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Formulation and Physical Evaluation of Papaya Leaf *(Carica papaya L.)* Ethyl Acetate Fraction Cream Preparation as Anti Acne Against *Propionibacterium acne* Bacteria

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Abstract: Acne or acne vulgaris is a disease in the form of inflammation of multiple sebaceous glands caused by the bacteria Propionibacterium acne. Papaya leaves are a plant that can potentially be used as an acne treatment. To determine the antiacne activity of papaya leaf ethyl acetate fraction cream preparations caused by Propionibacterium acne bacteria. The ethyl acetate fraction of papaya leaves are made into a cream preparation with varying concentrations of ten, fifteen, and twenty percent. The results of the cream preparation test met the physical property standards. Still, the viscosity in formulation three did not meet the standards, and formulas two and three did not meet the cream stability test standards. Antibacterial tests show that all formulas have inhibitory power against bacteria. The average inhibition zone results in formula one, formula two, and formula three were 4.99 ± 0.48 mm, 6.85 ± 0.48 mm and 10.12 ± 1.42 mm. Formula One papaya leaf fraction cream fulfills all the physical characteristics of the preparation. All papaya leaf ethyl acetate fraction cream preparations are antibacterial against Propionibacterium acne. So, research can be developed using the ethyl acetate fraction of papaya leaves in various preparations, and activity tests against other bacteria can be carried out.

Keywords: Antibacterial; *Carica Papaya L.*;*Propionibacterium acne.*

Introduction

The skin is the outermost organ that covers the human body. The skin's outer surface has pores (cavities) through which sweat comes out [1]. The skin functions as a body protector. Most people want white, healthy, clean, neat facial skin, especially women. However, many do not pay attention to skin type during treatment, causing new problems such as acne and dry skin [2]. Acne is one of the skin diseases that can reduce a person's self-confidence. Acne or *acne vulgaris* is a disease in the form of inflammation of several glands *Sebaceous Multiple* caused by bacteria *Propionibacterium acne*, *Staphylococcus epidermidis*, *and Staphylococcus aureus*, with blockage and buildup of keratinized material. The main causative bacteria in acne is *Propionibacterium acne* [3].

Propionibacterium acne is a gram-positive and aerobic bacteria, constituting the normal flora of the gland *Sebaceous* [4]. These bacteria can be non-pathogenic under normal conditions, but a change in skin condition can cause them to become invasive. Secretion of sweat glands and glands *Sebaceous*, which produces water, amino acids, urea, grams, and fatty acids, can be a source of nutrition for bacteria [5]. Role *Propionibacterium acne* In the pathogenesis of acne, triglycerides are prevented before free fatty acids that cause colonization by bacteria and inflammation. Antibodies to bacterial cell wall antigens increase inflammatory receptors through complement activity [6].

Currently, research on plants' antibacterial potential is being widely developed. Papaya leaves are one type of plant that is productive as an antibacterial. Based on research, Fitria (2015) showed that 70% ethanol extract of papaya leaves (*Carica papaya L*) has antibacterial activity with concentrations of 5.10 and 20% with inhibitory power of 13, 15, and 19 mm. Based on research, Hadizah (2022) proved that ethyl acetate fractions with concentrations of 10, 15, and 20% yielded an inhibitory power of 14.7, 16.4, and 18.7 mm. Papaya leaves contain alkaloids, flavonoids, tannins, and glycosides [9]. The antibacterial content (papain and carpain alkaloids) found in papaya leaves can be used as an antiacne in cosmetic products and is bacteriostatic [10]. The mechanism of alkaloid compounds as antibacterial is to inhibit the preparation of peptidoglycan in bacterial cells so that the cell wall layer is not formed intact and causes cell death in bacteria [11].

Based on these studies, developing a preparation that is easy to apply for antiacne treatment is necessary. Antiacne preparations such as gels, lotions, creams, and ointments are widely circulated in the market. In this study, a formulation of the cream preparation of ethyl acetate fraction of papaya leaves was carried out. Cream preparations are chosen because they provide moisture and have a longer contact time with the skin, so their antibacterial compounds can provide good activity [12].

