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Research article

Formulation and Physical Properties Evaluation of Tapak Liman Leaf Ethanol Extract (*Elephantopus Scaber* L.) Gel

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Abstract

Management of diabetic wounds is crucial to prevent severe complications including the potential of amputation. The conventional treatment includes antibiotics which resistance frequently arises. Tapak liman (*Elephantopus scaber* L.) leaf extract, as an antibacterial agent, is an alternative for treating diabetic wounds. For practical application, the extract was formulated into a gel. Therefore, this research aimed to determine the concentration of the gelling agent HPMC and the humectant propylene glycol to develop the optimal formula of the gel and meet the criteria for good physical properties. The analysis started with the identification and phytochemical screening of tapak liman leaf extract. Subsequently, the extract was formulated in the form of gels with concentration variations of HPMC and propylene glycol. The evaluation included the testing of organoleptic, viscosity, pH, spreadability, and adhesiveness. Meanwhile, data was subjected to normality tests followed by One-way ANOVA to achieve the best physical properties of the gel formula. Based on data analysis, it was indicated that increasing HPMC concentration and decreasing propylene glycol concentration did not significantly impact the pH value ($p>0.05$), but significantly increased the viscosity and adhesiveness, and decreased the spreadability of the gel ($p<0.05$). It can be concluded that a combination of HPMC 3% w/w and propylene glycol 14% w/w represented the best physical properties for the gel, which had pH value of 5.53 ± 0.075, viscosity of 2,283.10 ± 530.2867 cps, spreadability of 5.51 ± 0.07 cm and 18.81 ± 0.26 g.cm/second, and adhesiveness of 7.77 ± 1.14 seconds.

Keywords **:** Tapak liman leaf ethanol extract, Gel, HPMC, Propylene glycol

Introduction

Approximately, 15-25% of patients with diabetes mellitus (DM) have diabetic foot infections caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa* [1]. In this context, serious infections and amputation may occur when this wound is not treated [2]. The treatment given is generally antibiotics even though the use is highly susceptible to resistance. Therefore, other alternatives, such as ethanol extract of tapak liman leaf (*Elephantopus scaber* L.) are needed to treat diabetic wounds.

Ethanol extract of tapak liman leaf has antibacterial effects with a 20 mm and 18 mm diameter inhibition zone against *Staphylococcus aureus* and *Salmonella thypi* at the concentration of 100 mg/mL, respectively [3]. The presence of compounds and activity is confirmed by subjecting the extract to phytochemical screening as antibacterial through flavonoid, saponin, and tannin tests. The ethanol extract is formulated into gel to increase patient compliance. The gel provides a cooling effect when used with good spreading ability [4]. High water content in the gel base can affect hydration in the skin so it will increase the delivery for both hydrophilic and lipophilic drugs [5]. Therefore, gel is one of the promising topical preparations.

In this formulation, the gelling agent used is hydroxypropyl methylcellulose (HPMC) due to good swelling in water [6]. In addition, HPMC does not affect the difference in homogeneity and pH of the gel [7]. Another important ingredient is a humectant used to retain moisture in the skin. In this research, propylene glycol is used as a humectant because of its ability to retain moisture better than glycerin [8] and penetrate the skin [9]. According to Rowe et al. [10], an optimal concentration of propylene glycol as a humectant is approximately 15%.

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This study aim to determine the concentration of HPMC and propylene glycol as gelling agent and humectant to produce a gel with good physical properties. In this formulation, the ratio of HPMC used was 1%, 2%, and 3%, while propylene glycol was 16%, 15%, and 14%. Each formula was tested for physical properties including organoleptic, pH, viscosity, spreadability, and adhesion tests. In this context, the best formula for gel preparation of tapak liman leaf ethanol extract was obtained.

Materials and Methods

Materials

Materials included tapak liman leaf ethanol extract from PT Berkah Alam Nusantara, HPMC (Sigma), propylene glycol (Bratachem), methylparaben (Bratachem), propylparaben (Bratachem), aluminum chloride (Merck), sodium acetate (Merck), and distilled water. Instruments used in this study were pH meter (Lutron PH-208), mixer (EMV), viscometer (Rheosys Merlin), spreadability and adhesion test equipment.

