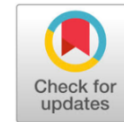




## Original Research



### *Evaluation of the anti-acne effectiveness of Andaliman (Zanthoxylum acanthopodium DC) nanoemulgel in propionibacterium acnes-induced male wistar rats*



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**Abstract:** Acne vulgaris is an inflammatory disorder of the pilosebaceous unit, characterized by lesions such as comedones, papules, pustules, nodules, and cysts. This study aimed to assess the effectiveness of Andaliman Extract Nanoemulgel (*Zanthoxylum Acanthopodium DC*) in treating acne lesions in male Wistar rats (*Rattus Novergicus*) induced with *Propionibacterium acnes*. This experiment involved 30 male Wistar rats aged 6-8 weeks, weighing 150-200 grams, divided into 6 groups: 1) normal, 2) negative control (*P. acnes* induction and base gel), 3) positive control (*P. acnes* induction and Mediklin TR gel), 4) Treatment 1 (*P. acnes* induction and 2% Nanoemulgel), 5) Treatment 2 (*P. acnes* induction and 3.5% Nanoemulgel), and 6) Treatment 3 (*P. acnes* induction and 5% Nanoemulgel). The Nanoemulsion was applied for 10 days to evaluate the healing of acne lesions on the skin of Wistar rats. The results indicate that Andaliman Extract Nanoemulgel significantly promoted the healing of lesions caused by *Propionibacterium acnes*. In conclusion, Nanoemulgel with Andaliman fruit extract at concentrations of 2% and 5% demonstrated the highest effectiveness in anti-acne treatment.

**Keywords:** Acne Vulgaris; Nanoemulgel Andaliman Extract; *Propionibacterium Acnes*.

## INTRODUCTION

Acne vulgaris (AV) is a chronic inflammatory condition of the pilosebaceous unit, primarily triggered by the accumulation of excess sebum and the proliferation of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*).<sup>1</sup> The condition commonly affects predilection sites such as the face, neck, shoulders, chest, back, and upper arms.<sup>2</sup> According to the Global Burden of Disease (GBD) report, the incidence of AV is approximately 85% among individuals aged 12–25 years, with the highest prevalence observed in females aged 14–17 years (83–85%) and males aged 16–19 years (95–100%).<sup>3</sup> A survey in Southeast Asia reveals that AV cases account for 40–80% of dermatological issues.<sup>3</sup> Based on the European S3 Acne Guideline, AV can be classified into comedonal acne, papulopustular acne (mild to moderate severity), severe papulopustular acne, moderate nodular acne, severe nodular acne, and conglomerate acne.<sup>4</sup>

The pathogenesis of AV is influenced by several factors, including increased sebum production, abnormal keratinocyte proliferation, bacterial colonization, and inflammation. These factors can be exacerbated by lifestyle choices, such as diet, inadequate skin hygiene, cosmetic usage, and stress.<sup>5</sup> Although various topical and systemic therapies are available for AV, many have

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DOI: [10.29238/teknolabjournal.v13i2.501](https://doi.org/10.29238/teknolabjournal.v13i2.501)

Received 02 July 2024; Received in revised form 18 October 2024; Accepted 09 December 2024

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limitations, including potential side effects, resistance, and high recurrence rates. These challenges highlight the need for alternative, effective treatments that leverage natural resources.

Indonesia, renowned for its biodiversity, has abundant natural resources that have been traditionally used for medicinal purposes due to their safety, availability, and minimal side effects.<sup>6</sup> One such resource is Andaliman (*Zanthoxylum acanthopodium* DC), a plant endemic to the North Tapanuli and Toba Samosir regions in North Sumatra.<sup>7</sup> Andaliman thrives at elevations of 900–2000 meters above sea level with an annual rainfall of 170–180 days.<sup>8</sup> Traditionally used as a spice in Batak cuisine and for medicinal purposes, Andaliman is rich in bioactive compounds such as flavonoids, alkaloids, saponins, and terpenoids.<sup>9</sup> These compounds exhibit a wide range of pharmacological activities, including antibacterial, anti-acne, anti-aging, antiviral, anticancer, antihyperglycemic, hepatoprotective, antifungal, and antipreeclampsia properties. Additionally, Andaliman is rich in essential oils with potent antibacterial and antioxidant activities.<sup>10</sup>