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Cream formulations are preferred because the cream is more evenly distributed, easier to clean, and less sticky, especially M/A (oil in water) type creams [13]. Cream preparations are often used as water-in-oil or oil-in-water emulsions, especially in cosmetics [14]. Cream can provide shiny, oily, moisturizing, easy to apply evenly, clean, rinse with water, and easily absorbed into the skin [15].

Research Methods

Plant Determination and Sample Preparation

Papaya leaf plant (determined) at the Laboratory of Ahmad Dahlan University Yogyakarta. California papaya leaves were obtained from Banjareja Village, Puring District, Kebumen Regency. Samples were dried in sunlight using a black cloth. The dry silica obtained is mashed with a blender and sifted using a mesh 40 into powder simplisia. (Laily, 2015).

Papaya Leaf Extract

Papaya leaf extraction (*Carica papaya L*) uses the maceration method. Dry powder is soaked for three days using 70% ethanol solvent and stirred every 24 hours at room temperature. Next, the resulting filtrate is evaporated using a *water bath.* Calculate the extract yield or comparison of the dry weight of the extract with the amount of raw material obtained [8].

$$Yield(\%) = \frac{final\ extract\ weight\ (g)}{amount\ of\ dried\ simplicia\ (g)} \text{ x } 100\%$$

Condensed ethanol extract of fractionated papaya leaves of as much as 10 grams dissolved using 70% ethanol as much as 50 ml, then put into a separate funnel. After that, put 50 ml of n-hexane into the split funnel and shake gently for 15 minutes until mixed until it separates into two layers: the top layer (n-hexane) and the bottom layer (ethanol) is taken n-hexane layer. The next fractionation uses the n-hexan fraction of papaya leaf ethanol residue using the same procedure but with an ethyl acetate solvent. Fractionation is repeated up to 3 times. [8].

Phytochemical Screening Test

The phytochemical screening test method is carried out by colour test using various reagents to identify secondary metabolite compounds in the form of alkaloids in the extract [17].

Thin-Layer Chromatographic Identification

Silica gel GF254 with a size of 10 x 2 cm silica plate in the oven for 10 minutes at a temperature of 100 °C. Ammonia (8.5:1.5) is saturated using methanol eluents. The ethyl acetate fraction is tolerated on a silica plate using capillary pipes placed on the *Chamber*. Wait until the eluent rises to the top of the silica plate. The eluted plate is observed in visible light using 365 nm UV light. In visible light, alkaloids are indicated by orange, bluish-purple, and brown patches. Mark the intended point and calculate the Rf value. Sprayed with Dragendorff to clarify the colour [18].

Formulation

Table 1. Cream Formulation Ethyl Acetate Fraction Papaya leaves 10%,15%,20%

Materials	Concentration			Negative Control
	FI	FII	F III	
Papaya leaf fraction	10 g	15 g	20 g	-
Stearate acid	12 g	12 g	12 g	12 g
TEA	3 g	3 g	3 g	3 g
Cetyl alcohol	2 g	2 g	2 g	2 g
Spritz	8 g	8 g	8 g	8 g
Propylene glycol	0.05 g	0.05 g	0.05 g	0.05 g
Methyl paraben	0.2 g	0.2 g	0.2 g	0.2 g
Aquades	Ad 100	Ad 100	Ad 100	Ad 100

Physical evaluation of papaya leaf ethyl acetate fraction cream preparations

Organoleptic test

Organoleptic tests of cream preparations are carried out visually to see the physical appearance of the preparation, as well as the shape, colour, and smell of the preparation made, and to determine the quality of the cream preparation.

pH Test

This test is carried out by inserting a pH meter into the formulation and observing the results of pH meter measurements up to 3 replications [19].

Homogeneity test

Apply 0.1g of the cream preparation evenly and place it on the glass object. Observe that if there are no details, then the cream preparation is said to be homogeneous [20].

Dispersion test

The cream dispersion test was carried out with a cream preparation weighing as much as 0.5 g, placed on top of Object Glass, and then closed. Then, on top of it, a weight of 50 grams is set for 1 minute. The load is then added 100 g again and let stand for 1 minute. Do the same so that the load becomes 150 g, 200 g, and 250 g. Measure the diameter on all four sides each time a load is added, observe and record, and test up to 3 replications [21].