Methods

Identification of tapak liman leaf ethanol extract

The identification determined the truth of tapak liman leaf ethanol extract to avoid errors during preparation. This included the color and odor of the extract as well as water and total ash content. Tapak liman leaf in 70% ethanol extract had a blackish-brown color and was odorless with a bitter taste [11]. Identification of the water content was carried out by the gravimetric method. A sample of 10 g was placed into a cup and heated at 105℃ for 5 hours. Subsequently, weighing was carried out every 1 hour until the difference was ≥ 0.25% with an accepted requirement of ≤12% [11]. Total ash content was heated and 2 g of the sample was placed on the silicate crucible. The sample was weighed and the requirement for total ash content did not exceed 8.9% [11].

Phytochemical screening of tapak liman leaf ethanol extract

Flavonoids, saponins, and tannins were measured, because they have antibacterial properties. In this context, 0.5 g of the extract was dissolved in 5 mL of 96% ethanol to conduct a flavonoid test, which was initiated by 0.1 g of magnesium powder and 10 drops of concentrated hydrochloric acid (HCl). The presence of the compound was reported through the formation of a red or orange color [12], while saponins test was performed with 0.5 g dissolved in 10 mL of hot water. Subsequently, saponins were reported by the formation of stable foam lasting no more than 1 minute after shaking the molution vigorously for 10 seconds [13]. Approximately 0.5 g of the sample was dissolved in 2 mL of distilled water for tannins test and the formation of a green-blue/black color showed the compound after 2-3 drops of 1% $FeCl_3$ were added [13].

Gel formulation of tapak liman leaf ethanol extract

The amount of each component of formula were presented in Table 1. HPMC was dissolved in 30 mL of distilled water that had been heated at 80-90℃ using a mortar until homogeneous. Methyl paraben and propyl paraben were then mixed into the solution using a mixer for 15 minutes at 200 rpm. The ethanol extract was dissolved using propylene glycol and mixed slowly with the first mixture. Subsequently, 100 mL of distilled water was added and homogenized using a mixer at 200 rpm for 15 minutes.

Table 1. Tapak liman leaf ethanol extract gel formula

Materials	Concentration (%) Formula		
	F1	F2	F3
Tapak liman leaf ethanol extract	0.1	0.1	0.1
HPMC	1	2	3
Propylene glycol	16	15	14
Methyl paraben	0.18	0.18	0.18
Propyl paraben	0.02	0.02	0.02
Aquadest ad	100	100	100

Physical properties evaluation of the gel

Physical properties test of the preparation included organoleptic, homogeinity, viscosity, pH measurement,

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spreadability, and adhesion test. Organoleptic tests were conducted by observing the tapak liman leaf extract gel based on shape, color, texture, and odor [14]. Homogeneity test was carried out by applying the gel to a glass and observing the presence of coarse grains on the glass [15].

Meanwhile, viscosity test was performed using the Rheosys Merlin VR using a 23 rpm spindle. The data obtained were rheograms and viscosity values [16]. The pH measurement started with calibration using standard solutions of pH 7 and 4. An electrode was inserted into the gel until a constant pH value was obtained [17]. The good pH value was in the range of 4.5-6.5 [18]. Spreadability test was conducted with a sample of 1.0 grams placed in between two glass plates after 1 minute. The upper plate was weighed. Then the sample given an additional weight of 150 grams for 1 minute and the average of the four sides diameter was measured. Calculation of gel spreadability using the Formula 1 [19]:

$$S = m\,x\,\frac{l}{t} \ldots\ldots\ldots(1)$$

in which S is the spreadability of the gel (g.cm/sec), m is the weight (150 gram + the upper plate weight), l is the spreading diameter of the gel (cm) after 60 seconds (t).

An adhesion test was conducted using 0.25 grams of gel samples. The sample was placed on a glass object weighed and covered with another. Subsequently, a load of 1 kg was applied and left for 5 minutes. The object glass was placed on the tool after lifting the load [20]. A total of 80 grams was added to the tool to record the time until the object glass was released. The requirement for good adhesion was more than 4 seconds [21].

Data Analysis

The results of the physical evaluation of the gel were analyzed using statistical products and services solutions (SPSS) software. The testing process started with determining normality using the Kolmogorov-Smirnov method and assessing homogeneity through the Levene test. The analysis continued using the One-way Analysis of Variance (ANOVA) method to observe differences between formulas when the data were normal and uniform ($p>0.05$). In contrast, Kurskal Wallis nonparametric test was used when not normally distributed or uniform. The data were reported to be significant when p-value <0.05.

