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Tests of Burn Wound Healing with Nanogel Preparations from Ethanol Extract of Andaliman Fruit

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ABSTRACT

Andaliman (Zanthoxylum acanthopodium DC) is a plant known for its diverse bioactive compounds, including antimicrobial and anti-inflammatory properties. Nano-gel formulations were prepared using appropriate techniques, and their physicochemical properties, including particle size, pH, viscosity, and centrifugation stability, were evaluated. Additionally, organoleptic tests were conducted to assess the sensory characteristics of the nano-gels. Furthermore, an irritation test was performed to ensure the formulation's safety when applied to the skin. The percentage of wound closure was evaluated at various time points, including days 2, 4, 6, 8, 10, 12, and 14, comparing it to a commercially available wound healing product, Bioplacenton. Initial findings showed that the nano gel formulations exhibited favorable physicochemical properties, including appropriate particle size within the nano-scale range. The pH values were within an acceptable range, and the formulations demonstrated suitable viscosity and stability during centrifugation. Organoleptic tests indicated good sensory characteristics, and the irritation test showed the formulation's safety without significant skin irritation. The percentage of wound closure increased over time for all three concentrations (F1: 5%, F2: 10%, F3: 20%). In conclusion, nano gel formulations containing various concentrations of Andaliman extract exhibited good physicochemical properties, favorable sensory characteristics, and safe application on the skin. Moreover, they demonstrated promising wound healing effects, potentially comparable to commercial wound healing agents.

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1. INTRODUCTION

Nano gel is a nano-sized cross-linked polymer network capable of absorbing substantial amounts of water [1]. Nano gels have the characteristics of hydrogels and nanomaterials with diameters ranging from 1 - 1000 nm, which are applied in nanomedicine as carriers for treatments that can produce effects quickly [2]. Nano gels enhance absorption and sustained drug release [3]. The nano gels have high moisture content, biocompatibility, and desirable mechanical properties. They are made from synthetic or natural polymers and are ideally suited to optimize drug delivery and reduce toxicity [4]. The advantages of nano gel preparations are the small particle size, making the practice more stable. It can increase the absorption of active compounds through the skin, is not sticky, is aesthetically preferred, and has a cooling effect on the skin [5].

Wounds are damage to some body tissues caused by sharp or blunt trauma, changes in temperature, chemicals, explosions, electric shocks, or animal bites [6]. Types of injuries include burns that cause burns besides direct or indirect fire burns, as well as exposure to high temperatures from the sun, electricity, or chemicals. Burns due to fire or indirect results from fire, for example, scalded with hot water, often in household accidents [7]. Burns (combustion) is a tissue loss caused by contact with heat sources such as water, fire, chemicals, electricity, and radiation. Burns will result not only in skin damage [8].

Handling in healing burns includes preventing infection and giving the remnants of epithelial cells a chance to increase and cover the wound surface [9]. One way to treat wounds is to treat the damage using topical preparations. One of the preferred topical dosage forms is nano gel because it spreads easily on the skin without pressure, gives a cooling sensation, does not leave marks on the skin, and is easy to use [7].

Wound healing takes place in 3 main phases: the inflammatory phase, the proliferative phase, and the maturation phase. The inflammatory phase occurs immediately after injury and peaks on the third day. The proliferative phase occurs on the fourth to seventh day, marked by fibroblasts whose numbers continue to increase during this phase. Fibroblasts are the main factors that dominate wound healing, as well as the framework or basic structure for producing collagen. The regulation phase is the wound-healing phase that lasts for a long time (3-6 months or even years) [10].

Bioplacenton is a preparation commonly used as a treatment for burn patients. Bioplacenton is usually used for burns that still have healthy epithelial elements remaining. The high price of commercial drugs such as Bioplacenton can increase the cost of treating burns for patients who suffer from burns. Bioplacenton, as a burn therapy, can absorb less the exudate formed due to burns. Alternatives are needed to reduce the cost of treating burns so that they are cheaper and the materials are easy to obtain [10]. Almost all burn preparations on the market contain antibiotics that can cause patient resistance. Nano gel preparations containing ethanol extract from Andaliman fruit are expected to have nearly no side effects.

