker for viscosity testing.

Extraction

A total of 200 grams each of red betel leaf powder and tapak liman leaf powder were macerated separately in a closed glass container at room temperature using 2,000 milliliters of 70% ethanol (1:10 w/v). The initial maceration was carried out for 24 hours, followed by two re-macerations with fresh solvent, each for the same duration. The combined filtrate from these three macerations was filtered and evaporated using a rotary evaporator to obtain a concentrated extract.

Qualitative Analysis of Flavonoid Content

The presence of positive flavonoid results was indicated by the formation of a red, yellow, or orange color (Umar & Pratama, 2025).

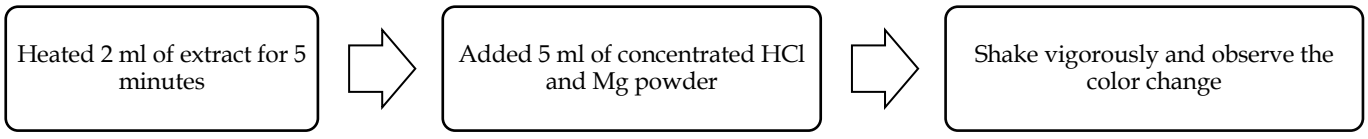


Figure 1. Qualitative analysis procedure for flavonoid compounds

Thin Layer Chromatography (TLC) Analysis

A thin-layer chromatography (TLC) plate was placed in a chamber containing a saturated solution (Astuti et al., 2023). The solution consisted of n-hexane and ethyl acetate solvents in a 1:9 ratio, and quercetin was used as a standard (Bialangi et al., 2022). A total of 10 µL of sample solution and 5 µL of quercetin standard solution were dropped at a distance of about 1 cm from the bottom of the plate using a micropipette or glass capillary.

A total of 10 µL of sample solution and 5 µL of quercetin standard solution were dropped at a distance of about 1 cm from the bottom of the plate using a micropipette or glass capillary. Next, the plate was placed in a chamber containing a saturated mobile phase (n-hexane and ethyl acetate). The plate was left until the eluent rose to almost three-quarters of the plate length

before being removed. The plate was then left to dry through an airdrying process. After that, the plate was sprayed with a detection reagent prepared as a 5% $AlCl_3$ solution. Observations were made under UV light with wavelengths of 254 and 366 nanometers (nm). The presence of spots in the same position and color as quercetin indicated the presence of quercetin or similar flavonoid compounds in the extract.

Nano Emulsion

The preparation of nano emulsion begins by mixing tween 80, PEG 400, and olive oil, followed by the addition of a combination of extracts according to the formula (F1, F2, and F3) while homogenizing with a magnetic stirrer at a temperature of 50°C for 15 minutes. After 15 minutes, distilled water is added little by little at a constant stirring speed. The homogeneous formulation is then put into a sonicator to produce and stabilize the nanoemulsion by breaking the oil droplets into nano sizes. The sonicator is set at a temperature of 35°C for 60 minutes.

Table 1. Nano emulsion formulation

Material	Function	Formulation		
		F1	F2	F3
Red betel leaf extract	Active ingredients	15%	10%	5%
Tapak liman leaf extract	Active ingredients	5%	10%	15%
Olive oil	Oil phase	8%	8%	8%
Tween 80	Surfactant	17%	17%	17%
PEG 400	Co-surfactant	5%	5%	5%
Aquadest	Solvent	Add 50 ml	Add 50 ml	Add 50 ml

Particle Size Test

Particle size testing using a Particle Size Analyzer tool with the working principle of this tool is Dynamic Light Scattering (DLS) (Windy et al., 2022). The tool used is the Malvern brand with model ZEN169 serial number MAL1186431.

Transdermal Patch

Before being formulated into a transdermal patch, the active ingredient is first made into a nanogel. This step aims to improve the stability and absorption of the active ingredient into the skin (Daryati et al., 2022).