Results and Discussion

Organoleptic, water content, and total ash content

The organoleptic test was carried out to determine the suitability of tapak liman leaf ethanol extract regarding appearance, odor, color, and taste. The results were presented in Table 2, and accordance with the Certificate of Analysis (CoA) of the tapak liman leaf extract. The extract had a moisture content of 6.4%. The value was consistent with the standard in the Indonesian Herbal Pharmacopoeia which was less than 12%. High water content can cause fungi or mold to grow in the extract, as a result, reducing its quality and its biological effectiveness [22], [23]. The results of total ash content of the extract were in line with Indonesian Herbal Pharmacopoeia standard, which reached 7.8% and did not exceed 8.9%. Hence, the extraction method used was consistent with existing standards [24].

Table 2. Organoleptic test results of tapak liman leaf ethanol extract

Parameter	Results
Appearance	Thick Extract
Color	Blackish-green
Odor	Typical
Taste	Bland

Phytochemical screening results

Phytochemical screening was conducted to confirm the presence of flavonoids, saponins, and tannins. The screening results showed that tapak liman leaf ethanol extract contained all three compounds, as presented in Table 3. Based on these results, it can be concluded that the tapak liman leaf extract contains flavonoids, saponins, and tannins, so it had the potential to have antibacterial activity. The occurrence of color changes, the formation of foam and sediment were caused by the reaction between the metabolite compounds contained in the extract and the reagents used. Flavonoid compound is one type of secondary metabolite found in plants, has various pharmacological effects, including antibacterial activity. The hydroxyl group on the C ring in the flavonoid structure allows the formation of a complex with proteins in bacteria, which can damage the bacterial membrane. The test produced positive result containing flavonoids in the form of orange ring formation after administration of Mg powder and concentrated HCl

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[25]. Saponin is a natural surfactant that can form stable foam when stirred with water [26]. The results of the saponin test showed positive results based on the formation of foam that remained stable for a period of 10 minutes (Table 3). Saponin, as an antibacterial, disrupt the surface tension of the cell wall, so that antibacterial substances can more easily enter the cell. Therefore, metabolism will be disrupted and bacteria will die [13]. Tannin is a phenolic compound that has the ability to interact and bind with other organic compounds containing amino acids and alkaloids [26]. Safera [27] explained that tannin can interfere with the peptidoglycan synthesis process. As a result, the formation of the cell wall becomes imperfect, bacterial cell lysis occurs through osmotic pressure or physical pressure, and ultimately the bacteria die. The tannin test on the tapak liman leaf extract showed positive results with the appearance of a blackish green color when the extract was reacted with 1% $FeCl_3$, Table 3.

Table 3. Phytochemical screening results of tapak liman leaf ethanol extract

Compound	Farmakope Herbal Indonesia Standard	Results
Flavonoids	Orange-yellow	Orange-yellow (+)
Saponins	Stable foam	Stable foam (+)
Tannins	Blackish-green	Blackish-green (+)

Physical evaluation of tapak liman leaf ethanol extract gel preparation

Organoleptic evaluation of the gel was carried out to examine the consistency, color and odor, as reported in Table 4. Based on the observations, variation concentration of HPMC and propylene glycol produced a liquid-to-thick consistency of tapak liman leaf ethanol extract gel. This was because the greater the concentration of HPMC, the thicker gel produced. The action mechanism of HPMC was to absorb and retain water to form a thick liquid mass. The higher the concentration of HPMC, the more liquid was retained and bound [28]. However, propylene glycol decreased viscosity of gel forming hydrogen bonds with water and causing the network to weaken [29], [30], [31]. The color produced in the three gel formulas of tapak liman leaf ethanol extract were clear, because the concentration of the extract used were relatively small and the formulas did not produce a distinctive odor.

Table 4. Organoleptic test results of tapak liman leaf ethanol extract gel

Parameter	Organoleptic		
	F1	F2	F3
Consistency	liquid	Slightly thick	Thick
Color	Clear	Clear	Clear
Odor	odorless	odorless	odorless

Based on its pH value (Table 5), this gel had a suitable pH, since the pH of the gel should be 4.5-6.5 (Shu, 2013), not too acidic which can cause skin irritation, and not too alkaline which can result in dry skin [32]. Based on the results, it was known that the variation in concentration of HPMC and propylene glycol did not affect the resulting pH value ($p>0.05$). These results were in accordance with research by Hidayah [7] which stated that differences in HPMC concentrations did not affect the pH value of the gel obtained.