Topical formulations, such as lotions, ointments, and creams, are commonly used for AV treatment. However, they often face limitations such as poor drug penetration, low drug-loading capacity, and stability issues.<sup>11</sup> Transparent gels, though offering improved stability, may not effectively deliver lipophilic drugs. To address these limitations, nanoemulgel formulations have been developed. Nanoemulgels are emulsions with droplet sizes ranging from 1 to 100 nm, suspended in a hydrogel base. This formulation enhances drug delivery by temporarily disrupting the lipid bilayer structure, allowing for better penetration of active substances.<sup>12-13</sup> The inclusion of oil, surfactant, and cosurfactant components further increases therapeutic efficacy.<sup>14</sup>

While previous studies have demonstrated the anti-acne potential of Andaliman fruit extract, there is limited research on its incorporation into advanced nanoemulgel formulations. Additionally, the effectiveness of nanoemulgel formulations of Andaliman extract in managing acne induced by *Propionibacterium acnes* in animal models remains unexplored. This study aims to evaluate the anti-acne efficacy of Andaliman nanoemulgel in white male Wistar rats induced with *Propionibacterium acnes*, addressing the gap in utilizing this potent natural resource in innovative drug delivery systems.

## MATERIAL AND METHOD

### 2.1. Materials and Tools

Wistar rats 6-8 weeks, oven, evaporator, blender, 40 mesh sieve, UV-Vis spectrophotometer, digital balance, Buchner funnel, filter paper, Particle Size Analyzer, magnetic stirrer, ultrasonicator, centrifuge, waterbatch, stirrer, vortex mixer, dissolution tester, laboratory glassware, analytical balance, stirrer, gloves, and documentation tools, Metil Paraben, Kitosan, Propyl Paraben, Methanol, Aquadest, Tween 80, PEG 400, Carbopol 940. Acetate Acid 1% and Ethanol 96%.

### 2.2. Methods

Two kilograms of Andaliman fruit were dried in an oven with a blower at 55°C for 5 hours. The dried fruit was then ground, yielding 700 grams of powder, and extracted via maceration. Methanol was used as the solvent with a ratio of 1:3 (w/v) Methanol serves as a polar and versatile solvent, capable of extracting both polar and non-polar components. The extraction process utilized various concentrations of methanol to optimize the yield of antioxidants<sup>15</sup>. According to Ghanimi R., *et al.* the methanol extract proven to have a greater concentration of flavonoids than the other extracts (such as ethanol, ethyl acetate and water extracts)<sup>16</sup>. The maceration process with the solvent was carried out for 24 hours.

The maceration filtrate was concentrated using an evaporator at 55°C, yielding a thick extract<sup>17</sup>.

Nanoemulsions were invented using spontaneous emulsification method. Emulsion system contain of an oil phase and water phase. Spontaneous emulsification technique was done by adding the oil phase to water phase dropwise<sup>18</sup>. During the water phase, Methyl Paraben and Propyl Paraben were dissolved in heated distilled water, which was then cooled, followed by the addition of Tween 80 in distilled water. The mixture was stirred using a magnetic stirrer for 30 minutes at 5000 rpm (Mass 1). PEG was then added to the andaliman extract and stirred with a magnetic stirrer for 20 minutes at 5000 rpm (Mass 2). Mass 1 and Mass 2 were gradually combined dropwise using a pipette. The mixture was then stirred with a magnetic stirrer for 8 hours at 5000 rpm and subsequently sonicated<sup>17</sup>.