Table 2. Nanogel formulation

Material	Function	Formulation		
		F1	F2	F3
Carbopol	Gelling agent	1%	1%	1%
PG	Humectant	5%	5%	5%
TEA	pH Stabilizer	2%	5%	5%
Nipagin	Preservative	0.1%	0.1%	0.1%
Aquadest	Solvent	Add 50 ml	Add 50 ml	Add 50 ml

The resulting nanoemulsion is then formulated into a nanogel. Nanogel production begins with the preparation of a gel base using aquadest and carbopol at a temperature of 50°C. After the gel base is formed, Propylene Glycol (PG) and nipagin are mixed into it while being homogenized with a magnetic stirrer. Then, TEA is gradually added to the gel base while continuing to be homogenized at a constant speed. Then, each nanoemulsion formula (F1, F2, and F3) is added to the gel base and homogenized again. The formed nanogel was carefully poured into flat glass molds and left to dry in an oven at 50°C and then placed in a desiccator for 24 hours (Kurnia & Dwi, 2021). The resulting patches were manually cut with sterile scissors to obtain a standard size and attached to prepared adhesive plaster (Purwandari et al., 2020).

Transdermal Pacth Characteristics Test

Organoleptic Test

Organoleptic observations include color, odor, and shape.

pH Test

The patch was placed in a porcelain dish containing 5 mL of distilled water (pH 6.5) and allowed to swell for two hours at room temperature. The pH was determined by placing pH paper on the surface of the patch.

Patch Thickness Testing

The thickness of three individual patches was measured for each formula to determine patch thickness. These measurements were taken using a vernier caliper at three different points (Kurnia & Dwi, 2021).

Weight Uniformity Test

The weights of the patches were measured using an analytical balance. Three patches were weighed individually, and the average weight was calculated (Kurnia & Dwi, 2021).

Elongation Percentage Test

The elongation percentage of a patch is tested by clamping it between upper and lower material clamps while applying a load or force. The elongation percentage is then calculated directly from the reading (Adiaswati et al., 2020).

Folding Resistance Test

Folding resistance is tested by repeatedly folding the patch in the same position. The number of folds is considered the fold resistance value. A patch with increased fold resistance indicates good film consistency and is less likely to break or tear during storage (Kurnia & Dwi, 2021).

In Vivo Testing

Mice were modeled as having diabetes mellitus by fasting for 8-12 hours. Their body weight and fasting blood glucose levels were measured prior to the administration of 120 mg/kg of body weight of alloxan intraperitoneally (Tamahiwu et al., 2023). The mice were then induced with 1% carrageenan via subcutaneous injection and incision-style wounds. *Staphylococcus aureus* was applied to accelerate gangrene formation. Transdermal patches consisting of red betel leaf and tapak liman (F1, F2, and F3), an antiseptic plaster (control +), and 0.9% NaCl (control -) were applied to the wounds. The patches were replaced daily, and the wounds were observed for seven to fourteen days based on drying time and narrowing of the wound diameter (Hendriati et al., 2022).

Result and Discussion

This study used plants that had passed identification tests at the Biology Laboratory of the Faculty of Mathematics and Natural Sciences, Universitas Negeri Semarang. The purpose of these tests was to verify the authenticity of the plants and prevent errors during material collection, as well as to prevent the mixing of plants with other plants (Klau & Hesturini, 2021). This study has also obtained ethical clearance from the Komisi Etik Penelitian Kesehatan (KEPK) of the Faculty of Medicine, Universitas Negeri Semarang, as evidence of ethical feasibility in research using test animals.

After the plants pass the determination test, they are then processed into simple medicines. These simple medicines are natural ingredients used as herbal or traditional medicines that have not undergone any processing (Lutfiah, 2022). The dried and ground plants then undergo an extraction process. Extraction involves separating soluble active compounds from plants using an organic solvent in the form of 70% ethanol (Triyanti et al., 2025). The reason for choosing 70% ethanol as a solvent is because ethanol can extract more active compounds than other types of organic solvents. The extraction method chosen was maceration. The maceration method was chosen because it is simple, easy, and does not involve heating, thereby minimizing the possibility of damage to the chemical compounds to be tested (Hasanah & Novian, 2020).