Adhesion test

Test the adhesion of the cream preparation, weigh 0.25 g, and then place it on two glass objects. Then, given a load of 1 kg for 5 minutes. After that,

the load is taken and released. Record the release time. Repeat up to 3 replications [22].

Viscosity test

The viscosity test is measured by *Brookfield viscometer* by pairing *Spindle* No. 7 contained in the tool, then measuring the tool at a speed of 50 rpm. The measurement results are recorded viscosity value (n) in centipoise (cps) [23].

Cream type test

Coloring method. The cream is applied to the glass of the object, then dipped with methylene blue, and the changes that occur are observed with a microscope. If *methylene blue* spreads evenly, then the type of cream is M/A, and if methylene blue is separated, then the cream is A/M (Husni *et al*., 2019).
Test the stability of the cream preparation.

The stability test of the cream is carried out using the cycling test method. The preparation of ethyl acetate fraction cream papaya leaves is stored at 4 ° C for 24 hours using a refrigerator, then removed and held at 40 ° C using an oven for 24 hours; the process is calculated as one cycle. The *cycling test was* carried out for six cycles, and each cycle was observed to have a stable separation or no results, so it can be said that the preparation is sound [25].

Antibacterial Activity Testing

A test of the antibacterial activity of papaya leaf ethyl acetate fraction antiacne cream preparation (Carica papaya L) was carried out using the well diffusion method. Tests were carried out on formulations 1, 2 and 3. Culture *Propionibacterium acne* with MHA media leaves to dry completely. Punch holes in the substrate with a pipette *Pasteur* positive control (clindamycin) and negative control (cream base) into the well hole using a metal spatel. Media that has been incubated at 37°C for 24 hours. Repeated for five replications. Upon completion, it is labelled with it. Then, the clear zone formed, which showed the growth of bacteria using a caliper. The inhibitory zone is measured in mm [26].

Result and Discussions

His determination resulted in the papaya leaves used, which came from Banjareja Village, Puring District, and the scientific name *Carica papaya* L.

The extraction results from 700 mg of papaya leaf powder extracted using 7 liters of 70% ethanol obtained a thick extract of 21.666 grams. The yield of ethyl acetate fraction of papaya leaves is 44.635. The organoleptic test results of papaya leaf extract have a characteristic odour, blackish-green colour, kenta shape, and bitter taste. The water content of papaya leaf extract is 1,612. The phytochemical screening results of extracts and fractions positively contain alkaloid compounds. The KLT test result of the ethyl acetate fraction of papaya leaves shows an Rf value of 0.6.25. Organoleptic results in formulations 1, 2, and 3 are light yellowish, dark, and blackish green.

Physical evaluation of cream preparations

Table 2. Organoleptic test results

Formulation	Result		
	Smell	Colour	Shape
1	Typical Extracts	Light yellowish green	Thick
2	Typical Extracts	Dark green	Thick
3	Typical Extracts	Blackish green	Thick

Organoleptic examination is an important parameter because it affects a person's level of interest. The results of an organoleptic examination of cream preparations showed that there were several colour differences in formulations 1, 2, and 3, namely Formulation 1 was yellowish-green, formulation 2 was solid green, and Formulation three was blackish-green with a characteristic odour of ethyl acetate fraction of papaya leaves. In terms of shape, each formula experienced differences in viscosity with the addition of papaya leaf fraction concentration.

Table 3. pH test

Formulation	Result			Average ±SD
	R1	R2	R3	
1	6.0	6.4	6.9	6.4±0.36
2	6.2	6.5	6.3	6.3±0.12
3	5.5	5.7	5.8	5.6±0.12

pH measurement is one of the parameters used to determine the level of acidity or alkalinity of the cream preparation. According to Murdiana (2022), the average pH value in the cream preparation is 4.5 to 6.5 according to the pH of human skin. pH testing of the preparation was carried out with as many as three replicates and ions, and the remaining sample was still within the predetermined standard range of 6. The pH value of the cream preparation produced affects the variation in the concentration of ethyl acetate fraction of papaya leaves. Still, all formulas have pH values that meet the pH value requirements in human skin. The evaluation results show that all formulas meet the pH value standard. Formula 1 has a better pH value, while Formula 3 has the lowest pH range.