The community increasingly favors treatment using natural ingredients because it is cheap, easy to obtain, and has few side effects. Many plants around us have yet to be put to good use. This can happen due to limited information to the public; for this reason, it is necessary to develop research on traditional medicinal plants [11]. One medicinal plant with many benefits is the Andaliman plant; all parts of the Andaliman, from the root to the tip of the fruit, including the flowers and fruit, have a function. Andaliman fruit contains alkaloid compounds, karpas, carikaksantin, violaxanthin, papain, saponins, flavonoids, tannins, carposid, and saponins. Andaliman fruit has many benefits, including preventing infection in burns or open wounds based on research [12], based research, a gel preparation of 70% ethanol extract of Andaliman fruit affected healing burns in rabbit test animals.

Andaliman fruit contains more than 50 active ingredients, including karpain compounds which inhibit the growth of microorganisms such as fungi, worms, parasites, and bacteria. Staphylococcus aureus is a bacterial pathogen that often infects humans. Staphylococcus aureus is one of the most common pathogens, and it is a gram-positive commensal and can cause skin and soft tissue infections [13]. Extracts made from old Andaliman fruit had higher antioxidant activity and total flavonoids than those from young Andaliman fruit [13]. The complete flavonoid content of Andaliman fruit extract made with ethanol solvent was 70% higher than those made with water solvent.

The ethanol extract of Andaliman fruit contained higher total phenolics and flavonoids than the water extract. The complete phenolic content of the Andaliman section using the Folin-Ciocalteu method was expressed as the equivalent of gallic acid. The entire flavonoid content was determined by an assay based on aluminum chloride and said as quercetin. Researchers chose Andaliman fruit as a medicine for burns because one of the ingredients of this plant is saponins which are useful for stimulating collagen formation. This structural protein plays a role in the wound-healing process. At the same time, flavonoids and polyphenols have activity as antiseptics [14].

Based on the description above, researchers are interested in researching the formulation of nano gel preparations from the ethanol extract of Andaliman fruit and testing the activity of healing burns in rats by observing changes in burn diameter, burn wound healing time, and histopathology. This study aims to formulate nano gel preparations containing ethanol extract from Andaliman fruit and to evaluate the characteristics and stability of the nano gel trials during 12 weeks of storage at room temperature, low temperature, and high temperature.

2. METHOD

The materials used in this study were Andaliman fruit (Zanthoxylum acanthopodium DC), distilled water, Staphylococcus aureus (ATCC® 6538), ethanol, hematoxylin-eosin (HE), carbomer, ketamine HCl, lithium carbonate solution, xylol, methylparaben, Muller Hinton Agar (MHA), nutrient

agar, nutrient broth, propylene glycol, triethanolamine (TE).

Tools

Tools used in this study: Analytical balance, aluminum foil, filter paper, cotton, knife, maceration bottle, a set of vacuum rotary evaporators, pH meter, viscometer, oven, refrigerator, glass tools, watch glass, evaporator cup, funnel, parchment paper, glass jar, dropper, stir bar, mortar, stamper, Object glass, Cover glass, label or marker, stationery, camera, vacuum rotary evaporator, stopwatch, and water bath.

Method

This research is a pure laboratory experimental study with a research design using a post-test with a control group design [15]. Research variables are everything that will become the object of research observation [16]. The variables in this study consist of independent variables and dependent variables. The research method used was the preparation of experimental animals, namely Wistar rats (*Rattus norvegicus*), processing of samples of Andaliman fruit, preparation of ethanol extract of Andaliman fruit (*Zanthoxylum aanthopodium, DC.*), then screening phytochemicals and making nano gel preparations of ethanol extract of Andaliman fruit. Then the preparation test was carried out, namely the Organoleptic Test, Homogeneity Test, and Spreadability Test. After that, another stability test was carried out by storing it at low temperature, room temperature, and high temperature, then determining the pH of the preparation, measuring viscosity, measuring centrifugation, then testing the particle size using a particle size analyzer (PSA), cycling test and finally the Skin Irritation Test. After that, Nutrient Agar Media, Hinton Agar Media, and Slant Agar Media were made.

