JTL 14 (1) JUNE 2025
Page: 21-30

Contents list available at Jurnal Teknologi Laboratorium

JURNAL TEKNOLOGI LABORATORIUM

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

Original Research

OPEN ACCESS

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The effectiveness of nanoemulgel of pomelo peel extract (Citrus maxima) on anti-acne in Rattus norvegicus rats induced by propionibacterium acnes

Sherly Wijaya, Sri Wahyuni Nasution Ali Napiah Nasution*

Department of Biomedical Sciences, Faculty of Medicine, Dentistry, and Health Sciences, Universitas Prima Indonesia, Medan, Indonesia

Abstract: Acne vulgaris is a skin condition caused by chronic inflammation of the pilosebaceous follicles due to excessive sebum accumulation in the skin pores. This experimental study aimed to evaluate the effectiveness of a nanoemulgel formulated with pomelo (*Citrus maxima*) peel extract in treating acne lesions in *Rattus norvegicus* rats induced with *Propionibacterium acnes*. The study involved 30 male *Rattus norvegicus* rats aged 12–14 weeks, weighing 150–180 grams, which were divided into six groups: (1) normal group, (2) negative control (*P. acnes* induction and gel base), (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 nanoemulgel was applied for 10 days to evaluate the healing of acne lesions on the rats' skin. The results showed that the nanoemulgel containing pomelo peel extract did not produce significant differences in lesion size among the treatment groups. These findings suggest that the nanoemulgel formulation used in this study did not demonstrate significant effectiveness in healing acne lesions in the *P. acnes*-induced rat model.

Keywords: Acne vulgaris; Nanoemulgel; Pomelo (*Citrus maxima*) peel extract; Propionibacterium acnes; Rattus norvegicus

INTRODUCTION

Acne vulgaris is a skin disease caused by chronic inflammation of the pilosebaceous follicles due to the accumulation of excess oil in the pores of the skin that can heal itself (self-limited disease).[1] The most common predilection site is the face but can occur on the neck, shoulders, chest, back and upper arms.[2] The prevalence of AV cases occurs at the age of 12-25 years around 85%, the highest prevalence occurs in women aged 14-17 years, 83-85%, and men 16-19 years, accounting for 95-100%.[3] Around 81% of acne is influenced by genetic factors and the rest is influenced by external factors such as air pollution, foods containing fat, oily facial skin,etc.[4]

The pathophysiology of AV includes several causal factors, the first increased sebum production or sebum hypersecretion where the adrenal glands secrete androgen hormones that affect sebum production, this excess oil production can cause follicle blockage and acne formation.[5] Second, follicular hyperkeratosis or keratinization, namely the release of epithelial cells in the hair follicle, is a natural process that will occur, but in acne there is hyperkeratinization and increased keratinocyte cohesion so that hair follicles become blocked.[6] Third, excessive proliferation of P. acne where the bacteria proliferate in the sebaceous follicles due to the large amount of sebum production and become a habitat for

Corresponding author.
E-mail address: alinapiahnasution@unprimdn.ac.id (Ali Napiah Nasution)
DOI: 10.29238/teknolabjournal.v14i1.572
Received 22 January 2025; Received in revised form 25 February 2025; Accepted 15 March 2025

bacterial growth. P. acne secretes lipase enzymes to break down triglycerides and fatty acids which can cause an inflammatory response to become closed comedo.[7]

The cause of acne can be triggered by bacteria, namely the bacteria Propionibacterium Acne, Staphylococcus epidermidis and Staphylococcus aureus, which are gram-positive anaerobic bacteria that have normal blooms on the skin.[8] The appearance of acne can make a person less self-confident and experience psychological disorders because they feel their appearance is disturbed.[9] Acne characteristics are divided into 2, which is non-inflammatory and inflammatory lesions. In non-inflammatory lesions in the form of blackheads which are divided into 2, namely closed comedones (blackheads) and open comedones (whiteheads). Inflammatory lesions in the form of papules, pustules, nodules and cysts.[10]

