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Research Article

Enhanced Antibacterial Activity of Piper betle Extract Niosome Serum Gel and Its Irritation Effects

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Abstract.
Masks are personal protective equipment essential for COVID-19 prevention, but for the use of masks has led to an increase in the severity of both acne (maskne) and rosacea (mask rosacea). Long-time mask-wearing can increase acne's flare by modifying the cutaneous facial microenvironment and triggering facial dermatoses. To minimize this, the skin needs to be protected by using an antibacterial product. This study aimed to develop and determine the antibacterial effect of *Piper betle* extract in niosome serum gel and its irritation effect. 5% *Piper betle* extract was formulated into a niosome system and incorporated into the serum gel with varying concentrations of 30%, 40%, and 50%. The niosome system was characterized by particle size, Polydispersity Index (PI), zeta potential, and pH value, and then evaluated physicochemical properties for niosome serum gel preparation. Further, the antibacterial effect against *Propionibacterium acne*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* was tested using a well-diffusion test. The preparation stability was evaluated using freeze-thaw methods, and the irritation test was assessed using the HET-CAM (Hen's Egg Chorioallantoic Membrane) method. The results showed that the preparation has a good physicochemical, while the best inhibition zone diameter was 7,29±0,21; 7,77±0,12; and 8,24±0,40, against *Pacne*, respectively. However, the results of the stability test of the preparation showed a significant change in the pH but had no irritation effect on CAM. It can concluded that the niosome serum gel of *Piper betle* extract has a potential antibacterial impact for acne, especially against *Pacne*.

Keywords: Piper betle, Niosome serum gel, antibacterial effect, stability, irritation effect

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1. INTRODUCTION

Maskne is a form of mechanical acne resulting from the increased duration of mask wear, referred to as the "O" zone area around the mouth. It is likely a disorder of follicular occlusion and directly related to mechanical stress (pressure, occlusion, friction) and microbiome dysbiosis (heat, pH, moisture from biofluids). It modifies skin microbiota

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and sebum production, which has increased facial dermatoses, i.e., rosacea, contact dermatitis, seborrheic dermatitis, and acne (1,2). This phenomenon significantly impacts one's psychological state, which is also supported by a study that states that adults and adolescents suffering from acne have higher rates of low self-esteem, anxiety, and depression than individuals without acne (3). So there must be a treatment to overcome it, and botanical actives with anti-inflammatory, antioxidant, sebum regulation and antimicrobial properties are preferred (2).

One of the acne therapies uses topical antibacterial agents from a natural source, such as piper betle leaf extract (PBLE). PBLE shows antiseptic, antibacterial, and antiviral properties due to the content of alkaloids, tannins, glycosides, saponins, phenol, flavonoids, steroids, proteins, amino acids, terpenoids, and isolated bioactive compounds such as phytol, acyclic diterpene alcohol, 4-chromanol, hydroxychavicol or 4-allylpyrocatechol, and allylpyrocatechols (4,5). The essential oil content of piper betel leaf is 56.3% and has antibacterial properties. The essential oils consisted of phenols (pyrocatechol, carvacrol, safrole, eugenol, and chavibetol) and terpenoids (1, 8- cineole, cadinene, camphene, caryophyllene, limonene, pinene, chavicol) (6). These compounds work as antibacterial agents through various mechanisms, i.e., Alkaloids can inhibit growth and kill bacteria by interfering with the permeability of cell walls and membranes, inhibiting nucleic acid and protein synthesis, and inhibiting bacterial cell metabolism from causing lysis; Tannins work by coagulating bacterial protoplasm, precipitating proteins, and binding proteins to inhibit the formation of bacterial cell walls; Saponins works by disrupting the stability of the bacterial cell membrane; Phenol acts as a toxin in the protoplasm, damaging and penetrating the bacteria cell wall; etc. (7). The ethanolic extract of PBLE had an inhibitory zone against *P. acne* of about 9.8mm, 15.85mm, and 17,35mm at percentages of 5%, 10%, and 15%, respectively (8); against *S. aureus* about 13,883±1.1496 mm and 16,767± 1.8779 mm at percentages of 10% and 30%, respectively (9); and against *S. epidermidis* about 18.0±1.91 mm at the percentage of 20% (10).

