

Formulation and characterization of nanoemulgel of ethanol extract of bay leaves (*Syzygium polyanthum*) as an anti-burn agent using the hot plate method using white wistar rats

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ARTICLE INFO

Article history:

Received Mar 26, 2025
Revised Mar 28, 2025
Accepted Apr 9, 2025

Keywords:

Bay Leaf
Burn Activity Test
Flavonoids
Nanoemulsion
Wounds

ABSTRACT

Introduction: Wounds are tissue damage that can cause functional disorders and risk of infection. Effective wound management is essential to accelerate tissue regeneration and prevent complications. Bay leaf extract (*Syzygium polyanthum*) contains bioactive compounds such as flavonoids, tannins, and saponins that have anti-inflammatory, antibacterial, and wound healing activities. However, the limited bioavailability and skin penetration of these active compounds are challenges in topical therapy. **Objective:** This study aims to develop and evaluate a topical drug delivery system based on bay leaf extract nanoemulsion as an alternative therapy to accelerate wound healing. **Method:** Extraction was carried out using ethanol solvent, then formulated into a nanoemulsion with oil, surfactant, and co-surfactant components. Formulation characterization was carried out by measuring particle size, polydispersity index, zeta potential, and physical stability tests. Evaluation of effectiveness was carried out using a wound model in Wistar rats with the hot plate induction method. Wound healing observations were carried out clinically and histologically for a period of 14 days. **Results:** The formulation results showed that the nanoemulsion had a particle size of <200 nm, PDI <0.5, and zeta potential of ± 25 mV, indicating good physical stability. Burn activity tests showed that topical administration of bay leaf extract nanoemulsion accelerated wound contraction, increased epithelialization, and improved tissue structure compared to the control group. **Conclusion:** Bay leaf extract can be formulated in a nanoemulsion-based nanoparticle delivery system that shows stable physical characteristics and is effective in accelerating wound healing.

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INTRODUCTION

Wounds are biological tissue damage that disrupts the structure and function of normal skin. The wound healing process is a complex biological mechanism consisting of several phases, namely hemostasis, inflammation, proliferation, and remodeling (Mamun et al., 2024). An imbalance in any of these phases can slow healing and increase the risk of infection, especially in open wounds or burns. Effective wound care aims not only to accelerate the healing process, but also to prevent local and systemic complications such as bacterial infection and further tissue damage (Kolimi et al., 2022).

Conventionally, wound healing is done by administering antiseptics, topical antibiotics or healing ointments such as silver sulfadiazine. However, long-term use of these agents often causes side effects such as skin irritation, hypersensitivity and microbial resistance (Mohan et al., 2019). Therefore, the natural-based treatment approach is starting to be considered as a safer and more environmentally friendly alternative. Various medicinal plants have been studied for their bioactive compound content that supports the wound healing process, one of which is bay leaves (*Syzygium polyanthum*) which are widely used in traditional medicine in Indonesia (Andini et al., 2024).

Bay leaves are known to contain active compounds such as flavonoids, tannins, saponins, alkaloids, and triterpenoids. Flavonoids act as antioxidants and anti-inflammatories that can accelerate epithelialization and the formation of new tissue, while tannins function as astringents that help control bleeding and accelerate the formation of granulation tissue (Kusumastuti & Jaya, 2022). However, the limitations of bioactive compounds in natural ingredient extracts are low bioavailability, limited solubility, and easy degradation, so that the effectiveness of topical therapy is less than optimal (Awlqadr et al., 2025).

To overcome these limitations, a more innovative drug delivery system is needed. One effective approach is the use of a nanoemulsion system, which is an oil-in-water dispersion system stabilized by surfactants with particle sizes on the nanometer scale. Nanoemulsions have the advantage of increasing the permeation of active substances through the skin, extending the contact time of the drug in the wound area, and increasing the stability of bioactive compounds against environmental degradation (Tayeb et al., 2021). With these characteristics, the formulation of bay leaf extract nanoemulsion as a topical preparation is expected to significantly increase the effectiveness of wound healing compared to conventional formulations.