Indonesia is a country that is rich in various types of plants and their benefits, one of which is the orange fruit (*Citrus*). There are many types of citrus fruit, for example the pomelo (*Citrus maxima*).[11] The skin of the fruit is yellowish green and has thick skin, then there is a white part that is like a sponge and the flesh of the grapefruit is pink and contains a juice sac.[12] The height of the grapefruit tree is around 5-15 meters with a tree diameter of 10-30 cm.[13] The part of the pomelo that is usually not consumed is the flesh part. But few of the people know that the skin of the pomelo has many benefits that can be utilized.[13] The skin of Bali oranges contains a lot of alkaloid compounds, flavonoids, lycopene, C vitamins.[14] Flavonoids in pomelo peel can act as free radical scavengers or antioxidants and can be used as anti-cholesterol.[15] And the most abundant are tannin compounds and pectin.[8] These compounds have benefits as antibacterials, antiacne, and antioxidants.[16]

Test animals that were used were induced by propionibacterium acnes bacteria and were given nanoemulgel. Nanoemulgel is a formulation of nanoemulsion which is incorporated on the basis of a gel preparation. The nanoemulgel is thermodynamically stable and transparent. Oil components, surfactants and cosurfactants can increase the penetration of active substances so that they will not increase the effectiveness of therapy.[17]

Based on previous experiments, it was found that the extract of pomelo peel has effectiveness against acne. Therefore, researchers did not examine the effectiveness of the nanoemulgel of pomelo peel extract (*Citrus Maxima Pericarpium*) against acne Rattus Norvegicus induced by Propionibacterium acnes.

MATERIALS AND METHOD

Experimental design

A total of 30 male *Rattus norvegicus* Wistar rats were divided into six groups, each consisting of five animals, as follows:

1. Group 1 (Normal Control): Rats were given only food and water without any treatment.
2. Group 2 (Negative Control): Rats were intradermally induced with *P. acnes* at a dose of 0.2 mg/kg BW and treated with gel base only.
3. Group 3 (Positive Control): Rats were intradermally induced with *P. acnes* at a dose of 0.2 mg/kg BW and treated with 0.05% tretinoin gel applied once daily.
4. Group 4 (Treatment 1 - 2% Nanoemulgel): Rats were intradermally induced with *P. acnes* at a dose of 0.2 mg/kg BW and treated with 2% nanoemulgel applied once daily for 14 days.
5. Group 5 (Treatment 2 - 3.5% Nanoemulgel): Rats were intradermally induced with *P. acnes* at a dose of 0.2 mg/kg BW and treated with 3.5% nanoemulgel applied once daily for 14 days.

6. Group 6 (Treatment 3 - 5% Nanoemulgel): Rats were intradermally induced with *P. acnes* at a dose of 0.2 mg/kg BW and treated with 5% nanoemulgel applied once daily for 14 days.

Material

The tools used in this experiment included an oven, rotary evaporator, blender, 40-mesh sieve, UV-Vis spectrophotometer, scales, Büchner funnel, spirit lamp, filter paper, Particle Size Analyzer, magnetic stirrer, ultrasonicator, centrifuge, water bath, stirrer, vortex mixer, dissolution tester, laboratory glassware, analytical balance, gloves, and documentation tools. The experimental animals used in this study were 30 male *Rattus norvegicus* (Wistar strain) rats, aged 12–14 weeks, weighing 150–180 grams, and in healthy condition.

The study utilized test materials derived from pomelo (*Citrus maxima*) peel extract, which was formulated into a nanoemulgel and used to treat *Propionibacterium acnes*-induced acne lesions in male *Rattus norvegicus* (Wistar strain) rats. The materials used included Methyl Paraben, Chitosan, Propyl Paraben, distilled water (*Aquadest*), Tween 80, PEG 400, Carbopol 940, 1% Acetic Acid, and 96% Ethanol.

Preparation of pomelo peel extract

The collected pomelo peels were thoroughly washed under running water and then dried in a drying cabinet for four days to prevent exposure to dust and direct sunlight. Once dried, the peels were ground into a fine powder using a blender. The extraction process was carried out using the maceration technique. A total of 700 grams of pomelo peel powder was dissolved in ethanol solvent at a 1:3 (w/v) ratio. The maceration process was conducted for 24 hours. The macerated filtrate was then concentrated using a rotary evaporator at 70°C with a rotation speed of 48 rpm to obtain a concentrated extract.

Nanoemulgel formulation

1. Nanoemulsion preparation
   a. Propyl Paraben and Methyl Paraben were dissolved in heated and cooled distilled water (Aquadest).
   b. Tween 80 was added to the cooled distilled water and stirred using a magnetic stirrer at 5000 rpm for 30 minutes (Mass 1).
   c. PEG 400 was added to the pomelo peel extract and stirred on a magnetic stirrer at 5000 rpm for 20 minutes (Mass 2).
   d. Mass 1 and Mass 2 were mixed dropwise while continuously stirring at 5000 rpm for 8 hours, followed by sonication.