The problem with natural sources is had not stable physically and chemically, which makes them not stable in the formulation. It is necessary to encapsulate PBLE in a proper system such as a niosome. Niosome is a non-ionic surfactant-based vesicle formed mainly by non-ionic surfactant and cholesterol incorporation as an excipient (11). Niosome has more excellent stability and fewer disadvantages when compared to liposome (12). Due to their entrapment efficiency percentage, the best combination of niosomal carriers was cholesterol, Tween 60, and Span 60 (13). In this study, the PBLE

niosome was incorporated into serum gel preparation because of its high content of water which can hydrate the skin (14).

2. MATERIALS AND METHOD

2.1. Materials

2.1.1. Materials

Piper betle was collected and extracted by Materia Medika Batu, East Java, Indonesia. Ethanol was purchased from Sigma Aldrich. Tween 60, Span 60, Cholesterol, PEG 400, sodium benzoate, carbopol, triethanolamine (TEA), propylene glycol, methylparaben, sodium metabisulfite, hen's egg, and distilled water were of technical grade. *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Propionibacterium acnes* were isolated from the Laboratory of Biomedical, Medical Faculty of the University of Muhammadiyah Malang.

2.1.2. Tools

Particle Size Analysis and Zetasizer (Malvern), Analytical balance (Metler Toledo), pH meter (Schott), viscometer (Brookfield), double beam UV-Vis Spectrophotometer (Shimadzu), homogenizer (Heidolph), autoclave (All American), Laminar Air Flow (Biobase), incubator (Memmert), vernier calipers, micropipette (DragonLab), petri dish and other glassware.

2.2. Methods

2.2.1. PBLE Niosome Preparation

Niosome was prepared by thin layer hydration method using the ratio of cholesterol : Tween 60 : Span 60 (0.29:3.27:2.1). In the preparation of niosome, PEG 400 is added as a solubilizer (15) and sodium benzoate as preservative. PBLE is also incorporated into this preparation. The formula can be seen in **(Table 1)**.

TABLE 1: PBLE Niosome Formula.

Ingredient	Concentration (%)
PBLE	5
Span 60	2.1
Tween 60	3.27
Cholesterol	0.29
PEG 400	15
Sodium benzoate	0.1
Distilled water	until 100%

2.2.2. Characterization of PBLE Niosome

The physical characterization of the PBLE niosome included particle size, particle distribution (polydispersity index), and zeta potential (16). All assessments were completed in triplicate.

2.2.3. PBLE Niosome Serum Gel Preparation

The formulation of niosome serum gel preparation was made according to the formula presented in **(Table 2)**. Serum gel was made in three formulas where each formula contains 30%, 40%, and 50% PBLE niosome. Carbopol was developed in an amount of distilled water and developed by the presence of TEA. Methylparaben as a preservative and sodium metabisulfite as an antioxidant dissolved in propylene glycol before being added to the carbopol solution. Lastly, PBLE niosome and fragrance were added to the mixture and stirred until homogenous. After made the niosome serum gel, the physicochemical characterization test, antibacterial activity, stability, and irritation test were conducted.

TABLE 2: PBLE Niosome Serum Gel Formula.

Ingredient	Concentration (%)		
	Formula 1	Formula 2	Formula 3
PBLE Niosome	30	40	50
Carbopol	0.5	0.5	0.5
Propylene glycol	5	5	5
Methylparaben	0.03	0.03	0.03
Sodium metabisulfite	0.01	0.01	0.01
TEA	until pH 4.50 – 5.00		
Fragrance	until enough		
Distilled water	until 100%		

2.2.4. Characterization of PBLE Niosome Serum Gel

Physicochemical characterization of PBLE niosome serum gel included organoleptic test (color, texture, odor, and homogeneity), pH value, viscosity, and spreadability measurement.