The viscosity value described the resistance of the gel to flow. Drugs are more difficult to release from the base when the gel has a higher viscosity because it reduces diffusion [33]. However, low viscosity reduces the contact time of gel with the skin and its therapeutic effectiveness. A good gel has a viscosity 2,000-4,000 cps [19], [34] and only F3 was in the required range (Table 5). The higher the concentration of HPMC used, the viscosity significantly increased ($p <0.05$). HPMC is a cellulose derivative which when dispersed in water, polymer molecules entered the cavities in water molecules, causing a swelling process. This caused hydrogen bonds between the hydroxyl groups of the polymer and water. The higher the concentration of HPMC, the more hydroxyl groups bound to water, forming a semi-solid mass and increasing viscosity [28], [17]. In contrast, propylene glycol reduced viscosity because it weakened the strength of the polymer structure due to hydrogen bonds between propylene glycol and the gelling agent. This meant that as the concentration of propylene glycol increased, the viscosity decreased [29], [30], [31]. The three formulas demonstrated the non-Newtonian flow of the pseudoplastic type at 25°C. This type of gel has the advantage of being thick when stored, and it is easier to remove from the container since the viscosity is lower [35].

The spreadability test determines the ability of gel preparation to spread on the surface of the skin when applied. The requirement for a good spreadability diameter of the gel was 5-7 cm [19], and after using Equation 1, the value ranges from 17.044-23.861 g.cm/sec [36]. Based on the results, only F2 and F3 met the quality of good spreadability (Table 5).

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The data of the spreadability value between formulas differed significantly ($p<0.05$). The higher the propylene glycol added to the formula, the higher the spreadability. This was because propylene glycol could bind with water, thus maintaining the presence of water in the gel. In contrast, as explained above, increasing the amount of HPMC increased the viscosity of the gel, as a result the spreadability decreased [37].

Meanwhile, the adhesion test determines the ability of the gel to maintain contact with the skin surface, and an ideal adhesion is not less than 4 seconds. Prolonged contact of the gel with the skin enhances the absorption process and effectiveness of the active substance. As a result, the absorption process of active substances through the skin will also be more optimal [38]. The results of the adhesion test can be found in Table 5. As seen in Table 5, it was known that the higher the HPMC content in each formula, the longer the gel adhered to the skin surface. This phenomenon was caused by the ability of HPMC to form colloids with the addition of hot water [10]. Colloid formation occurred because the dispersed substance absorbed the dispersing medium, resulting in it becoming thicker and stickier. Colloid formation increased as HPMC concentration increased, increasing the adhesion of the gel to the skin.

Based on the analysis results, it was known that increasing the concentration of HPMC resulted in increased viscosity and adhesiveness, and decreased the pH value and spreadability with a significant difference ($p <0.05$). In terms of viscosity, only F3 met the target. Based on the data from the gel spreadability test results of the three formulas, only F2 and F3 met the gel spreadability requirements. In addition, only F3 met the requirements for good gel adhesion. High adhesiveness of the gel was expected to provide optimal therapeutic effects [39]. Based on the results of the pH test, the three formulas had pH values that met the requirements according to the skin pH range of 4.5-6.5. Based on all the evaluation results of the tapak liman leaf extract gel, it was concluded that F3 with an HPMC concentration of 3% and propylene glycol 14% was the best formula that met the requirements for good gel physical properties.

Table 5. Physical properties of tapak liman leaf ethanol extract gel

Parameter		Formula		
		F1	F2	F3
pH		5.86±0.26	5.60±0.07	5.53±0.08
Viscosity (cps)		149.42±42.71	1,203.44±154.18	2,283.10±530.29
Adhesiveness (sec)		1.59±0.57	2.08±0.51	7.77±1.14
Spreadability	Diameter (cm)	8.09±0.13	6.81±0.19	23.22±0.64
	Spreadability (g.cm/sec)	41.37±0.47	23.22±0.64	18.81±0.26

Conclusion

Based on the results, the greater concentration of HPMC resulted in increased viscosity and gel adhesion. However, spreadability decreased with increasing viscosity of the gel. The formula of tapak liman leaf ethanol extract that met the requirements of physical properties was found in F3 with a concentration of 3% HPMC and 14% propylene glycol.

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Declaration

Author contribution : Citra Ariani Edityaningrum proposed the topic and research methodologies, Niken Pratiwi drafted the proposal and performed analysis, and Khairun Nisa presented the data and discussion.

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Ethics Declaration : As the authors, we confirm that this work has been written based on ethical research principles in compliance with our university's regulations and that the necessary permission was obtained from the relevant institution during data collection. We fully support CliPs commitment to upholding high standards of professional conduct and practicing honesty in all academic and professional activities.

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