The Nanoemulgel was prepared by first dispersing 10mL of carbopol 940 in warm distilled water for 24 hours and dissolving chitosan in 10 mL of 1% acetic acid. The dissolved chitosan was neutralized with 10 mL of 0.1 N NaOH until reaching pH 5. A portion of the swollen Carbopol 940 was transferred to a mortar and mixed with methylparaben dissolved in 96% ethanol until homogenous. Triethanolamine was added and mixed until homogenous. The remaining nanoemulsion and carbopol were slowly added while stirring until a homogeneous gel mass formed. Chitosan was then slowly added while stirring until a homogeneous gel mass formed<sup>14,19</sup>. Carbopol 940 was widely use as gelling agent in cosmetic, known for its excellent compatibility, stability, non-toxic nature, and soft application on the skin. It serves several functions, including maintaining emulsion stability, suspending solid particles in liquids and regulating the consistency of cosmetic formulations<sup>20</sup>. Meanwhile Chitosan enhance the mechanical structures of Nanoemulsion through electrostatic interactions and increasing the stability of the emulsified system<sup>21</sup>.

Subsequently, 30 male Wistar strain rats were acclimatized for 1 week.

Wistar rats were randomly divided into six groups where each group consisted of 5 individuals:

1. Group 1 = Normal, no stressed.
2. Group 2 = Negative control, induced *P.acnes* 0.2 mg/kgBB within intradermal, gel base.
3. Group 3 = Positive control, induced *P.acnes* 0.2 mg/kgBB within intradermal, Mediklin TR gel applied on skin once a day for 10 days.
4. F1 = Treated 1, induced *P.acnes* 0.2 mg/kgBB within intradermal, Nanoemulgel 2%.
5. F2 = Treated 2, induced *P.acnes* 0.2 mg/kgBB within intradermal, Nanoemulgel 3,5%.
6. F3 = Treated 3, induced *P.acnes* 0.2 mg/kgBB within intradermal, Nanoemulgel 5%.

Each control and treatment group was induced with Propionibacterium acnes. On the 2nd day post-induction, acne lesions were measured. In the treatment group, Nanoemulgel was applied topically once a day to the rats' skin and observed for up to 10 days.

The data analysis using IBM SPSS 25 involved acne severity, which was initially analyzed using descriptive statistics. Subsequently, the normality of the data distribution was assessed using the Shapiro-Wilk test. This test was selected due to small sample size and it appropriateness for detecting deviations from normality. If the data followed a normal distribution, the analysis continued with One Way ANOVA and Post Hoc tests. However, if data transformation did not achieve normality, non-parametric analysis such as the Kruskal-Wallis test was used instead.

## RESULTS AND DISCUSSION

Andaliman fruit, scientifically known as *Zanthoxylum Acanthopodium*, was extracted using the maceration method, resulting in a methanol extract with the following characteristics:

**Table 1. Characteristic of *Zanthoxylum Acanthopodium* fruit Extract**

Characteristic	Amount
Fesh Herbal Weight (gr)	2 kg
Weight Herbal Powder (gr)	700 g
Solvent Volume (ml)	5000 ml
Extract Weight (gr)	75.30 g
Yield (%)	10.76 %

Table 1 shows that 2 kilograms of fresh andaliman fruit, yielded 75.3 grams of extract. Therefore, the yield obtained from the methanol extract of andaliman is 10.76%. Andaliman fruit extract underwent a phytochemical analysis consisting of phytochemical screening followed by flavonoid, alkaloid and total tanin measurements. Screening of phytochemical results are described in Table 2.

**Table 2. Phytochemical screening of Methanol *Zanthoxylum Acanthopodium* fruit Extract**

Phytochemical	Reagents	Results
Flavonoid	FeCl <sub>3</sub> 5%	+
	Mg(s) + HCL(p)	-
	NaOH 10%	-
	H <sub>2</sub> SO <sub>4</sub> (p)	-
Alkaloid	Bouchardart	+
	Mayer	+
	Wagner	+
	Dragendorff	+
Terpenoid dan Steroid	Lieberman-Burchard	-
	Salkowsky	-
Tanin	FeCl <sub>3</sub> 1%	-
Saponin	Aquadest+Alkohol 96%	+
Glycoside	Mollish	+
Antosianin	HCL 2M	-