Table 4. Homogeneity tests

Formulation	Result
1	Homogeneous, no coarse grain
2	Homogeneous, no coarse grain
3	Homogeneous, no coarse grain

The homogeneity test shows that each formula is homogeneous due to the absence of different particles and has an even color. Homogeneous cream preparations are of good quality because all ingredients and active substances are mixed evenly and evenly distributed when applied to the skin, and there are no

solid parts [28]. The homogeneity test is carried out to determine the mixture of ingredients in the formulation ideally so that it is expected to have a similar effect on each preparation use [29].

Table 5. Viscosity test results

Formulation	Result			Average±SD
	R1	R2	R3	
1	7.040	7.280	7.680	7.333±0.26
2	4.300	4.500	4.600	4.466±0.12
3	3.040	3.200	3.520	3.253±0.19

A viscosity test is a parameter carried out to determine the concentration or viscosity of the preparation, which will affect the ease of application of the preparation [30]. The higher the concentration of papaya leaf fraction, the more it reduces the viscosity of the preparation so that the resulting cream is not too thick. The viscosity of the cream preparation affects the adhesion produced, affecting the duration of contact of the cream with the skin so that the desired therapeutic effect can be achieved (Forestryana, 2020). The viscosity measurement results show that all formulas meet the criteria for cream preparations. The standard viscosity of cream preparations is 2,000-50,000 cp [27]. The evaluation results of Formula 1, formulation 2, and Formulation 3 meet the viscosity standards of all formulas, showing that Formula 1 has the best viscosity range. Suitable viscosity will have a high value because the higher the viscosity of a material, the more complex the movement of particles will be, making the material more stable.

Table 6. Stickiness results

Formulation	Result			Average±SD (seconds)
	R1	R2	R3	
1	4.37	4.45	4.49	4.56±0.04
2	4.02	4.08	4.12	4.40±0.04
3	1.45	1.58	1.25	1.42±0.13

Adhesion tests are carried out to determine the length of time the cream contacts with the skin until the expected therapeutic effect can be achieved. A good cream preparation has a stickiness of more than 4 seconds. Based on the adhesion test results, formulation three cream preparations have no good adhesion, while formulations 1 and 2 have good adhesion. The difference in the concentration of ethyl acetate fraction of papaya leaves affects the adhesion obtained. The higher the concentration of ethyl acetate fraction of papaya leaves, the lower the adhesion obtained. The evaluation results of formulas 1 and 2 meet the stickiness standard of more than 4 seconds.

Table 7. Dispersion test results

Formulation	Result			Average±SD
	R1	R2	R3	
1	5.4	5.2	5.7	5.4±0.20
2	6.4	6.2	5.8	6.1±0.24
3	6.7	6.4	6.2	6.4±0.20

The dispersion test aims to determine the speed of the cream's spread on the skin when applied so that its reach is known to provide therapeutic effects. The difference in concentration affects the dispersion power produced. Good dispersion has a spreading requirement of 5 to 7, according to Fabiana (2019). The higher the addition of the ethyl acetate fraction of papaya leaves, the greater the viscosity and adhesion of the cream, resulting in more excellent dispersion. The load given will gradually provide better dispersion so that drug penetration will be more optimal. The spreadability test results have met the requirements of good spreadability. Formula 3 shows the best dispersion. Formula 3 has a higher dispersion power than other formulas due to the concentration of ethyl acetate fraction of papaya leaves added to a higher base.

Table 8. cream type test results

Formulation	Reagent	Result	Type
1	Dripped *methylene blue*	Undispersed	A/M
2	Dripped *methylene blue*	Undispersed	A/M
3	Dripped *methylene blue*	Undispersed	A/M

The cream type test is carried out to determine the type of cream contained in the preparation. In this study, the method is colouring with *methylene blue* on cream preparations. The results that after being monitored using a microscope, the three formulations of antiacne creams are included in the type of cream A / M. This is based on the results of microscope observations using a magnification ratio of 40 times to 60 times *methylene blue* does not mix with formulations.