Extract Yield

Table 3. Percentage of extract yield

Extract Name	Weight (gram)	Yield (%)
Red betel leaf	35.20	17.60
Tapak liman leaf	19.80	9.90

The results of 200 grams of red betel leaf and tapak liman leaf simplicia that had been extracted using 70% ethanol solvent yielded 17.6 and 9.9% respectively. These results are in accordance with the Indonesian Herbal Pharmacopoeia standards, which stipulate that the percentage of ethanol extract yield for red betel leaf must not be less than 17.0%, while for tapak liman leaf it must not be less than 5.5% (Courtney, 2017). Based on this, the extract yield obtained in this study has met the standard quality requirements for herbal extracts.

Qualitative Analysis of Flavonoid Content

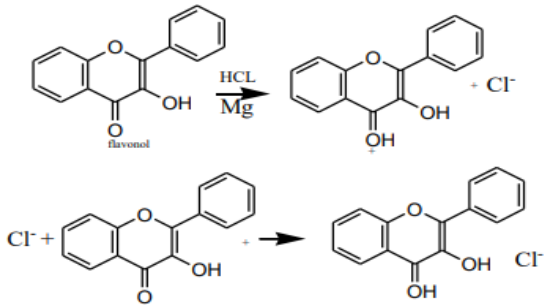


Figure 2. Flavonoid reaction equation (Sitepu et al., 2020)

Based on the results of qualitative tests of flavonoid content, both red betel leaf extract and tapak liman leaf extract showed the presence of flavonoids as indicated by a change in color to brick red and orange. The formation of color changes, red, orange to purplish red indicates the presence of flavonoids, if an orange color change occurs it indicates the presence of flavones, chalcones, and aurones. Flavonoids due to a yellow color change caused by a reduction reaction by Mg^{2+} carried out in an acidic environment with the addition of concentrated HCl, so that reduction with Mg and HCl causes a reddish yellow, orange or even purplish red color (Rizal & Salman, 2022).

Thin Layer Chromatography (TLC) Analysis

Table 4. Results of Rf values on 254 nm and 366 nm UV lamps

Sample	Code	Rf value	Color	
			UV 254 nm	UV 366 nm
Red betel leaf extract	Rf 1	0.70	Chocolate	Fluorescent Magenta
Quercetin	Rf 2	0.65	Chocolate	Glowing Green
Red betel leaf extract	Rf 3	0.70	-	Fluorescent Magenta

Thin Layer Chromatography (TLC) analysis was conducted to obtain a preliminary profile of the flavonoid content in red betel leaf extract. Based on Table 4, the extract showed an Rf value of 0.70, while the quercetin reference exhibited an Rf value of 0.65 under the same solvent conditions (La et al., 2021). The close Rf values indicate that the compounds in the extract may possess similar polarity and chromatographic behavior to quercetin. The Rf value indicating the presence of flavonoids is in the range of 0.2-0.75. The observation of brown spots at 254 nm and fluorescent magenta under 366 nm UV light also supports the possible presence of flavonoid-like compounds (Deviani et al., 2024). These results provide an early indication of flavonoid components in the extract, which can be further characterized using more specific analytical methods such as HPLC or mass spectrometry to confirm compound identity.

Particle Size Test of Preparations

Nanogel preparations consist of nano emulsions and gels, where nano emulsions are one type of preparation that can increase drug permeability on the membrane surface (Purwandari et al., 2020). Nanoparticle technology itself has been widely developed in drug delivery systems, with particle sizes ranging from 10–1000 nm (Windy et al., 2022).