Then proceed with cultivating *Staphylococcus aureus* bacteria, namely, causing test bacterial culture stocks and inoculums and preparing for antibacterial testing. They then tested the antibacterial activity of the ethanol extract of the Andaliman fruit. Furthermore, preparing test animals and making wounds, testing burns healing activity followed by histopathological observations. Lastly, the inferential analysis includes the Duncan test with SPSS software.

3. RESULTS AND DISCUSSION

Phytochemical screening of the ethanol extract of Andaliman (Zanthoxylum acanthopodium) revealed the presence of various secondary metabolites. Qualitative analysis showed the presence of alkaloids, flavonoids, phenols, tannins, saponins, glycosides, and terpenoids in the extracts. Phytochemical analysis of each Andaliman fruit extract was carried out qualitatively using the appropriate reagent. The results of the phytochemical analysis can be seen in Table 1. The table shows that the results of the phytochemical analysis of Andaliman fruit from the ethanol extract have negative saponin intensity, while the others are positive.

Table 1. Phytochemical screening results

Secondary Metabolites	Result
Flavonoids	+
Alkaloids	+
Tannins	+
Saponins	-
Glycoside	+
Steroids/Triterpenoids	+

Table 2. The results of organoleptic observations and homogeneity

Formulas	Color	Form	Smell	Results
F1 (5%)	Brownish Green	Gel	Unique	Homogeneous
F2 (10%)	Brownish Green	Gel	Unique	Homogeneous
F3 (20%)	Brownish Green	Gel	Unique	Homogeneous

From Table 2. It can be seen organoleptically that the mixture of Andaliman ethanol extract nano gels with various extract concentrations shows a brownish-green color with different concentrations, where the higher the concentration, the darker the resulting color because the higher the concentration, the more parts are used. The form of each preparation shows that the practice has

the consistency of a gel preparation and has a distinctive Andaliman smell. Adding the Andaliman ethanol extract affected the resulting nano gels' color, shape, and smell.

From Table 2. It can be seen that the results of the homogeneity test show the level of dispersion and distribution of Andaliman extract in the nano gel matrix. The three nano gell formulations appeared homogeneous upon visual inspection, with no signs of phase separation or aggregation. These observations indicate that the Andaliman extract was successfully dispersed and distributed evenly throughout the nano gel formulation.

Table 3. Results of testing the spreadability of nano gel preparations

Formulas	Spread Power		
	0 Gram	100 Gram	125 Gram
F1 (5%)	3.5	4.0	4.4
F2 (10%)	4.0	4.5	4.8
F3 (20%)	4.2	4.7	4.9

The spreadability test was carried out using a glass slide and measuring the diameter of the circular droplets formed when a quantity of the nano gel formulation was placed on the surface. The droplet diameter indicates how far the nano gel formulation can spread. However, it is important to note that optimal spreadability may depend on the specific application and desired coverage area. In conclusion, the nano gel formulations prepared using different concentrations of Andaliman extract exhibited different spread levels. Higher concentrations of Andaliman extract result in increased spreadability, which allows the nano gels to cover a larger surface area. These findings have implications for the formulation and application of nano gels for the topical delivery of Andaliman extract in various pharmaceutical and cosmetic applications.

Table 4. Results of organoleptic examination of nano gel preparations

Observation		One month			Two months			Three months		
		F1	F2	F3	F1	F2	F3	F1	F2	F3
Room Temperature	Color	BG	BG	BG	BG	BG	BG	BG	BG	BG
	Smell	Unique	Unique	Unique	Unique	Unique	Unique	Unique	Unique	Unique
	Form	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel
	Homogeneity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	pH	6.38	6.36	6.34	6.34	6.33	6.31	6.32	6.30	6.28
Low Temperature	Color	BG	BG	BG	BG	BG	BG	BG	BG	BG
	Smell	Unique	Unique	Unique	Unique	Unique	Unique	Unique	Unique	Unique
	Form	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel
	Homogeneity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	pH	6.38	6.34	6.35	6.36	6.34	6.32	6.33	6.34	6.32
High Temperature	Color	BG	BG	BG	BG	BG	BG	BG	BG	BG
	Smell	Unique	Unique	Unique	Unique	Unique	Unique	Unique	Unique	Unique
	Form	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel	Gel
	Homogeneity	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
	pH	6.40	6.38	6.34	6.31	6.29	6.27	6.19	6.18	6.12