2.2.5. Antibacterial Activity

The in vitro antibacterial profile was observed using the well-diffusion method against *P. acne, S. aureus, and S. epidermidis*. Placed niosome serum gel preparations of PBLE with different levels of variation (30%, 40%, and 50%) were in 200µL of other wells. Furthermore, dripped the distilled water used as a negative control and clindamycin gel as a positive control into the wellbore as much as 200µL. Then the petri dishes were incubated at 37°C for 24 hours. Observations were made after 1x24 hours of incubation. Antibacterial activity was expressed by measuring the diameter of the inhibition zone (clear area) using a caliper. Performed each sample in triplicate (17).

2.2.6. Stability Testing

Stability testing was held using the freeze-thaw method. 10g sample of PBLE niosome serum gel was placed into vials and stored at 4±2°C for 24 hours, then transferred at 40±2°C for 24 hours (counted as one cycle). Then, repeated this for up to 6 cycles (12 days) (18). The organoleptic and pH values were evaluated at the end of the cycle.

2.2.7. Irritation Testing

Irritation testing was carried out using Hen's Egg Test Chorioallantoic Membrane (HET-CAM). About 300g sample of PBLE niosome serum gel was put into CAM and examined for about 300 seconds, then evaluated for irritant parameters (lysis, hemorrhage, and coagulation) using the score (19). This test also used sodium lauryl sulfate as positive control and distilled water as a negative control.

3. RESULTS AND DISCUSSIONS

3.1. PBLE Niosome Characterization

PBLE niosome physical characterization is shown in **(Table 3)**. The average size of the vesicle can be classified as a giant unilamellar vesicle because the size of the vesicles was more than 1.0μm (Zhang & Sun, 2021). It was also found that the particle size distribution of the PBLE niosome was a polydispersed vesicle because it had a polydispersity index value >0.7 (21). The PBLE niosome had a zeta potential value <-30mV. Zeta potential can be either negative or positive and can range from –200 to 200 mV, depending upon the electrochemical behavior of the particle interface. Generally, a large value (i.e., over 30 mV or below –30 mV) indicates that a sample is stable and unlikely to aggregate or coalesce. In addition, a large value means that the surfaces of particles are highly charged and repel each other. The presence of cholesterol is also made the niosome more stable (22). Increasing cholesterol content will increase the hydrophobicity and stability of bilayer vesicles and decrease the permeability (23) because the system will be more intact and ordered as a barrier for drug release and also reduce drug leakage by improving the fluidity of the bilayer membrane (24).

TABLE 3: PBLE Niosome and PBLE Niosome Serum Gel Characteristics Result.

Parameter	PBLE Niosome	PBLE Niosome Serum Gel		
		F1	F2	F3
Particle size (nm)	3400 ± 445.31			
Polydispersity Index	0.780 ± 0.19			
Zeta Potential (mV)	-146.5 ± 92.66			
pH		4.73 ± 0.006	4.80 ± 0.006	4.84 ± 0.006
Viscosity (cps)		733.33 ± 28.87	666.67 ± 57.74	616.67 ± 28.87
Spreadability (cm)		6.53 ± 0.06	5.43 ± 0.12	5.33 ± 0.06

3.2. PBLE Niosome Serum Gel Characterization

The organoleptic observations showed that PBLE niosome serum gel was blackish green, odorless, and had a viscous texture due to using a gelling agent. It is also easy to apply, has light to spread, absence of coarse particles, and shows no phase separation. Based on characteristic physicochemical measurements **(Table 3)**, the pH value of PBLE niosome serum gel remained within the acceptable pH of topical preparations (4.5 – 6.5) (25). The different concentrations of PBLE niosome had different viscosities. As seen in **(Table 3)**, the higher concentration of PBLE niosome resulted in serum gel preparation with lower viscosity. Likewise, the spreadability test results decrease with an increase

in PBLE. This result is not in accordance with the theory that the value of viscosity and spreadability is inversely proportional (26).