2. Gel base preparation
   a. Carbopol 940 was dispersed in 10 mL of hot distilled water and left to expand for 24 hours.
   b. Chitosan was dissolved in 1% acetic acid (10 mL) and alkalized with 10 mL of 0.1N NaOH until the pH reached 5.
   c. The expanded Carbopol 940 was transferred to a mortar, and methylparaben dissolved in 96% ethanol was added. The mixture was stirred until homogeneous.
   d. Triethanolamine was added and mixed until homogeneous.
   e. The remaining nanoemulsion and Carbopol 940 were added gradually while stirring continuously to form a homogeneous gel.
   f. Chitosan was then added slowly while continuing to stir until a uniform gel mass was obtained.

Bacterial suspension preparation

A *Propionibacterium acnes* bacterial suspension was prepared by inoculating *P. acnes* culture onto Nutrient Agar (NA) medium and incubating at

38°C for 24 hours. The bacterial colonies were then transferred into a 5 mL centrifuge tube and centrifuged at 5000 rpm for 15 minutes. The bacterial pellet was resuspended in 2 mL of 0.9% sodium chloride solution and homogenized.

Data analysis

Data were analyzed using IBM SPSS 25. The degree of lesion severity was evaluated using descriptive statistics. The normality of the data was assessed using the Shapiro-Wilk test. If the data were normally distributed, statistical analysis was conducted using a One-Way ANOVA followed by a post-hoc test. If the data were not normally distributed after transformation, a non-parametric Kruskal-Wallis test was performed.

RESULTS AND DISCUSSION

The ethanol extract of Bali orange (pomelo) peel was screened for the presence of secondary metabolites using various reagents, as shown in Table 1. The results indicate the presence of alkaloids, tannins, saponins, and glycosides, while flavonoids and terpenoids/steroids were only partially detected or absent.

Alkaloids were confirmed to be present in the extract, as indicated by positive reactions with all four reagents: Dragendorff, Bourchardat, Mayer, and Wagner. This suggests that the Bali orange peel extract contains significant alkaloid compounds, which are known for their antimicrobial and anti-inflammatory properties, making them potentially beneficial in treating bacterial infections such as *Propionibacterium acnes* in acne lesions. For flavonoids, only two out of four tests yielded positive results. A reaction was observed with $FeCl_3$ 5% and H_2SO_4 (p), but NaOH 10% and Mg + HCl (p) tests were negative. This suggests that some flavonoid subclasses may be present, but not in significant quantities. Since flavonoids have strong antioxidant and anti-inflammatory effects, their partial presence could still contribute to the extract's potential skin benefits.

The screening for triterpenoids/steroids using Liebermann-Burchard and Salkowski reagents produced negative results, indicating that these compounds are either absent or present in very low concentrations. As triterpenoids and steroids are often associated with wound healing and anti-inflammatory effects, their absence suggests that other compounds, such as alkaloids and tannins, may play a more dominant role in the extract's biological activity.

The extract tested positive for saponins, as indicated by the reaction with a mixture of distilled water and 96% alcohol. Saponins are known for their antimicrobial and emulsifying properties, which could enhance the formulation's ability to disperse active ingredients in nanoemulgel preparations. The presence of tannins, confirmed by a 1% $FeCl_3$ test, indicates that the extract contains compounds with astringent and antimicrobial properties, which could help in reducing acne lesions by tightening skin pores and inhibiting bacterial growth.

Finally, the extract was found to contain glycosides, as confirmed by a positive reaction with the Molisch test. Glycosides can exhibit various biological activities, including antioxidant, anti-inflammatory, and antimicrobial effects, which may contribute to the therapeutic potential of the nanoemulgel formulation.

The screening results suggest that the ethanol extract of Bali orange peel contains alkaloids, tannins, saponins, and glycosides, all of which are known for their antimicrobial and anti-inflammatory properties. These findings indicate that the extract may have potential applications in acne treatment, particularly in inhibiting *P. acnes* growth and reducing inflammation. However, the absence of terpenoids/steroids and the partial presence of flavonoids suggest that additional components may be needed to enhance the formulation's therapeutic effects.