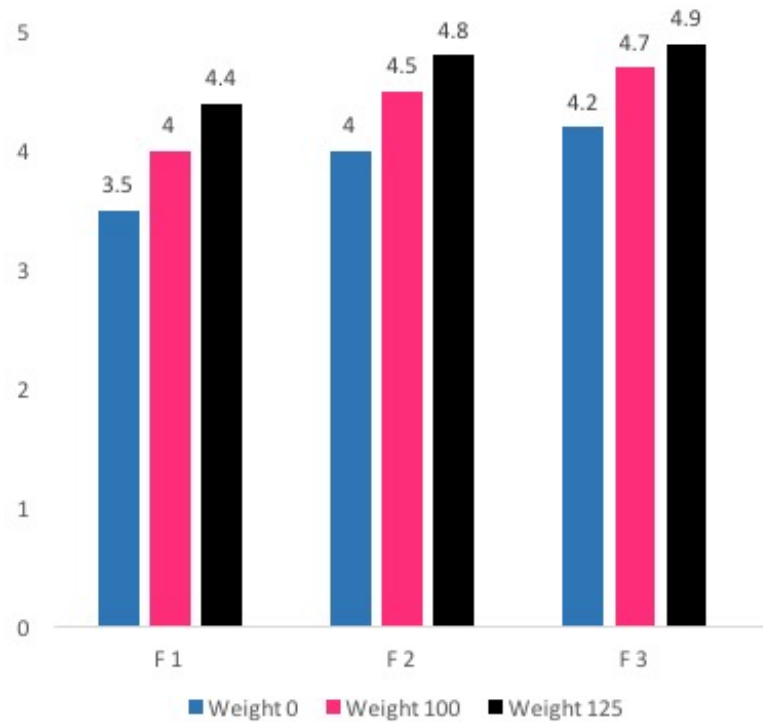
Based on Table 2, phytochemical screening showed that the *Zanthoxylum Acanthopodium* fruit extract had phytochemicals, including flavonoid, alkaloid, saponin dan glycoside.

**Table 3 Evaluation of Organoleptic physics characteristic of *Zanthoxylum Acanthopodium* fruit extract**

Organoleptic Evaluation	F1	F2	F3
Odor	distinctive smell	distinctive smell	distinctive smell
Color	brown	brown	brown
Appearance	nanoemulgel	nanoemulgel	nanoemulgel
Homogeneity	homogen	homogen	homogen
pH	6.42	6.38	6.36

Based on Table 3 The physics characteristic of Nanoemulgel *Zanthoxylum Acanthopodium* fruit extract has the same odor, color, appearance, and homogeneity, with a pH range of 6.36-6.42. Spreadability shown on Table 4

**Table 4 Spreadability of physics characteristic of *Zanthoxylum Acanthopodium* fruit extract**



Formulation	F1			F2			F3		
Weight (gr)	0	100	125	0	100	125	0	100	125
Spreadability (cm)	3.5	4.0	4.4	4.0	4.5	4.8	4.2	4.7	4.9

**Table 5 Comparison of Acne Severity Measurement**

Groups	Mean Average	Mean Score
Group 2	13.33 ± 3.00	12.58
Group 3	13.17 ± 3.17	11.26
F3	13.83 ± 5.00	13.63
F2	11.83 ± 3.00	9.59
F1	12.50 ± 5.00	13.22

Table 5 presents the results of Kruskal-Wallis test, which showed a significant difference between treatment groups indicates the effectiveness of Andaliman Nanomulgel in reducing acne lesions. Analysis of mean ranks indicated that group F3 had a higher average rank (Mean Rank = 13.63) compared to group 2 (Mean Rank = 11.26), group 3 (Mean Rank = 12.58), F2 (Mean Rank = 9.59), and F1 (Mean Rank = 13.22). The significant Kruskal-Wallis test values (Asymp. Sig. < 0.05) for all treatment groups suggest a significant difference in treatment effects on different days of experimentation (H1, H3, H6, H8, H10).