Table 5. Particle Size Analyzer (PSA) test results

Sample Name	Particle Size (nm)	Result
Formula 1	74.46	
Formula 2	108.20	
Formula 3	118.7	

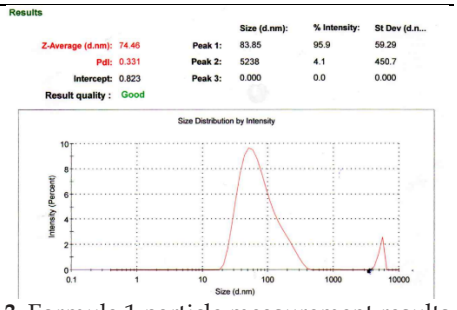


Figure 3. Formula 1 particle measurement results

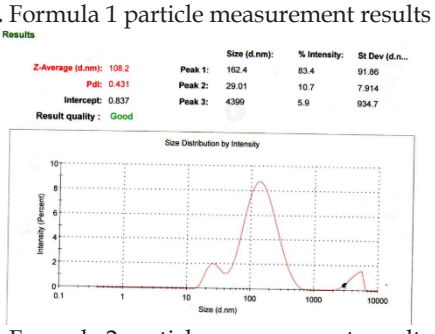


Figure 4. Formula 2 particle measurement results

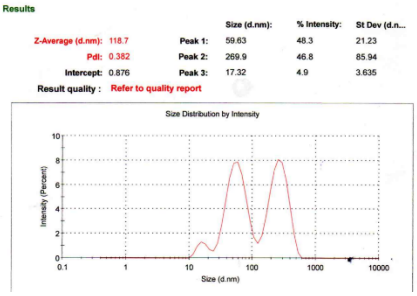


Figure 5. Formula 3 particle measurement results

Nanoparticles are generally defined as particles with diameters ranging from 1 to 1000 nanometers (nm). Particles smaller than 200 nm are considered suitable for nanomedicine applications because they can improve drug transport and transdermal absorption (Zielińska et al., 2020). As shown in Table 3, the particle sizes of the three formulations—74.46, 108.2, and 118.7 nm—fall within the nanoparticle range, indicating that the nanogel system was successfully formed. The relatively small particle size of these formulations shows good potential for even drug distribution and effective penetration through the skin barrier.

Transdermal Patch Characteristics Test

Test Organoleptic Test

The organoleptic test was conducted visually. The results showed that all three patch formulas had an elastic texture, indicating good flexibility. All formulas were deep green and had a distinctive dried leaf odor.

pH Test

Table 6. Transdermal patch pH test results

Sample Name	Result	Average
Formulation 1 replication 1	6	
Formulation 1 replication 2	6	6.33
Formulation 1 replication 3	7	
Formulation 2 replication 1	6	
Formulation 2 replication 2	6	6
Formulation 2 replication 3	6	
Formulation 3 replication 1	6	
Formulation 3 replication 2	7	6.33
Formulation 3 replication 3	6	

pH measurement of a preparation is carried out to ensure its safety during use (Sarumpaet et al., 2025). Tests of the three formulas yielded an average pH result of 6. The pH test requirement for transdermal patches is a pH range that is safe for the skin, namely 4.5-6.0 (Mallaka et al., 2024).

Patch Thickness Test

The thickness test on transdermal patches aims to determine the uniformity of the thickness of the transdermal patches produced (Makkayu et al., 2025).

The average results of each patch thickness test in each formula (F1, F2, and F3) were 0.113 ± 0.023 mm, 0.110 ± 0.01 mm, and 0.106 ± 0.011 mm, respectively. The requirement for patch thickness is that it must not exceed 1 mm. If the patch is too thick, it will be difficult for the active ingredient to diffuse through the polymer matrix and be released effectively (Supriadi & Sherlyke, 2023). The results indicate that all formulas meet the standard for transdermal patch thickness, showing uniformity and ease of application on the skin surface. The relatively small and homogeneous thickness values suggest good dispersion of the polymer and extract mixture during the casting process. This uniformity is important to ensure consistent drug release rates and optimal adhesion when applied to the skin.

Table 7. Patch thickness test results

Sample Name	Result (mm)	Average	Stdv
Formula 1 replication 1	0.1		
Formula 1 replication 2	0.14	0.113	± 0.023
Formula 1 replication 3	0.1		
Formula 2 replication 1	0.12		
Formula 2 replication 2	0.11	0.110	± 0.01
Formula 2 replication 3	0.1		
Formula 3 replication 1	0.1		
Formula 3 replication 2	0.12	0.106	± 0.011
Formula 3 replication 3	0.1		

Weight Uniformity Test

The weight uniformity test aims to ensure the consistency of patch weight in each formula (Makanoneng et al., 2025).