Table 1. Screening results of ethanol extract of bali orange peel

No	Secondary Metabolites	Reagent	Results
1.	Alkaloid	Dragendorf	+
		Bourchardat	+
		Mayer	+
		Wagner	+
2.	Flavonoid	NaOH 10%	-
		FeCL3 5%	+
		Mg + HCL (p)	-
		H2SO4 (p)	+
3.	Troterpenoid/Steroid	Lieberman-bourchat	-
		Salkowsky	-
4.	Saponin	Aquadest + Alkohol 96%	+
5.	Tanin	FeCL3 1%	+
6.	Glikosida	Mollish	+

Table 2 presents the descriptive test results for rat size measurements across different experimental groups, including the negative control, positive control, and three treatment groups (2%, 3.5%, and 5% nanoemulgel formulations). The negative control group recorded the highest mean rat size at 0.16 ± 0.121, whereas the lowest mean sizes were observed in the 3.5% and 5% treatment groups**,** both at 0.12 with slightly different standard deviations **(**0.097 and 0.102, respectively**).** The positive control group and the 2% nanoemulgel treatment group had similar mean values of 0.13**,** indicating no major differences between them.

Table 2. Descriptive statistics of rat size measurements in control and treatment groups

Rat Size Lesion									
					95% CI for Mean				
	N	Mean	SD	SE	Lower	Upper	Min	Max	p-value
Control (-)	35	0.16	0.121	0.021	0.12	0.20	0	0	0.465
Control (+)	35	0.13	0.119	0.020	0.09	0.17	0	1	
2%	35	0.13	0.108	0.018	0.10	0.17	0	0	
3.5%	35	0.12	0.097	0.016	0.08	0.15	0	0	
5%	35	0.12	0.102	0.017	0.09	0.16	0	0	
Total	175	0.13	0.110	0.008	0.12	0.15	0	1	

Noted:
SD: Standar deviation; SE: Standar Error; CI: Confidence level

The standard deviation values were relatively small across all groups, ranging from 0.097 to 0.121**,** which suggests minimal variation within each group. The standard error values, ranging between 0.016 and 0.021, indicate that the sample means are fairly stable and provide a reliable representation of the population. The 95% confidence intervals further show that the mean values of each group fall within a narrow range, reinforcing the consistency of the data.

Interestingly, the minimum values recorded for all groups were zero, indicating that some individual rats in each group showed no measurable response in size lesion variation. The maximum values varied slightly, with most groups reaching 0, except for the positive control group, which had a maximum value of 1**.**

The p-value of 0.465 suggests that there is no statistically significant difference in rat size among the groups, meaning that the different concentrations of nanoemulgel treatment did not cause significant variation in size lesion when compared to the controls. Overall, the results indicate that the nanoemulgel formulations, regardless of concentration, did not significantly influence rat size lesion in this study. The similarity in means across groups suggests that the treatment had no observable effect on growth or any major physiological changes related to body size lesion.

Based on the results of the descriptive test showing the average size lesion of the rats in each group, it can be seen that the negative control group has a slightly larger size compared to the positive control group and other treatment groups. However, further analysis using the Kruskal-Wallis test showed no significant difference between the groups. This shows that administration of Nanoemulgel of pomelo peel extract at various concentrations does not provide a significant effect on the size lesion of the skin induced by *Propionibacterium acnes*.

The effect of active compounds in pomelo peel extract on acne treatment can be influenced by many factors, including concentration and dosage form.[24] Although nanoemulsion is considered effective in increasing the absorption of active ingredients, the results of this study show that under these experimental conditions, its effectiveness is not significant enough. This is related to other factors that have not been considered in this study, such as the response of the experimental to infection and the optimal concentration of the active ingredients in Nanoemulgel.[25] In previous studies, the use of pomelo peel extracts has shown the potential for antioxidants and antibacteries, but in this study, the use of nanoemulgel prepations is not enough to provide an effective active ingredient concentration to produce significant therapeutic effects on *P.Acnes* infection conditions.[26]

The results showed no significant difference between the treatment group and the control group in terms of mouse size related to the mechanism of the active ingredient in topical treatment. The applied concentration of the orange peel extract Nanoemulgel, although designed with various variations, may not have been high enough to induce significant morphological changes in the tested ratts.[27] Although the active ingredients in grapefruit are known to have anti-inflammatory and antibacterial potential, the biological response that occurs can be highly dependent on the degree of penetration, stability, and bioavailability of the active ingredients in the affected ratts, which can vary depending on the formulation used.[28]