Mean rank analysis showed treatment F3 had the highest average rank, followed by F1, group 3, group 2, and F2. This indicates that Andaliman

Nanoemulgel, especially in treatment F3, which contains the highest bioactive compounds in 5% Nanoemulgel.

*Propionibacterium acnes* is a bacterium that causes acne vulgaris<sup>22</sup>. *Propionibacterium acnes* produces proteins that degrade skin tissue, leading to inflammation. Phytochemical screening data of methanol extract from Andaliman revealed the presence of several phytochemical compounds such as flavonoids, alkaloids, saponins, and terpenoids. According to research of (Fajryana et al., 2022), these compounds have been found to inhibit the growth of *Propionibacterium acnes*<sup>23</sup>.

According to (Ira Syaputri et al., 2022), flavonoids are effective antimicrobial agents against various microorganisms because they have the ability to form complexes with bacterial cell proteins through hydrogen bonding. This interaction destabilizes the bacterial cell wall and cytoplasmic membrane, rendering the proteins biologically inactive, thereby rendering the bacterial cell proteins inactive biologically. Alkaloids possess antibacterial properties by intercalating with DNA, disrupting the peptidoglycan components of bacterial cells. Saponins absorbed onto the cell surface cause damage by increasing membrane permeability, leading to cell death. Terpenoid compounds inhibit bacterial growth by disrupting the formation process of cell membranes and walls<sup>24</sup>. Research of Nafyad *et.al.*, Methanol crude extracts showed better antimicrobial activity in medicinal plants<sup>25</sup>. Study conducted by Chiuman *et.al.*, proves Methanol and Nanoemulsion Andaliman showed antibacterial activities against E.Coli<sup>26</sup>. Methanol extract are limited solubility in water, it penetrate the outer membrane of bacteria and disturbed cellular function, metabolism, and loss of cellular constituents, leading their death<sup>27</sup>.

Nanoemulgel is a type of emulsion with droplet sizes ranging from 1-100 nm. It is suspended in a hydrogel making it ideal for topical delivery. According to (Imanto et al., 2019) and (Indalifiany et al., 2021), nanoemulgel is one of the most promising topical delivery systems because it offers dual release capabilities: gel and nanoemulsion<sup>14,28</sup>. The addition of drug solutions can enhance stability and drug release. In this study, the administration of 5% and 2% Andaliman Nanoemulgel was effective as an antimicrobial and anti-inflammatory agent. The Kruskal-Wallis test revealed that treatment F3 demonstrated the most significant reduction in acne severity, as indicated by a mean rank of 13,63. Based on the study of Amelia *et al.*, proves that higher concentration of Andaliman shown to be more effective in inhibiting bacteria growth<sup>29</sup>.

These findings are consistent with research conducted by (Hanum Ismanelly and Laila, 2018), where ethanol extract of Andaliman significantly healed acne within 4 weeks. Physical observations also showed a reduction in inflammation levels due to the properties of Andaliman that are absorbed by the skin, influenced by metabolism, moisture, and skin thickness. Flavonoids present in Andaliman are effective antibacterial and anti-inflammatory agents for acne-prone skin<sup>30</sup>.

## CONCLUSION

Based on the research findings, the following conclusions can be drawn from this study: Nanoemulgel Andaliman fruit extract at doses of 5% and 2% are the most effective doses in reducing the number of acne lesions and decreasing inflammation. The phytochemical screening of methanol extract from Andaliman identified several compounds including flavonoids, alkaloids, saponins, and terpenoids. These phytochemicals effectively act as antimicrobial agents that inhibit acne in rats. The results suggest that Andaliman Nanoemulge, particularly at 5% concentration, could be developed as an alternative topical treatment for acne vulgaris, offering potential benefits over conventional therapies due to its natural origin and effectiveness.



## AUTHORS' CONTRIBUTIONS

All authors contributed equally to this work.

## FUNDING INFORMATION

Self Funding.

## DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author on reasonable request.

## DISCLOSURE STATEMENT

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors. The data is the result of the author's research and has never been published in other journals.

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