Cream preparations that have been tested for physical evaluation are then carried out stability tests using *the cycling test* method to determine the stability of the preparation during the storage process. Observations were made by storing the cream preparation at 4°C for 24 hours and then transferring it at 40°C in the oven for 24 hours. The treatment is one cycle, and the cycle carried out in the stability test is six cycles to clarify the changes that occur. The examination results show that formulation 1 is stable during storage for six cycles. In contrast, formulations 2 and 3 undergo a separation phase due to the influence of temperature changes after storage for six cycles. This happens because formulas two and three contain more ethyl acetate fraction of papaya leaves so that synthesis (breakdown of the cream phase) can occur, which is influenced by temperature. Based on the results of physical evaluation tests, formula one preparations are the best formula where formula 1 meets all suitable cream parameters. While Formulation 2 only meets four kinds of parameters, and Formulation 3 only meets three parameters.

Table 9. Results Cream stability test

Formulation	Result					
	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle5	Cycle 6
1	None	None	None	None	None	None
2	exist	exist	exist	exist	exist	exist
3	exist	exist	exist	exist	exist	exist

Table 10. Antibacterial Activity Test Results

Treatment	Diameter of the Inhibitory Zone					Average	Category
	R1	R2	R3	R4	R5		
Formula 1	4.45	4.85	4.85	4.9	5.9	4.99±0.483	Weak
Formula 2	6.8	6.15	6.55	7.25	7.5	6.85±0.482	Keep
Formula 3	8.55	9.6	9.95	11.1	11.4	10.12±1.423	Keep
Control-	0	0	0	0	0	0±0	None
Controls +	15.75	17.2	18	18.7	19	17.73±1.168	Strong

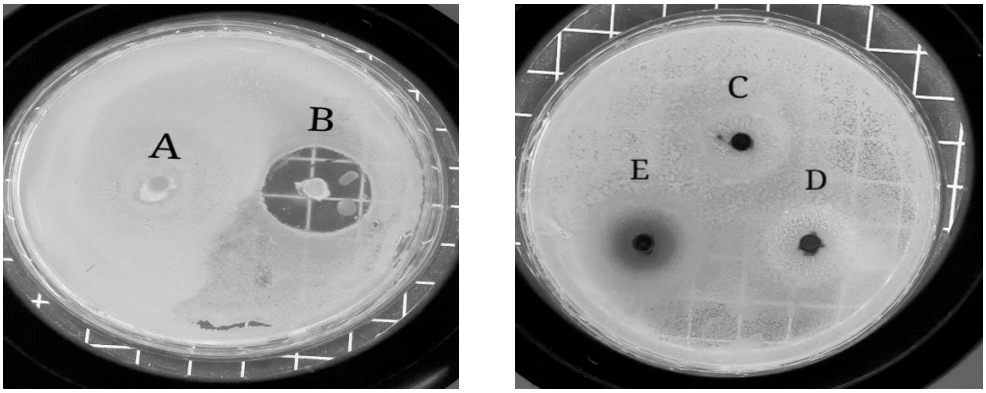

Figure 1. Test results of antibacterial activity of *Propionibacterium acne*
Description: A: Negative Control; B: Positive Control; C: Formulation 1; D: Formulation 2; E: Formulation 3.

The evaluation of the diameter of the inhibitory zone shows that the cream formula of the ethyl acetate fraction of papaya leaves can inhibit antibacterial activity. The results of antibacterial activity testing on negative controls did not show the presence of an inhibitory zone. The positive control showed antibacterial solid activity with an average diameter of 20.32±1.16 mm. The antibacterial activity of formula 1 has an intermediate inhibitory zone of 4.99±0.48 mm, which is included in the weak category. In contrast, formulations 2 and 3 have an average inhibitory zone of 6.19±0.48 mm and 9.45±1.42 mm, which is included in the medium category.

Conclusion

The ethyl acetate fraction of papaya leaves (*Carica papaya L*) can be made into cream preparations, meeting all good physical characteristics in formulation 1 with a concentration of 10%. Antibacterial activity against *Propionibacterium acne bacteria* with moderate inhibitory power in formulation two and formulation three, which have an average diameter of 6.85±0.48 mm and 10.12±1.42 mm. Hope for future research to develop research using ethyl acetate fraction of papaya leaves into various preparations and conduct activity tests on other bacteria. Further testing is necessary by taking antibacterial compounds in papaya leaves that are productive and strong.

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