Nanoemulgel can bring therapeutic benefits, its effect on the inflammatory response that occurs in acne lesions may be more complex, involving interactions between other biological factors such as the body's cucumber system or the presence of other components in the lesion.[29] Although grapefruit peel extract contains active compounds such as flavonoids and alkaloids that have anti-inflammatory and antibacterial potential, the results of this study indicate that the formulation in the form of nanoemulgel has not had a significant effect on the size of mice induced by Propionibacterium acnes. This is in line with the findings of Amalyuri et al. (2022) and Sari et al. (2024) which state that the effectiveness of active ingredients is greatly influenced by concentration and dosage form. In addition, although nanoemulgels are designed to enhance the absorption of active ingredients, factors such as penetration, stability, and bioavailability remain major challenges in achieving the desired therapeutic effects.[30]

The absence of a significant therapeutic effect in this study, despite the known antibacterial and antioxidant potential of pomelo peel extract, can be attributed to several key factors that differentiate it from the study conducted by Eid et al. (2023).[26] One of the most crucial aspects is the concentration and bioavailability of the active ingredient**.** While pomelo peel extract contains compounds with antimicrobial properties, the nanoemulgel formulation used in this research may not have been able to deliver a sufficiently high concentration of

these active compounds to effectively inhibit *Propionibacterium acnes*. In contrast, incorporated benzoyl peroxide nanoparticles into a lemongrass oil nanoemulgel, which likely provided a more potent antibacterial effect due to the well-established efficacy of benzoyl peroxide in acne treatment.

Another important factor to consider is the formulation stability and drug release efficiency. Nanoemulgel preparations are designed to enhance the solubility and penetration of active compounds, but their effectiveness depends on how well the active ingredients are incorporated and released at the target site. In this study, the nanoemulgel containing pomelo peel extract may not have achieved optimal penetration into the skin or may have had a slower or insufficient release of active compounds, reducing its antimicrobial impact. In contrast, Eid et al. (2023)[26] utilized benzoyl peroxide nanoparticles, which are specifically designed to enhance penetration and controlled drug release, ensuring a more consistent and sustained antibacterial effect.

Additionally, the differences in the antimicrobial agents used between the two studies could also explain the varying outcomes. Benzoyl peroxide is **a** well-documented and highly effective topical agent used in acne treatment due to its ability to generate reactive oxygen species that kill acne-causing bacteria. On the other hand, while pomelo peel extract contains natural antibacterial compounds such as flavonoids, tannins, and saponins, these compounds may not be as potent or stable in the given formulation, resulting in a weaker antibacterial response.

Overall, while pomelo peel extract has demonstrated promising antioxidant and antibacterial properties in previous research**,** the results of this study suggest that the nanoemulgel formulation used was not sufficient to provide an effective concentration of active ingredients needed to produce significant therapeutic effects against *P. acnes*. In contrast, the study by Eid et al. (2023)[26] likely benefited from the use of benzoyl peroxide nanoparticles**,** a well-established anti-acne agent, combined with a nanoemulgel system designed for enhanced stability and drug delivery. These differences highlight the importance of formulation optimization and active ingredient selection in developing effective nanoemulgel-based acne treatments.

CONCLUSION

This study evaluated the effectiveness of a nanoemulgel formulation containing pomelo **(***Citrus maxima***)** peel extract in treating acne lesions induced by *Propionibacterium acnes* in *Rattus norvegicus***.** The findings revealed that while the nanoemulgel formulation was successfully developed and applied, it did not produce significant therapeutic effects in reducing acne lesions when compared to control groups. The absence of a notable effect suggests that the active compounds in the pomelo peel extract were either insufficient in concentration or not optimally released in the nanoemulgel formulation**,** limiting their antimicrobial activity against *P. acnes*. Further research is necessary to optimize the nanoemulgel formulation**,** potentially by enhancing the stability, concentration, and bioavailability of active compounds or by incorporating synergistic antibacterial agents to improve efficacy. These findings highlight the importance of formulation strategies in developing effective nanoemulgel-based treatments and provide valuable insights for future research on plant-based therapeutic agents for acne treatment.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to this work

FUNDING INFORMATION

No funding was received for this research.

DATA AVAILABILITY STATEMENT

The utilized data to contribute to this investigation are available from the corresponding author upon 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 results from the author's research and has never been published in other journals.

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