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The Effect of Green Betel Leaves Extract Concentration in Hydrogel Acne Patch from Breadfruit Starch on the Antibacterial Activity of *S. Aureus* and *P. Acnes*

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Abstract. Betel leaf (*Piper betle* L.) is a natural antibacterial source, the leaves contain phenolic compounds. Acne patch is a patch that covers acne and prevents bacterial contamination. The acne patch in this study was made from natural breadfruit starch polymer (*Artocarpus altilis*) combined with betel leaves. The purpose of this study is to determine the physical quality and the effect of green betel leaf extract concentration acnes in hydrogel acne patch preparations made from breadfruit starch on the antibacterial activity of Staphylococcus aureus and Propionibacterium. The antibacterial test method used in this study is the disc diffusion method. The results of the physical quality test of all acne patch formulas meet the requirements. The strongest antibacterial activity was found in the formula containing 125% extract, with an inhibition zone of 17 mm against S. aureus and 32,02 mm against P. acnes. The data analysis using One Way Anava, the yield of p-value of 0.000 (<0.005), indicating that of the green betel leaf extract concentration variation have an effect on the antibacterial activity against *S. aureus* with a strong category and *P. acnes* with a very strong category. The highest concentration of green betle leaf extract was significantly increase the antibacterian activity of bradfruit acne patch.

1 Introduction

Acne can affect a person's self-confidence as it is directly related to facial appearance but is not dangerous. About 30-50% of people with acne tend to feel inferior due to the appearance of acne which disrupts their appearance. Acne-causing bacteria include *Staphylococcus aureus, Propionibacterium acnes,* and *Staphylococcus epidermidis*. (22,25). One of solution for acne treatment was using antibiotics. However, the use of antibiotics as an acne treatment needs to be reconsidered to reduce the development of antibiotic resistance (15).

Several herbal plants were proven to have antibacterial activity, each containing different compounds and mechanisms of activity (2). Green betel leaf is a plant that has been familiar to us. From ancient times to the present, green betel leaf is still used as a raw material for making medicines because of its benefits for the body. Green betel leaf

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extract contains antiseptic substances that can kill bacteria and fungi and has antioxidant properties (11). Green betel leaf contains several active compounds, such as phenols, saponins, tannins, and flavonoids. These compounds serve as antibacterial. Phenolic compounds and their derivatives can denature bacterial cell proteins. The phenolic compound gives betel a distinctive smell and has a bactericidal property five times stronger than phenolic compounds in other plants (9,20).
Several preparations can be used to treat acne, such as gels, lotions, creams, ointments, and patches. Patch preparation is a form of acne treatment recently developed. Cosmetic patches work by being applied to the skin's surface to deliver active ingredients that benefit the skin, such as reducing acne on the facial skin (1).
Hydrogel acne patches are the most common type of patches used to treat acne because they are waterproof on the surface, protecting acne from secondary infections, absorbing acne fluid, and relatively cheaper to produce compared to microneedle patches (19). The hydrogel composition consists of synthetic polymers containing polyvinyl alcohol and chitosan (7).

Breadfruit (*Artocarpus altilis*) is a well-known plant in Indonesia. This fruit contains various nutrients, including 68% starch, 4% protein, and 1% fat on a dry basis. Carbohydrate polymers that have the potential as raw materials for hydrogels include cellulose, starch, pectin, chitosan, carrageenan, and alginate (8,24). The natural polymer from breadfruit starch can be used in hydrogel production, considering that synthetic polymers were less environmentally friendly due to their difficulty in decomposing. In addition, synthetic polymers will become increasingly scarce over time and relatively high in price.

Based on the background, researcher was interested to formulating hydrogel acne patch from breadfruit starch with variations in green betel leaf ethanol extract concentrations and conducting antibacterial activity tests against S. aureus and P. acnes bacteria.

2 Methods

This research is a quantitative experimental study aimed at determining antibacterial activity through the inhibition zones produced. The inhibition zones against bacteria were analyzed using SPSS statistics to determine the causal relationship or influence between variables (34).

2.1 Tools

The tools that used in this research include glassware, oven, incubator, autoclave, analytical balance, caliper, LAF.

2.2 Materials

The materials used in this research include breadfruit starch, green betel leaf extract, aquadest, 70% ethanol, carbopol, glycerol, Propylene Glycol (PG), Hydroxy Propyl Methyl Cellulose (HPMC), Mueller Hinton Agar (MHA) media, Nutrient Agar (NA) media, Staphylococcus aureus bacteria, Propionibacterium acnes bacteria, blank disk, Clindamycin cream, 96% alcohol, crystal violet stain, safranin stain, iodine solution. The betel leaves that used were obtained from Boyolali and identified at B2TOOT. A total of 10 kg of fresh green betel leaves were sorted, dried, and oven-dried to obtain

betel leaf powder. The betel leaf powder was extracted with 70% ethanol solution by maceration.