3.3. Antibacterial Activity

Based on **(Table 4)**, we can see that PBLE niosome serum gel preparations showed the diameter of the zone of inhibition against *Propionibacterium acnes, Staphylococcus aureus, and Staphylococcus epidermidis*. The inhibition zone diameter increased significantly with the addition of active ingredients, and Formula 3 (PBLE niosome 50%) has the largest inhibition zone diameter value compared to formulas 1 and 2. Formula 3 also has almost the same inhibitory diameter as the positive control used, especially against *Propionibacterium acnes*. This phenomenon is similar to the study (27), where PBLE is better at against *P. acne*.

TABLE 4: PBLE Niosome Serum Gel Antibacterial Activity Result.

Samples	Inhibition Zone Diameter (mm)		
	against P. acne	against S. aureus	against S. epidermidis
Positive Control (Clindamycin gel)	9.84 ± 0.50	28.17 ± 0.41	22.03 ± 0.56
Negative control	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Formula 1	7.29 ± 0.21	6.54 ± 0.43	6.30 ± 0.04
Formula 2	7.77 ± 0.12	6.82 ± 0.67	6.56 ± 0.11
Formula 3	8.24 ± 0.40	7.44 ± 1.01	7.31 ± 0.47

3.4. Stability Testing

A stability test was conducted to physically and chemically determine the system resilience of niosome serum gel when stored in extreme conditions. As we see in **(Table 5)**, there are no changes and phase separation in the organoleptic parameter. But there is a difference in pH values significantly. It can be concluded that the niosome serum gel system formed represents the instability of the niosome serum gel system in the presence of pH value change.

3.5. Irritation Testing

As we have seen in **(Table 6)**, the preparation showed a 0 irritation score, which means there is no hemorrhage, lysis or coagulation in all three formulas. This phenomenon

TABLE 5: PBLE Niosome Serum Gel Stability Activity Result.

Formula	Parameters		
	Organoleptic	pH value	
		Before	After
F1	No color change, odor change, and phase separation	4.73±0.006	4.49±0.010
F2		4.80±0.006	4.57±0.006
F3		4.84±0.006	4.61±0.006

can happen because of the addition of carbopol as a gelling agent, which has a cooling effect when used (28). This result indicates that the preparation is safe to use.

TABLE 6: PBLE Niosome Serum Gel Irritation Activity Result.

Samples	Irritation Score	Interpretation
Positive Control (SLS)	10.18 ± 2.68	Strong irritation
Negative Control (Distilled water)	0	No irritation
Formula 1	0	No irritation
Formula 2	0	No irritation
Formula 3	0	No irritation

4. CONCLUSION

Based on the research results, it can conclude that the three formula has good physico-chemical characteristics. However, the niosome system still has too large a particle size. The preparation is chemically unstable during storage using the freeze-thaw method, but they have no irritating effect on Chorioallantoic Membrane (CAM). It indicates that the preparation is safe to use. Due to the inhibition diameter zone against *Propionibacterium acnes, Staphylococcus aureus*, and *Staphylococcus epidermidis* formula three (50% PBLE niosome) has the best antibacterial activity, especially against *Propionibacterium acnes.* It is necessary to re-optimize the niosome formula to obtain better characteristic results.

5. AUTHORS' CONTRIBUTIONS

Santika Tri Wahyuni: Validation, Investigation, Resources, Project administration, Funding acquisition

Dyah Rahmasari: Conceptualization, Methodology, Validation, Writing, Visualization, Project administration

Rifqi Sandi Nugroho: Software, Investigation, Resources, Funding acquisition

Ilham Agusta: Formal analysis, Investigation, Resources, Funding acquisition

Revie Dithya Kurnia Daminda: Software, Investigation, Resources, Funding acquisition

Riko Vikri Sundugesti: Investigation, Resources, Data curation, Funding acquisition

Dian Ermawati: Conceptualization, Methodology, Formal analysis, Supervision

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