This study aims to develop and evaluate the formulation of bay leaf extract nanoemulsion as an anti-wound agent, focusing on physical characterization (particle size, polydispersity index, zeta potential) and wound healing effectiveness test. It is expected that this formulation can be a safe, effective, and local natural material-based alternative solution for wound care.

RESEARCH METHOD

Tool

The equipment used in this study included a digital scale (Mettler Toledo®), ultraturax homogenizer (IKA T25 digital), analytical balance (Mettler Toledo), magnetic stirrer (IKA® C-mag HS 10), hot plate (Oxone®), particle size measuring instrument (PSA) (Malvern Instruments Ltd), pH meter (Mettler Toledo®), Transmission Electron Microscope (TEM, JEOL JEM 1400, Japan), rotary evaporator, and commonly used glassware and stirring rods (Pyrex®).

Material

The materials used include bay leaves (*Syzygium polyanthum*) (Manoko Lembang Experimental Garden), sunflower oil as the oil phase (Jan Dekker International, Netherlands), distilled water as the water phase, surfactants in the form of hydrogenated castor oil (Cremophor RH40) (EVONIC Indonesia) and Plantacare 1200 (BASF), and co-surfactant Polyethylene Glycol 400 (PEG 400) (Merck).

Detailed Procedure

Bay leaves (*Syzygium polyanthum*) were collected and checked for suitability through a determination process to ensure that the species are appropriate. In addition, the additional materials used were evaluated for suitability based on references from the Handbook of Pharmaceutical Excipients (HOPE) (Primary, 2024).

Making Bay Leaf Extract

A total of 500 grams of bay leaf simplicia powder was macerated with 5000 mL of 96% ethanol for 3 days (3×24 hours) with periodic stirring. After the maceration process, the solution was filtered using batis cloth and filter paper. Furthermore, the solvent was evaporated using a rotary evaporator at a temperature of 50°C until a thick bay leaf extract was obtained (Christian et al., 2022).

Phytochemical Screening

Phytochemical screening was performed to detect several compounds in bay leaf extract. The extract was stored in a glass bottle in the refrigerator during the experiment. To test the flavonoid content, 2 ml of the extract was mixed with 1 ml of 2N sodium hydroxide solution, and the appearance of a yellow color indicated the presence of flavonoids. The alkaloid test was performed by adding Mayer, Dragendorf, and Wagner reagents to the sample; a positive reaction was indicated by the formation of precipitates in two or more reagents. For quinones, 1 gram of sample was added to 100 ml of hot water, boiled, filtered, and a drop of 1N NaOH was added; a color change to red indicated a positive result. Saponins were tested by mixing 0.5 g of sample with 10 ml of distilled water, and if a stable foam formed for 7 minutes after the addition of 1N HCl, then positive saponins were detected. Tannins were tested by dissolving 0.5 g of sample in 10 ml of distilled water and adding 2-3 drops of FeCl₃; a color change to green or blackish blue indicated the presence of tannins. Finally, terpenoids or steroids are tested by dissolving 0.5 g of sample in distilled water, adding chloroform and acetic acid, then dripping concentrated H₂SO₄; a color change to red or purple indicates a positive result (Praptiwi et al., 2020).

Preparation of Bay Leaf Extract Nanoemulsion

Nanoemulsion was made by mixing Mixture A, which consists of bay leaf extract (*Syzygium polyanthum*) and oil phase (sunflower oil), with Mixture B, which consists of surfactants (Cremophor RH 40 and Plantacare® 1200) and co-surfactants (PEG400). After Mixture B was added to Mixture A, distilled water was added, and the mixture was stirred using a magnetic stirrer at a certain optimal temperature, speed, and duration to produce a stable and transparent nanoemulsion. The optimal conditions for this process are at a temperature of 50°C, a stirring speed of 750 rpm, and a mixing time of 30 minutes (Fitri et al., 2019; Indratmoko et al., 2021).