The breadfruit starch that used was obtained from Kartasura, Sukoharjo. The peeled breadfruit was blended and sedimented for one day to obtain breadfruit starch sediment.

2.3 Procedure

2.3.1 Formulation

The formulation of the hydrogel acne patch made from breadfruit starch with betel leaf extract was developed using carbopol, HPMC, and breadfruit starch for one day. In this research *Acne Patch* Hydrogel was made in three variation of formula with differences betel leaf extract concentration, and one formula without betel leaf extract as negative control for experimental method.

Table 1. *Acne Patch* Hydrogel Formula (29)

Ingredient	Amount (%)			
	F1	**F2**	**F3**	**F0**
Carbopol	0,75	0,75	0,75	0,75
HPMC	0,55	0,55	0,55	0,55
Breadfruit starch	0,45	0,45	0,45	0,45
Propylene Glycol (PG)	2	2	2	2
glycerol	12,5	12,5	12,5	12,5
Betel leaf extract (BLE)	3,125	6,25	12,5	-
Aqua destilata	Ad 100	Ad 100	Ad 100	Ad 100

Note:
F0= Control patch formula without BLE
F1= Patch formula with 3,125% BLE
F2 = Patch formula with 6,25% BLE
F3 = Patch formula with 12,5% BLE

The procedure to make betel leaf extract *Acne Patch* Hydrogel was by developed HPMC and carbopol with aqua destilata into a homogeneous polymer mixture and then added the propylene glycol, and glycerol in beaker glass. The addition was done on a hot plate while stirring with a magnetic stirrer, and then after base of hydrogel was mix well, added the betel leaf extract after obtaining a homogeneous mixture then pour in petri dish as patch mold dried by oven.

2.3.2 Quality test

The physical quality test on patch formula parameters carried out include organoleptic tests, pH tests, weight uniformity tests, folding resistance tests, thickness uniformity tests, drying shrinkage, water content tests, and moisture absorption tests. Organoleptic testing is carrying out visual observations regarding the color, smell and texture of the patch (14). pH test was carried out by dissolving the patch in 10 ml of CO_2

free distilled water and then leaving it for 1 hour. This test uses a pH meter. The weight uniformity test was carried out by weighing 4 patches randomly then calculating the average weight and determining the SD and CV values by Nitiariksa and Sukmawati, 2021. Thickness uniformity testing was carried out by measuring 4 patches taken randomly using a caliper. Then the average thickness is calculated. Folding resistance testing is carried out by manually folding the patch in the same place until it breaks. The folding resistance value of a patch is expressed based on the number of folds before breaking (6).

Drying loss testing is carried out by weighing the patch preparation then placing it in a desiccator containing calcium chloride at room temperature for 24 hours, then removing it and weighing it again until it reaches a constant weight, to determine drying loss (17). Water content testing is carried out by weighing the patch preparation and then placing it in the oven for 1 hour at a temperature of 105 ± 5℃. Remove and cool using a desiccator, after cooling, weigh again. The treatment was carried out repeatedly until a constant weight was obtained to determine the water content (4). Moisture absorption testing was carried out by weighing the patch preparation and then storing it in a desiccator at room temperature for 24 hours. The patch preparation was then exposed to a temperature of 40℃ in a climatic chamber for 24 hours and weighed again (10).

2.3.2 Antibacterial activity test

Antibacterial activity testing was carried out aseptically using the disk diffusion method, namely using a blank disk soaked in the hydrogel base of each formula. Staphylococcus aureus and Propionibacterium acnes bacterial suspensions were spread using a sterile cotton swab (30).

3 Results and Discussion

3.1 The Quality test result

The results of the physical quality test of the breadfruit starch hydrogel acne patch are presented in the following table:

Table 2. Organoleptic result

Formula	Color	Aroma	Texture
F0	white	Unscented	Smooth and elastic
F1	Brown	Aroma of betel leaves	Smooth and elastic
F2	Brown	Aroma of betel leaves	Smooth and elastic
F3	Brown	Aroma of betel leaves	Smooth and elastic

Table 3. pH result

Formula	x pH ± SD	Standards of pH [12]	Interpretation
F0	5,79 ± 0,005774	5-6,5	Qualify
F1	6,14 ± 0,015275		Qualify
F2	6,06 ± 0,01		Qualify
F3	6,16 ± 0,01		Qualify