Note: F1 (5%), F2 (10%), F3 (20%), BG: Brownish Green

Table 5. Results of organoleptic examination of nano gel preparations

Storage		Viscosity (Cp)		
Temperature	Time	F1 (5%)	F2 (10%)	F3 (20%)
Room	Before	2547.0	2737.2	3790.6
	After	1257.0	1454.4	1967.3
Low	Before	2547.0	2737.2	3790.6
	After	1081.1	1368.0	1388.6
High	Before	2547.0	2737.2	3790.6
	After	946.6	1254.1	1262.9

Table 6. Spreadability test results

Temp	Formulas	Spreadability Before Storage (cm)			Spreadability After Storage (cm)		
		0 Gram	100 Gram	125 Gram	0 Gram	100 Gram	125 Gram
Room	F1	3.5	4.0	4.4	4.2	4.7	5.0
	F2	4.0	4.5	4.8	4.4	5.0	5.3
	F3	4.2	4.7	4.9	4.8	5.2	5.5
Low	F1	3.6	4.0	4.5	4.3	4.8	5.0
	F2	4.1	4.4	4.8	4.5	5.1	5.3
	F3	4.2	4.8	5.0	4.7	5.3	5.6
High	F1	3.5	4.1	4.4	4.3	4.9	5.2
	F2	4.0	4.4	4.8	4.5	5.3	5.6
	F3	4.2	4.6	4.9	4.9	5.5	5.8

Organoleptic tests were performed to evaluate the sensory properties of the nano gel formulations made with different concentrations of Andaliman extract (F1: 5%, F2: 10%, F3: 20%). This test assesses sensory attributes such as color, smell, consistency, and overall appearance. In terms of color, all three nano gel formulations showed similar appearance, without any significant difference between concentrations. The color of the nano gel ranges from translucent to slightly opaque in appearance, depending on the concentration of Andaliman extract. Formulations appear consistent and visually appealing.

Regarding the smell, the nano gel formulation has a distinctive aroma associated with Andaliman extract. Odor intensity varied with Andaliman extract concentration, with higher concentrations (F2 and F3) showing a stronger aromatic profile than 5% concentration (F1). The aroma of the nano gel is described as distinctive, herbal, and slightly stingy, reflecting the natural smell of Andaliman.

Consistency, an important attribute in topical formulations, was assessed through touch perception. The nano gel formulation was found to have a smooth and uniform texture, indicating a homogeneous distribution of the Andaliman extract in the gel matrix. The consistency remained consistent at different concentrations, indicating that the nano gel formulation retained its physical properties. Overall, the nano gel formulation prepared with Andaliman extract is visually appealing, exhibits a characteristic aroma, and has the desired consistency.

Sensory evaluation showed that the concentration of Andaliman extract (F1: 5%, F2: 10%, F3: 20%) did not significantly affect the color, odor, or consistency of the nano gel. Sensory attributes of nano gel formulations are important factors that can influence user acceptance, compliance, and overall satisfaction. The results of the organoleptic tests showed that the nano gel formulations with different concentrations of Andaliman extract had good sensory characteristics, making them potentially suitable for topical application. However, it is important to note that individual preferences and cultural variations can affect the perception of sensory attributes.

Table 7. The results of the preparation of the pH and viscosity (Cp)

Formulas	pH	Viscosity (Cp)
F1 (5%)	6.42 ± 0.06	2737.2
F2 (10%)	6.38 ± 0.06	3790.6
F3 (20%)	6.36 ± 0.06	2547.0

Test Results in Table 8. The pH of the nano gel formulations prepared with different concentrations of Andaliman extract (F1: 5%, F2: 10%, F3: 20%) was determined to assess the acidity or basicity of the formulation. The consistency of the pH values at different concentrations showed that adding Andaliman extract had no significant effect on the edge of the nano-gels. This indicates that the nano gel formulation remains stable and maintains a consistent pH level. It should be noted that the slightly acidic pH of the nano gel formulation may contribute to its compatibility with the skin, as it is closer to the physiological pH of the skin. This can reduce the risk of skin irritation or disruption of the skin's natural barrier when the nano gel is applied. Overall, the pH measurement of the nano gel formulation containing various concentrations of Andaliman extract showed a slightly acidic pH value. This pH range suits topical applications, matching the skin's natural pH. Consistent pH values at different concentrations indicate the stability and compatibility of the nano gel formulation with the skin.

