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Cream Optimization of Ethanol Extract of Duku Leaves (*Lansium Domesticum Corr.*) as Antibacterial Against *Staphylococcus Aureus*

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ABSTRACT

Introduction: The secondary metabolites flavonoids and triterpenoids in duku leaves have antimicrobial properties. Cream have some drawbacks, including fragility to erratic stirring, brittleness when dried up, and poor storage stability. Triethanolamine reacts with stearic acid will form triethanolamine stearate which can increase stability of the cream. This research aimed to find the ideal ratio of stearic acid to triethanolamine for making an antibacterial composition.
Methods: Optimization of the cream is carried out by Simplex Lattice Design method, made 8 run with the smallest proportion of stearic acid 15g and the highest 17g, and the smallest proportion of triethanolamine 2g and the highest 4g. Responses used in Simplex Lattice Design, namely pH, viscosity, adhesion, and spreadability. T-test was used to verification of the optimal formula and ANOVA was used to analysis of antibacterial data.
Results: The optimal formula was 17 grams of stearic acid and 2 grams of triethanolamine make the optimal cream. The test results show that there is no significant difference between the optimal formula and the predictions in the Simplex Lattice Design software, with a pH of 6.33±0.033, a viscosity of 179.67±0.333, an adhesion of 1.377±0.038, and a spreadability of 5.133±0.044. The best formula has moderate antibacterial activity (6.62±0.007 mm inhibition zone) against *Staphylococcus aureus.*
Conclusion: The optimal formula has good physical properties and is efficacious as an antibacterial.

Keywords: Optimization; Cream; Duku leaves; Simplex Lattice Design; *Staphylococcus aureus.*

INTRODUCTION

One or more components are dissolved in a suitable base to make a semi-solid preparation known as a cream. The advantages of creamy formulations include ease of use, non-stickiness, uniform distribution, and easy removal with water. Cream preparations have a number of disadvantages, including breakage due to erratic mixing, drying and spoiling, and poor storage stability [1].

Based on the shortcomings of the cream, the emulsifier has an important role in cream preparations. A good emulsion system and a stable preparation cannot be achieved without the addition of an emulsifier during cream making [2]. One of the most widely used emulsifiers are stearic acid and triethanolamine. By reacting with bases potassium hydroxide (KOH) or triethanolamine, stearic acid functions as an emulsifier in the manufacture of creams. The high content of stearic acid creates a thick base and changes the viscosity of the cream. By reacting with stearic acid, the anionic emulsifier triethanolamine forms stearate TEA, which increases the stability of O/W emulsions [3].

The Simplex Lattice Design technique is an option to achieve an optimal formula. The formulation may have an optimal ratio of ingredients with respect to certain variables determined using this technique [4]. The gram-positive bacterium *Staphylococcus aureus* is a major source of skin and soft tissue infections. Staphylococcus aureus, a normal flora of human skin, can develop an infection that manifests as ulcers [5].

Duku plant is a potential antibacterial plant medicine. Duku leaf extract contains flavonoids and triterpenoids which have antibacterial properties [6]. Duku leaf infusion also shows antibacterial activity against *Escherechia coli, Staphylococcus aureus,* and *Bacillus subtilis* [7]. Duku leaf extract lotion using 96% ethanol solvent with a concentration of 4%, 8%, and 12% has a strong category of antibacterial activity [6].

Based on this background, this study attempted to develop cream preparations of duku leaf ethanol extract by combining stearic acid and TEA using Simplex Lattice Design in Software Design Expert 13 to obtain the most optimal results of cream preparations which further meet the requirements for making creams and exhibit antibacterial activity against *Staphylococcus aureus*.

METHOD

Tools and materials

Pipette, beaker (Iwaki/pyrex), Erlenmeyer (Iwaki/pyrex), volumetric flask (Iwaki/pyrex), measuring cup (Iwaki/pyrex), spatula, filter paper, tamfer, pestle, electric beater (Ohaus) are among the the instruments use in this investigation, viscometer Rion VT-04, rotary evaporator IKA RV 10, maceration containers, porcelain dishes, cream containers, petri dishes, water bath.

The materials used in this study included duku leaves (*Lansium domesticum* Corr.) taken from Wirun Village, Mojolaban, Sukoharjo, 70% ethanol (Medika), cetyl alcohol (Bratachem), propylenglicol (Bratachem), Nipagin (Bratachem), Nipasol (Bratachem), stearic acid (Bratachem), TEA (Bratachem), aquadest, Mg + HCl reagent for the test of flavonoids, chloroform, acetic anhydrous acid, concentrated sulfuric acid, genalten cream (Ifars), *Staphylococcus aureus* bacteria

Course of research

Manufacture of duku leaf extract

Duku leaves are dried in the sun and then covered with a black cloth. The dried simplicia was crushed using a blender and sieved using a 60 mesh sieve. 500 grams of simplicia powder soaked in 7.5 parts of 70% ethanol, i.e. 3750 ml, left to stand for 5 days with constant stirring every once a day, then the macerate was filtered through a flannel cloth. Then macerate again using the remaining solvent, which is 1250 ml, let stand for 2 days with constant stirring once a day, then filter again with filter paper. The resulting filtrate was evaporated with a rotary evaporator at 50ºC, then filtered again with filter paper. then evaporated with a water bath to obtain a thick extract[5].

Phytochemical screening

Flavonoid

Examination of flavonoid was carried out by means of 100 mg of concentrated extract dissolved in 70% ethanol solvent then added 10 mL of hot distilled water into the solution, then taken 5 mL added 0.1 gram of magnesium powder and added 1 mL of HCl. The formation of a red, yellow or orange solution indicates the presence of flavonoid [8].