The average results of each patch weight uniformity test in each formula (F1, F2, and F3) were 341.2 ± 7.448 mg, 400.466 ± 10.050 mg, and 420.667 ± 18.100 mg, respectively. These results indicate that the three patch formulas have relatively uniform weights, indicating that the printing and weighing processes have been carried out consistently.

Table 8. Weight uniformity test results

Sample Name	Result (mg)	Average	Stdv
Formula 1 replication 1	332.8		
Formula 1 replication 2	347.0	341.20	± 7.45
Formula 1 replication 3	343.8		
Formula 2 replication 1	389.7		
Formula 2 replication 2	402.1	400.46	± 10.05
Formula 2 replication 3	409.6		
Formula 3 replication 1	425.3		
Formula 3 replication 2	400.7	420.66	± 18.10
Formula 3 replication 3	436.0		

Percentage Elongation Test

Table 9. Percentage elongation test results

Sample Name	Result (%)	Average (%)
Formulation 1 replication 1	17.5	
Formulation 1 replication 2	21.875	19.375
Formulation 1 replication 3	18.75	
Formulation 2 replication 1	26.25	
Formulation 2 replication 2	25.875	25.75
Formulation 2 replication 3	25.125	
Formulation 3 replication 1	19.625	
Formulation 3 replication 2	22.125	21.875
Formulation 3 replication 3	23.875	

The average results of each patch elongation percentage test in each formula (F1, F2, and F3) were 19.365, 25.75, and 21.875%, respectively. Based on the results of these tests, it was found that F2 had the highest elongation capacity, which indicates better elasticity compared to F1 and F3.

Folding Resistance Test

Folding resistance testing was conducted by repeatedly folding the patch in the same position. Increased folding resistance of a patch indicates that the patch has good film consistency, so that it does not easily break or tear during storage (Magfirah & Utami, 2022).

Table 10. Folding resistance test results

Sample Name	Result (x fold)	Average	Stdv
Formulation 1 replication 1	197		
Formulation 1 replication 2	201	201	± 4
Formulation 1 replication 3	205		
Formulation 2 replication 1	210		
Formulation 2 replication 2	207	207.33	± 2.52
Formulation 2 replication 3	205		
Formulation 3 replication 1	208		
Formulation 3 replication 2	211	204	± 3.61
Formulation 3 replication 3	203		

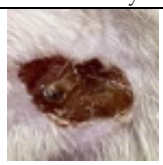
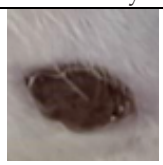
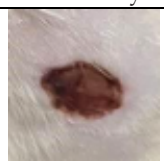
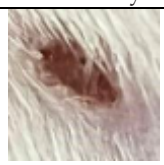
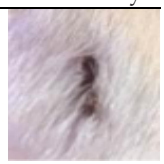
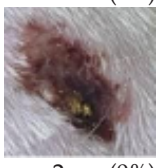
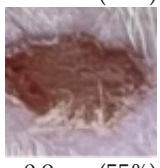
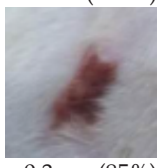
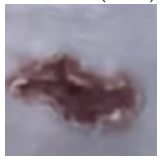
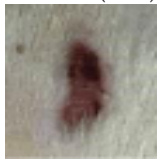
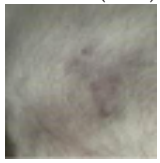
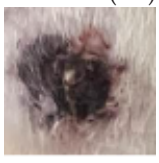
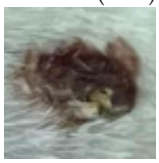
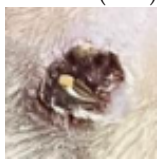
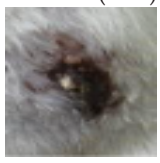
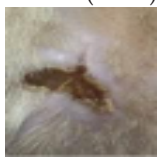
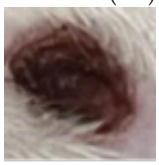
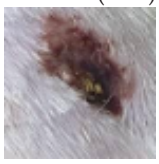
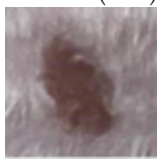
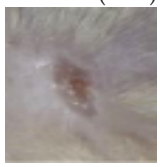
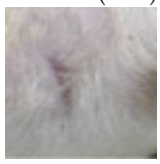
In Vivo Test

After administering the transdermal patch preparation for 7 days to the test animals, the results are as shown in Table 11.