The results from Table 6. The viscosity measurements of nano gel formulations containing different concentrations of Andaliman extract (F1: 5%, F2: 10%, F3: 20%) showed increased viscosity with higher concentrations. The viscosity values obtained indicate that the nano gel formulation has a semi-solid consistency, indicating its suitability for topical applications. The nano gel's viscosity profile contributes to its texture and long contact potential on the skin surface, providing a basis for further formulation optimization.

Table 8. Results of centrifugation, examination of particle size, and irritation of the preparations

Formulas	Centrifugation	Particle Size	Irritation
F1 (5%)	No Phase Separation	50.16	Non-Irritating
F2 (10%)	No Phase Separation	109.08	Non-Irritating
F3 (20%)	No Phase Separation	227.62	Non-Irritating

Table 8. The results of the centrifugation test showed that the nano gel formulation containing various concentrations of Andaliman extract (F1: 5%, F2: 10%, F3: 20%) showed good stability and resistance to phase separation. These findings demonstrate the physical integrity and homogeneity of the nano gels, indicating their suitability for potential applications in topical formulations. Table 9. Results of particle size analysis of the nano gel formulations containing different concentrations of Andaliman extract (F1: 5%, F2: 10%, F3: 20%) showing varying particle sizes. The nano gels exhibit nanoscale dimensions, indicating their potential for effective delivery and interaction with biological systems. The particle size results contribute to the overall characterization of nano gel formulations and provide insight into their potential applications in the pharmaceutical and biomedical fields.

Table 9 shows that the irritation test results showed that the nano gel formulation containing different concentrations of Andaliman extract (F1: 5%, F2: 10%, F3: 20%) did not cause significant skin irritation or sensitization effects. These findings demonstrate the potential safety and non-irritating nature of the nano-gels. The cycling test results in Table 9 showed no change in the Andaliman ethanol extract nano gel preparation regarding the practice's color, shape, and smell. The provision of extreme temperatures and high stress given to the trials during storage does not affect the stability of the nano gel preparations, so they do not cause changes to the preparations.

The results of the antimicrobial test in Table 10 show that the extract and nano gel formulation showed inhibitory activity against the test bacteria. At a concentration of 5% (F1), Andaliman ethanol extract showed moderate antibacterial activity against Staphylococcus aureus. The section effectively inhibits bacterial growth, demonstrating its potential as a natural antibacterial agent. Nano gel formulations made using Andaliman extract at concentrations of 10% (F2) and 20% (F3) showed increased antibacterial activity against Staphylococcus aureus. Increasing the concentration of Andaliman extract in the nano gel formulation increased antibacterial effectiveness. The nano gel acts as a carrier system, facilitating the controlled release of Andaliman extract and increasing its interaction with bacteria, thus enhancing its antibacterial effect.

The antibacterial activity of the Andaliman extract and the nano gel formulation can be attributed to bioactive compounds such as alkaloids, flavonoids, phenols, and terpenoids identified in the phytochemical screening. These secondary metabolites are known for their antimicrobial properties and may contribute to the observed antibacterial effects. The findings of this study

highlight the potential of the Andaliman ethanol extract and nano gel formulation as natural antibacterial agents against Staphylococcus aureus. Nano gel as a delivery system for Andaliman extract can be further improved. Its antibacterial properties provide a promising approach for developing new antimicrobial agents.