Characterization of Bay Leaf Extract Nanoemulsion

Characterization of nanophytosomes includes testing of particle size, polydispersity index. Particle size and polydispersity index were measured using Particle Size Analyzer (PSA) Malvern ZSP Zetasizer (UK) by dispersing the sample in distilled water to a volume of 10 ml, then put into a disposable cuvette for analysis. Meanwhile, the zeta potential was also measured using PSA after the sample was diluted with distilled water to the same volume, and a dip cell electrode was used to cover the cuvette before the measurement was carried out. This method allows for accurate determination of particle size and zeta potential values (Fitri et al., 2019; Jafar et al., 2025).

Making Bay Leaf Nanoemulgel

The making of nanoemulgel is done with the first steps, namely by weighing the ingredients, then carbomer is dispersed in pure hot water as much as 20 times its weight, then added to the base mixture and stirred until homogeneous. Propylene glycol, glycerin and pure water are added and homogenized with a stirrer at a speed of 500 rpm for 15 minutes. Then

Triethanolamine is added little by little while homogenized with a stirrer until a gel base is formed (Annaura et al., 2022).

Burn Activity Test

Preparation of test animals in this study involved 2-3 month old male Wistar rats weighing 250-300 grams which were acclimatized for one week to ensure adaptation. The health of the rats was observed by observing their physical condition, and healthy rats did not experience weight loss exceeding 10%. The rats were divided into five treatment groups, where the first group was not treated, while the other groups received various treatments with bay leaf extract (*Syzygium polyanthum*) and positive and negative controls. Testing of burn healing activity was carried out by making burns using a hot iron plate and treating the wounds for 14 days, measured using a caliper (Ben Attia et al., 2024; Hidayah et al., 2022).

RESULTS AND DISCUSSIONS

Bay leaves (*Syzygium polyanthum*) used in this study have been collected and their identification has been carried out by the Biology Laboratory of FMIPA Universitas Padjadjaran, ensuring that the species used are correct and authentic. All additional materials used in the formulation process have also been evaluated for their suitability based on references from the Handbook of Pharmaceutical Excipients (HOPE), which shows that all excipients used are safe and suitable for nanoemulsion formulation (Primary, 2024).

The maceration process of bay leaf simplicia powder produces a thick greenish brown extract with a distinctive consistency, indicating that the extract is obtained optimally. Evaporation of the solvent using a rotary evaporator at a temperature of 50°C is efficient, producing a concentrated extract that is ready to be used in the formulation process. The yield obtained shows good extraction results and is representative of the active compound content in bay leaves (Christian et al., 2022).

The results of the phytochemical screening test on bay leaf extract showed the presence of various secondary metabolite compounds. The alkaloid test using Mayer, Dragendorff, and Wagner reagents gave positive results, marked by the formation of white, brick red, and brown deposits. Flavonoid compounds were detected through color changes in the amyl alcohol layer. The tannin test also showed positive results, with a color change to greenish black in the FeCl₃ reagent, 31% and white precipitate in 1% gelatin reagent. The saponin test produces stable foam, indicating the presence of saponin compounds. The triterpenoid test shows a bluish green color, indicating the presence of triterpenoid compounds. However, the test for quinone compounds showed negative results because there was no color change to red. Overall, bay leaf extract was shown to contain alkaloids, flavonoids, tannins, saponins, and triterpenoids, which have the potential to contribute to the pharmacological activity of the extract (Praptiwi et al., 2020).

Table 1. Phytochemical screening of bay leaf extract

Compound Groups	Literature	Test Results	Information
Alkaloid	Alkaloids react with Mayer, Dragendorff, and Wagner reagents.	Produces white (Mayer), brick red (Dragendorff), and brown (Wagner) precipitates.	+
Flavonoid	Flavonoids show color changes in the amyl alcohol layer.	Shows discoloration of the amyl alcohol layer	+
Quinone	Quinones produce a red color when they react with certain reagents.	It does not show red color, which means no reaction occurred.	-
Tannin	Tannin gives a greenish black color when tested with FeCl ₃ and produces a white precipitate when	Shows a greenish black color when tested with FeCl ₃ and produces a white precipitate when mixed with gelatin.	+