Table 4. Weight Uniformity Result

Formula	x Weight Uniformity ± SD	%CV	Standards of Weight Uniformity	Interpretation
F0	0,1 ± 0,000624	1%	SD ≤ 0,05 dan CV ≤ 5%	Qualify
F1	0,11 ± 0,001861	2%		Qualify
F2	0,12 ± 0,004403	3%		Qualify
F3	0,13 ± 0,005074	4%		Qualify

Table 5. Thickness Uniformity

Formula	x Thickness Uniformity ± SD	Standards of Thickness Uniformity [14]	Interpretation
F0	0,72 ± 0,05	≤1mm	Qualify
F1	0,8 ± 0,08		Qualify
F2	0,77 ± 0,09		Qualify
F3	0,78 ± 0,05		Qualify

Table 6. Folding Resistance

Formula	x Folding Resistance ± SD	Standards of Folding Resistance [28]	Interpretation
F0	208 times ± 0,0000	≥ 200 kali	Qualify
F1	211 times ± 0,0000		Qualify
F2	209 times ± 0,0000		Qualify
F3	212 times ± 0,0000		Qualify

Table 7. Drying Shrinkage

Formula	x Drying Shrinkage ± SD	Standards of Drying Shrinkage	Interpretation
F0	4,72 ± 0,65	≤ 9,29%	Qualify
F1	5,68 ± 0,34		Qualify
F2	6,07 ± 0,40		Qualify
F3	7,16 ± 1,61		Qualify

Table 8. Water Content

Formula	Water content ± SD	Standards of Water content [4]	Interpretation
F0	1,22 ± 0,05	≤ 10%	Qualify
F1	4,56 ± 0,44		Qualify
F2	5,56 ± 1,05		Qualify
F3	6,23 ± 1,69		Qualify

Table 9. Moisture Absorption Test Results

Formula	Moisture Absorption ± SD	Standards of Moisture Absorption [18]	Interpretation
F0	4,73 ± 0,20	3,52-9,79%.	Qualify
F1	7,76 ± 0,67		Qualify
F2	8,79 ± 1,06		Qualify
F3	9,21 ± 0,98		Qualify

The organoleptic test results for formula without extract (F0) are white, odorless, and have a smooth and elastic texture. All formula was having brown color. These three formulas have a distinctive betel aroma with a smooth, elastic texture. The texture of the oil produced on the patch is due to the essential oil content in green betel leaf extract. Betel leaves contain 55% essential oil from the group of phenolic compounds and several derivatives such as cavibetol and chavicol (31). The results of the odor in formulas F1, F2, F3 was a distinctive smell of betel because betel leaves contain the compound chavicol. The chavicol compound is the most abundant compound contained in betel leaf essential oil which gives betel leaves a distinctive odor (32).

The results of pH testing on formulas F0, F1, F2, and F3 for acne patch hydrogel breadfruit preparations with varying concentrations of betel leaf extract produced a pH in each formula, namely 5.79; 6.14; 6.06; and 6.16. The pH results in the formula are influenced by the storage time of the betel leaf extract so that the pH between formulas is less stable. All four patch formulas were a good pH that was in 5-6.5 [12]. The results of weight uniformity in all formulas meet the requirements, namely SD ≤ 0.05 and CV ≤ 5% (29).

The thickness of the patch is tested with a caliper. The thickness of the patch is influenced by the technique of pouring the hydrogel patch base into the mold and is also influenced by the weight of the patch formed from each formula. A good patch thickness is less than 1 mm (14). The fold resistance test is a test that aims to determine the elasticity and flexibility of a patch by folding it at the same angle (16). The folding resistance test results of all formulas met the requirements, namely ≥ 200 times (29). The drying shrinkage, water content and moisture absorption test results for all formulas meet the requirements.

Drying shrinkage testing was carried out with the aim of checking the amount of water loss in the patch preparation, if the patch is too dry it can cause brittleness and the patch will break easily (18). Based on the study of Shivaraaj *et al*. (2010) the water content test was carried out to evaluate the water content in the patch preparation. If the water content is too high, it can cause microorganism contamination so that the stability of the patch formula will be reduced. The patch's moisture absorption capacity test was carried out to determine the patch's ability to absorb moisture when applied to the skin. The patch's good moisture absorption capacity is 3.52-9.79%. Patch preparations that have good moisture absorption can influence the elasticity of the resulting patch (33).