Table 9. Test results for preparation test cycles

Observation			Preparation Cycle Test					
			1	2	3	4	5	6
Formula 1	Color		BG	BG	BG	BG	BG	BG
	Smell		Unique	Unique	Unique	Unique	Unique	Unique
	Form		Gel	Gel	Gel	Gel	Gel	Gel
	Homogeneity		Yes	Yes	Yes	Yes	Yes	Yes
	pH		6.40	6.38	6.37	6.35	6.34	6.32
	Spread ability (cm)	0 gram	4.2					
		100 grams	4.7					
		125 grams	5.0					
	Viscosity (Cp)		1257.0					
Formula 2	Color		BG	BG	BG	BG	BG	BG
	Smell		Unique	Unique	Unique	Unique	Unique	Unique
	Form		Gel	Gel	Gel	Gel	Gel	Gel
	Homogeneity		Yes	Yes	Yes	Yes	Yes	Yes
	pH		6.38	6.36	6.35	6.33	6.31	6.30
	Spread ability (cm)	0 gram	4.4					
		100 grams	5.0					
		125 grams	5.3					
	Viscosity (Cp)		1967.3					
Formula 3	Color		BG	BG	BG	BG	BG	BG
	Smell		Unique	Unique	Unique	Unique	Unique	Unique
	Form		Gel	Gel	Gel	Gel	Gel	Gel
	Homogeneity		Yes	Yes	Yes	Yes	Yes	Yes
	pH		6.35	6.34	6.33	6.31	6.29	6.28
	Spread ability (cm)	0 gram	4.8					
		100 grams	5.2					
		125 grams	5.5					
	Viscosity (Cp)		1455.4					

Note: BG: Brownish Green

Table 10. Antibacterial test results

Group	SA bacteria	PA bacteria
	Mean Diameter (mm) ± SD	
Negative	0.00 ± 0,00b	0.00 ± 0.00b
Positive	20.67 ± 0.21a	20.77 ± 0.31a
F1 (5%)	9,03 ± 0.35ab	8.97 ± 0.35ab
F2 (10%)	10.07 ± 0.59ab	10.33 ± 0,71ab
F3 (20%)	11.50 ± 0.44ab	12.13 ± 0.21ab

Note: There is a difference in the negative group
b There are differences in the bioplacenton group

Table 11. Results of healing burns

Group	Mean Diameter (mm) ± SD by day						
	0	2nd	4th	6th	9th	12th	14th
Negative	20.44 ±	19.12	18.34	17.22	15.94	13.92 ±	9.86 ±

	0.21	± 0.35	± 0.63	± 1.02a	± 1.25a	1.30a	1.56a
Bioplacenton	20.42 ± 0.22	18.72 ± 0.91	17.72 ± 0.57	14.74 ± 1.37	5.82 ± 5.99b	1.16 ± 2.59b	0.42 ± 0.94b
F1 (5%)	20.46 ± 0.19	18.84 ± 0.70	17.84 ± 0.64	16.78 ± 0.50a	14.28 ± 2.47a	1.26 ± 1/86a	7.98 ± 0.46ab
F2 (10%)	20.26 ± 0.18	18.70 ± 0.39	18.12 ± 0.86	17.16 ± 1.29a	14.52 ± 2.15a	11.4 ± 2.77a	6.94 ± 0.62ab
F3 (20%)	20.32 ± 0.33	18.14 ± 1.18	17.06 ± 1.29	15.18 ± 1.82	13.9 ± 3.84a	9.02 ± 3.69ab	3.68 ± 3.36b

Note: There is a difference in the negative group
b There are differences in the bioplacenton group

As shown in Table 11, the results of wound healing studies indicated that nano gel formulations containing various concentrations of Andaliman extract (F1: 5%, F2: 10%, F3: 20%) showed promising effects in enhancing wound healing. Observations at various times indicate significant advances in wound closure and tissue regeneration. Comparison with the Bioplacenton group further supports the efficacy of the nano gel formulation in facilitating the wound healing process.

4. CONCLUSION

The conclusions drawn from this research Andaliman fruit ethanol extract can be formulated into a nano gel preparation with the best concentration of 20% as a wound healer. Andaliman fruit ethanol extract nano gel has a high level of stability. These findings have implications for the formulation and application of nano gels for the topical delivery of Andaliman extract in various pharmaceutical and cosmetic applications.

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