Compound Groups	Literature	Test Results	Information
Saponins	mixed with gelatin. Saponins display a stable foam when shaken.	Shows stable foam.	+
Steroids/Triterpenoids	Triterpenoids produce a clearly visible bluish green color.	Shows a bluish green color.	+

Bay leaf extract nanoemulsion was successfully obtained by mixing bay leaf extract and sunflower oil, followed by the addition of surfactants and co-surfactants. The mixture was stirred at a temperature of 50°C, a speed of 750 rpm for 30 minutes, producing a stable and transparent nanoemulsion (Indratmoko et al., 2021). The bay leaf extract nanoemulsion that was formed was then characterized, including particle size, polydispersity index, zeta potential (Jafar et al., 2022).

Table 2. Formulation and characterization of h-1 bay leaf extract nanoemulsion

Code	H-1 Formulation					Z-Ave		ZP
	Bay Leaf Extract	Sunflower Oil	Cremophor	Plantacare	PEG 400	nm	PdI	mV
F1	0.075	3	1,911	-	3	1321.0 ± 535.5	333 ± 576.8	-33.63 ± 5.25
F2	0.075	1.65	8.45	-	3	190.20 ± 1.84	0.25 ± 0.01	-11.33 ± 1.05
F3	0.075	0.93	11.72	-	3	51.49 ± 0.69	0.31 ± 0.03	-11.10 ± 1.56
F4	0.075	0.97	11.72	-	3	20.78 ± 3.33	0.26 ± 0.04	-14.13 ± 1.12
F5	0.075	2.32	7.18	-	3	42.97 ± 25.72	0.22 ± 0.14	-11.93 ± 1.12
F6	0.075	3	-	11.05	3	113.67 ± 2.06	0.29 ± 0.04	-7.71 ± 1.36
F7	0.075	1.65	-	9.52	3	245.63 ± 2.65	0.17 ± 0.02	-29.83 ± 0.83
F8	0.075	0.93	-	10.22	3	172.27 ± 3.19	0.24 ± 0.03	-32.60 ± 0.66
F9	0.075	0.97	-	12.26	3	51.06 ± 11.97	0.42 ± 0.05	-35.77 ± 4.80
F10	0.075	2.32	-	10.78	3	168.83 ± 7.39	0.96 ± 576.8	-32.40 ± 3.61

Table 3. Formulation and characterization of h-30 leaf extract nanoemulsion

Code	H-30 Formulation					Z-Ave		ZP
	Bay Leaf Extract	Sunflower Oil	Cremophor	Plantacare	PEG 400	nm	PdI	mV
F1	0.075	3	1,911	-	3	376.45 ± 60.56	0.99 ± 0.01	-26.65 ± 1.15
F2	0.075	1.65	8.45	-	3	239.95 ± 2.05	0.36 ± 0.03	-12.20 ± 1.22
F3	0.075	0.93	11.72	-	3	70.59 ± 2.35	0.40 ± 0.05	-14.60 ± 0.64
F4	0.075	0.97	11.72	-	3	22.90 ± 4.08	0.21 ± 0.08	-3.52 ± 0.31
F5	0.075	2.32	7.18	-	3	28.28 ± 1.57	0.47 ± 0.05	-6.05 ± 0.64
F6	0.075	3	-	11.05	3	137.80 ± 1.01	0.34 ± 0.02	-17.30 ± 1.45
F7	0.075	1.65	-	9.52	3	357.30 ± 8.25	0.26 ± 0.02	-17.15 ± 2.21
F8	0.075	0.93	-	10.22	3	303.60 ± 5.86	0.58 ± 0.03	-32.60 ± 1.15
F9	0.075	0.97	-	12.26	3	84.99 ± 32.31	0.32 ± 0.05	-41.15 ± 3.99
F10	0.075	2.32	-	10.78	3	346.70 ± 246.8	0.80 ± 0.23	-37.55 ± 0.91

Particle size characterization showed that the smallest particle size on day 1 (D-1) was obtained in formula F4 with a size of 20.78 ± 3.33 nm, while on day 30 (D-30) the smallest particle size was also shown by formula F4, which was 22.90 ± 4.08 nm. Overall, all formulas showed particle sizes below 1000 nm, which means they are still within the ideal nanoparticle size range and according to standards for nanoemulsion systems. This indicates that room temperature during storage does not cause significant changes in particle size, maintaining the physical stability of the system. Small and stable particle size is important because it affects the bioavailability and efficiency of absorption of active ingredients (Gawin-Mikolajewicz et al., 2021; Jafar et al., 2020).