Based on macroscopic observations, the application of transdermal patches containing red betel leaf and tapak liman extracts showed a significant acceleration in the healing process of gangrene wounds. The diameter of the wound, which was initially around 2 cm, showed a progressive reduction in all treatment groups compared to the control group. This study included two control groups: a negative control group (untreated wounds) and a positive control group (given standard medication). The negative control group showed slower healing progress, with necrotic tissue still visible on the fifth day. In contrast, the positive control group showed gradual wound improvement, confirming the reliability of the experimental design.

Among the three formulations, Formula 3 showed the highest wound closure rate, achieving complete healing on day 7 with a 100% reduction in wound diameter. Formulas 1 and 2 also showed significant healing acceleration effects, albeit at a slightly slower rate. The faster recovery in Formula 3 may be due to the synergistic effects of the active compounds in red betel leaf and tapak liman extracts, which contain flavonoids, tannins, and saponins known to have antibacterial and anti-inflammatory activities. Overall, these findings indicate that all formulations effectively promote the healing of gangrene wounds compared to the untreated group, with Formula 3 providing the most optimal results.

Table 11. Results of observation and measurement of the gangrene wound healing process

	Day 0	Day 1	Day 3	Day 5	Day 7
Formula 1					
	2 cm (0%)	1.6 cm (20%)	1.2 cm (40%)	0.7 cm (65%)	0.2 cm (100%)
Formula 2					
	2 cm (0%)	1.7 cm (15%)	0.9 cm (55%)	0.6 cm (70%)	0,3 cm (85%)
Formula 3					
	2 cm (0%)	1.7 cm (15%)	1 cm (50%)	0.4 cm (80%)	0.0 cm (100%)
Negative					
	2 cm (0%)	1.7 cm (15%)	1.6 cm (20%)	1.3 cm (35%)	1.3 cm (35%)
Positive					
	2 cm (0%)	1.5 cm (25%)	1.13 cm (43.5%)	0.3 cm (85%)	0.1 cm (95%)

Conclusion

This study successfully produced a transdermal patch-based nanogel preparation containing a combination of red betel leaf (*Piper crocatum*) and tapak liman leaf (*Elephantopus scaber L.*) extracts. Formula 3, with a 3:1 ratio of red betel leaf extract to tapak liman leaf (*Elephantopus scaber L.*) extracts, exhibited physical characteristics suitable for topical preparations, with a pH of 6.7, an average thickness of 0.106 ± 0.011 mm, and a particle size of 118.7 nm. All of these parameters were within the acceptable range for stability and skin compatibility. In vivo test results showed that Formula 3 exhibited a 100% wound closure rate on day 7, while the negative control group did not show complete healing. Thus, the results of this study indicate that nanogel preparations based on a combination of red betel leaf extract and tapak liman have the potential to be further developed as an alternative topical therapy for diabetic gangrene wounds.

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Author Contributions
Conceptualization, H.A.M. and N.A.S.G.P.; methodology, H.A.M., N.A.S.G.P., and F.P.W.M.; formal analysis, H.A.M. and A.R.A.I.; investigation, H.A.M., N.A.S.G.P., F.P.W.M., and A.R.A.I.; resources, F.P.W.M.; data curation, writing—original draft preparation, visualization, project administration, H.A.M.; writing—review and editing, supervision, R.S.D.; funding acquisition, none. All authors have read and approved the final version of the manuscript.

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Conflicts of Interest
The authors declare no conflict of interest.

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