3.2 The Antibacterial Activity

The results of testing the antibacterial activity of the breadfruit starch hydrogel acne patch are presented in the following table:

Table 10. Antibacterial activity on S. Aureus

Formula	Antibacterial activity on *S. Aureus*		Antibacterial activity on *P. Acnes*	
	Inhibition zone (mm) ± SD	**Activity**	**Inhibition zone ± SD**	**Activity**
Positive Control	21,76 [a] ± 1,81	Very strong	31,82[a] ±1,29	Very strong
F0	0 [b] ± 0	No antibacterial activity	0[b]	No antibacterial activity
F1	10,8 [c] ± 0,8	Moderate	22,74[c] ±0,90	Very strong
F2	13,76 [d] ± 0,77	Strong	27,19[d] ±1,29	Very strong
F3	17 [e] ± 0,5	Strong	32,02[a] ±1,14	Very strong

Note:
SD: Standard Deviation. Different letters in each form indicate significant differences between groups. a = Positive control (Clindamycin) is significantly different from all formulas and negative control (F0) with a sig value. 1.00 > 0.05; b = Negative control, namely the formula without extract, is significantly different from F1, F2, and F3 as well as the positive control (Clindamycin) with a sig value. 1.00 > 0.05; c = Formula 1, namely the formula with 3.125% betel leaf extract, which is significantly different from F2, F3, negative control (F0), and positive control (Clindamycin) with a sig value. 1.00 > 0.05; d = Formula 2, namely the formula with 6.25% betel leaf extract, is significantly different from F1, F3, negative control (F0), and positive control (Clindamycin) with a sig value. 1.00 > 0.05; e = Formula 3, namely the formula with 12.5% betel leaf extract, which is significantly different from F1, F2, negative control (F0), and positive control (Clindamycin).

Table 11. Antibacterial activity on *P. Acnes*

Formula	**Inhibition zone ± SD**	**Activity**
Positive Control	31,82[a] ±1,29	Very strong
F0	0[b]	No antibacterial activity
F1	22,74[c] ±0,90	Very strong
F2	27,19[d] ±1,29	Very strong
F3	32,02[a] ±1,14	Very strong

Note:
Different letters indicate significant differences between groups. a = positive control and F3 are in one subset and are significantly different from F0, F1, and F2 with a sig value. 0.819>0.05. b = F0 is significantly different from F1, F2, F3 and the positive control with a sig value. 1,000>0.05. c = F1 is significantly different from F0, F2, F3 and positive control with a sig value. 1,000>0.05. d = F2 is significantly different from F0, F1, F3 and positive control with a sig value. 1,000>0.05.

Antibacterial activity on *S. Aureus* bacteria of patch have very strong inhibition zone in the positive control (Clindamycin), that was 21.76 ± 1.81, the F0 formula which was a negative control did not have an inhibition zone or no antibacterial activity, the F1 formula with a concentration of betel leaves 3.125% produces an inhibition zone of 10.8 ± 0.8 which is classified as moderate, then the F2 formula with a betel leaf concentration of 6.25%

produces an inhibition zone of 13.76 ± 0.77 which is classified as strong, and for the F3 formula with a betel leaf concentration of 12, 5% produces an inhibition zone of 17 ± 0.5 which is considered strong. This is in accordance with research by Purnamaningsih (2017), which states that the higher the extract concentration, the higher the diameter of the inhibition zone.

The results of the antibacterial test for *P. acnes* in the positive control were able to inhibit bacteria with an average inhibition zone of 31.82 mm ± 1.2918. The negative control formula 0 (F0) acne patch preparation without the addition of extracts did not inhibit *P. acnes* bacteria. This was due to the absence of active substances that could inhibit these bacteria. Formula 1 (F1) which is a preparation with 3.125% extract is able to inhibit 22.74 mm ± 0.90, formula 2 (F2) with 6.25% extract is able to inhibit 27.19 mm ± 1.29, while in formula 3 (F3) containing 12.5% extract was able to inhibit 32.02 mm ± 1.14.

Data analysis using SPSS with One Way Anava parameter test showed a significance value of each inhibition zones formula p sig.=0.000 (< 0.05) which mean that each formula was a significant difference in the treatment of the antibacterial activity of *S. Aureus* and *P. Acnes.*

The limitation in this research was in the formulation of acne patch. In this research was used patri dish as hydrogel film mold, and then cut the film in a circular shape. The procedure was made by traditionally in lab scale, Hopefully the next research can make the patch with proper modern acne patch maker or mold.

5. Conclusion

Based on research results on the physical quality of acne patch formulas F0, F1, F2 and F3 meet the requirements. The strongest antibacterial activity was produced by a formula containing 12.5% betel leaf extract, based on analysis using One Way Anava the result showed that sig ρ. value. = 0.000 (< 0.05), it concluded green betel leaf extract variations concentration on patch formula giving effect to antibacterial activity of *S. Aureus* and *P. Acnes.* The highest concentration of green betel leaf extract was significantly increase the antibacterial activity of breadfruit acne patch.

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