The PdI value provides an overview of the homogeneity of particle size distribution in the nanoemulsion system. At H-1, the smallest PdI was obtained from formula F7 (0.17 ± 0.02), while at

H-30, the smallest PDI value was shown by formula F4 (0.21 ± 0.08). Generally, a PDI value <0.3 indicates a narrow particle size distribution and a homogeneous system. Although there are several formulas with slightly higher PDIs (up to 0.80), most formulas still show good size distribution characteristics, indicating that the system is still quite stable and does not experience significant particle coalescence during storage (Jafar et al., 2021; Wanjiru et al., 2022).

Zeta potential reflects the surface charge of the particles, which plays a role in determining the electrostatic stability of the system. At H-1, the highest ZP value was shown by formula F9 (-35.77 ± 4.80 mV), while at H-30, the highest value was found in formula F9 (-41.15 ± 3.99 mV). In general, ZP values above ± 25 mV indicate good electrostatic stability because the repulsive force between particles is strong enough to prevent aggregation. Almost all formulas are in this range, indicating that the nanoemulsion system has a high electrostatic stability potential, so it is not easy to experience sedimentation or flocculation during storage (Jafar et al., 2020; Sahin et al., 2022).

Bay leaf extract nanoemulgel was successfully made by dispersing carbomer in hot water, then mixing it with propylene glycol, glycerin, and pure water (Annaura et al., 2022). The formulated nanoemulsion and nanoemulgel were then continued with testing on the healing process of burns in male white rats of the Wistar strain. The results showed differences in the extent of burns between treatment groups on the 7th, 14th, and 21st days. (Ben Attia et al., 2024). Wound area measurements are performed to assess the effectiveness of each treatment in accelerating the wound healing process.

Table 4. Burn area of test animals

Treatment Group	Mouse	Burn Area (mm ²)		
		Observation Results for the 2nd Day		
		7	14	21
Group 1	1	716.13	707.85	660.66
	2	724.9	530.1	412.92
	3	596.65	542.43	750.23
Group 2	1	656.88	576.97	231.66
	2	848.25	522.56	486.76
	3	576.3	624.25	563.82
Group 3	1	588.3	559.52	453.25
	2	714.78	657.04	652.72
	3	582.65	480.6	403.9
Group 4	1	551.76	538.47	410.22
	2	596.4	560.86	792.86
	3	1169.74	799.12	878.24
Group 5	1	581.04	628.46	636.32
	2	665.28	749.7	716.28
	3	662.76	542.27	474.78

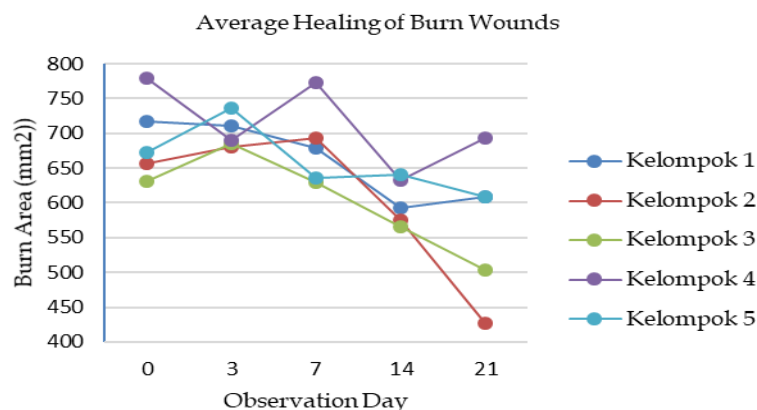


Figure 1. Average burn wound healing graph over 21 days

Group 1 (No Treatment/Negative Control) showed an inconsistent decrease in wound area. On the 7th day, the average wound area was still quite large, and on the 14th day there was even a significant increase in rat number 2 (from 724.90 mm² to 530.10 mm², then decreased to 412.92 mm² on the 21st day). Meanwhile, the other rats also showed an uneven decrease. Overall, this group reflects the slowest wound healing process compared to other groups, indicating that without treatment, the burn wound healing process is less effective and unstable (Bintarti & Widayawari, 2022).

Group 2 (Bioplacenton / Positive Control) showed a gradual and relatively consistent decrease in wound area across all mice. For example, in mouse number 1, there was a decrease from 656.88 mm² (day 7) to 576.97 mm² (day 14) and 231.66 mm² (day 21). Other mice also showed a similar trend. These results indicate that Bioplacenton as a positive control is able to accelerate the wound healing process significantly and stably, as expected from a clinically proven wound healing agent (Ling et al., 2022).

Group 3 (NE Gel Blank) showed quite varied wound healing. In rat number 1, there was a decrease from 588.30 mm² (day 7) to 559.52 mm² (day 21), but increased on day 14. Rat number 2 showed quite good healing from 714.78 mm² to 657.04 mm², while rat number 3 experienced a fairly consistent decrease. Overall, this blank gel showed a better healing effect than the negative control, but was still less than optimal because it did not contain active ingredients (Sghier et al., 2024).

Group 4 (NE Bay Leaf Extract) showed a fairly positive healing trend. Mice number 1 and 2 experienced a gradual decrease in each observation. However, in mouse number 3 there was a spike in wound area on day 14 (up to 1198.94 mm²), which was likely caused by individual factors or local inflammatory processes unrelated to the treatment. However, the average data showed that bay leaf extract nanoemulgel had the potential to significantly accelerate the wound healing process compared to the negative control and blank gel (Chhabra et al., 2023).

Group 5 (Nanoemulgel) also showed quite good results. Rat number 3 experienced a decrease in wound area from 662.76 mm² to 542.27 mm². Other rats also experienced a decrease, although fluctuations were still seen in some individuals. Although not as effective as the group with bay leaf extract, these results indicate that the nanoemulgel base itself already provides support for the wound healing process, and its potential can be further optimized by adding active ingredients (Sghier et al., 2024).

From all the observed data, the nanoemulgel group with bay leaf extract (Group 4) showed the most promising potential in accelerating burn wound healing, followed by the Bioplacenton group (Group 2). The difference between the nanoemulgel groups with and without extracts indicates that the combination of advanced formulations with herbal active ingredients is able to provide better therapeutic effects (Miastkowska et al., 2023). Interindividual variation remains a factor to consider in the interpretation of results, but the overall trend strengthens the potential use of nanoemulsion-based phytotherapy as an alternative topical treatment of burns (Preeti et al., 2023).

CONCLUSION

The bay leaf extract nanoemulsion formula showed good physicochemical characteristics, with a particle size of <1000 nm, a polydispersity index (PDI) of <0.5 reflecting a homogeneous particle distribution, and a zeta potential of ± 25 mV indicating the stability of the dispersion system. These parameters indicate that the nanoemulsion-based delivery system in gel form is able to increase the stability and penetration potential of active compounds from bay leaf extract and is easy to apply to the skin. The results of testing the activity of second-degree burns in white rats (*Rattus norvegicus*) showed that bay leaf extract nanoemulgel accelerated wound healing by significantly reducing the wound area compared to the negative control group. This activity is supported by active compounds such as quercetin and kaempferol which act as anti-inflammatory, antibacterial,

and antioxidants. Thus, bay leaf extract in the form of nanoemulgel preparations not only shows superior physicochemical characteristics, but also has the potential as an effective alternative topical agent in treating burns.

ACKNOWLEDGEMENTS

The authors would like to thank the Faculty of Pharmacy, Bhakti Kencana University, for assisting in the completion of this research.

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