Triterpenoid

Examination of triterpenoids was carried out by the Liebermann-Bourchard reaction. 50 mg of the extract dissolved in chloroform then added Liebermann-Burchard reagent (acetic anhydrous acid-H2SO4) showed positive results with a brown color change[9].

Manufacture of duku leaf ethanol extract cream

Tabel 1. Formulations of duku leaf ethanol extract cream

Ingredients grams	F 1	F 2	F 3	F 4	F 5	F 6	F 7	F 8
Duku leaf extrac	8	8	8	8	8	8	8	8
Setil alkohol	4	4	4	4	4	4	4	4
Stearic acid	17	17	15,5	15	15	16,5	16	16
TEA	2	2	3,5	4	4	2,5	3	3
Gliserin	4	4	4	4	4	4	4	4
Propilenglikol	7	7	7	7	7	7	7	7
Nipagin	0,2	0,2	0,2	0,2	0,2	0,2	0,2	0,2
Nipasol	0,02	0,02	0,02	0,02	0,02	0,02	0,02	0,02
Aquadest ad	100	100	100	100	100	100	100	100

Cream is prepared by placing the oil phase (stearic acid and cetyl alcohol) in a porcelain cup and melting it at 70^0C in a water bath. Simultaneously TEA, propylene glycol, glycerin, and distilled water form the aqueous phase, which is added to the beaker along with the nipagin. The liquid oil phase is placed into the mortar which has been heated to 70^0-75^0 Celsius and stirred thoroughly. A creamy consistency is achieved by gradually adding the aqueous phase while stirring continuously. A little ethanol extract from duku leaves is added to the cream mass all at once and stirred until the mixture is smooth [10].

Cream Formula Optimization

Simplex Lattice Design is used to optimize the basic ingredients of stearate sour cream and triethanolamine using only two variables. Cream formulations can be improved by adjusting the pH, viscosity, adhesion and spreadability.

Verification of the optimal formula was carried out by analyzing the physical properties of the following preparations:

Organoleptic test

Color, odor, and cream consistency are part of the organoleptic evaluation[11].

Homogeneity test

One gram of cream is spread on a glass plate, massaged, then touched. If the cream is completely smooth, then there won't be any lumps in it[12].

pH test

Cream containing 0.5 g of duku leaf extract was diluted with 10 ml of distilled water and weighed. Then, check the pH of the solution using a meter. To avoid skin irritation, a high quality cream should have a pH value between 5 and 7 [10].

Cream type test

To carry out the cream type test, 0.5 g of cream was added to a test tube and then diluted with water. Cream of the O/W type if it can be diluted, and of the W/O type otherwise [12].

Viscosity test

The cream mixture was measured using a series 2 viscometer stirrer, designed for medium-thickness mixtures, in a Rion VT-04 beaker. The viscometer needle will show a scale that corresponds to the thickness of the sample being examined. The RION VT-04F viscometer is the instrument of choice. The cream should have a viscosity between 50 and 200 dPas [13].

Adhesion test

A glass dish with a surface of 2.5 cm2 is used to distribute 1 g of cream. A 500g load was applied for 5 minutes before being released, and the plate was then subjected to an 80g release load for evaluation. When the two plates are separated from each other, the time is recorded. There are three rounds of replication. If the test results show a time of more than 1 second, the cream is considered to have a strong adhesiveness [14].

Spreadability test

First 1g of cream is weighed and spread on a glass plate. After 1 minute, the diameter of the cream smear is measured. Next, 50g of weight was added and allowed to stand for 1 minute. Then the diameter of the cream spread was measured three times after gradually adding a 50 gram load and letting it stand for 1 minute each time. If the cream can be applied in a thickness of 7–5 centimeters, it is considered a topical preparation [13].

Optimal formula antibacterial test

The well technique is a microbiological test in which the radius of the well is measured to determine the effectiveness of the treatment in inhibiting the development of *Staphylococcus aureus*.

Preparation of the test bacterial suspension

A tube is made with 10 ml of 0.9% NaCL, and the test bacterial sample is dipped into it with a sterile wire until the color becomes cloudy according to the Mc standard Farlands 0.5 [15].

Antibacterial test

Pipette 0.1 ml of bacterial suspension. Then it is poured into a petri dish. Then the melted MHA media was poured into the petri dish and then homogenized. Use 6mm boorprof to perforate the bacteria-injected media. Then, place as little as 0.1 g of the optimal cream formulation, the negative control, and the positive control into each container of the MHA medium. Incubation 24 hours at 370 Celsius. Take a caliper, look closely to see how much clear area has developed around the hole [15].

Data analysis

Data analysis was carried out using the simplex lattice design method using software design expert version 13 and then the optimal formula will be verified using the t-test method. SPSS version 25 is used to perform the Analysis of Variance (Anova) test and check the results of the antimicrobial test. Before carrying out the ANOVA test, it is ensured that the data is normal and homogeneous.

RESULT

Duku Leaf Extract

Maceration, a type of cold extraction, is used for the actual extraction. Because 70% ethanol is non-specific and non-toxic, it was chosen as the extraction solvent. The yield of duku leaf extract obtained was 18.01% w/w. The results of the identification of secondary metabolic compounds showed that the ethanol extract of duku leaves contained flavonoids and triterpenoids.

Tabel 2. Phytochemical Screening Result

Compound	Reactor	Observation	Result
Flavonoid	Magnesium powder + HCl	Yellow solution	+
Triterpenoid	Asam Asetat Anhidrat + H_2SO_4	Dark brown solution	+

Information : (+) : there is content

Cream Physical Test Result

Organoleptic

Organoleptic evaluation looked at the finished cream made from ethanol extract of duku leaves and recorded the appearance, smell, shape, and texture. The eight variations have a soft brownish green color, smooth, pungent smell, semi-solid shape, and texture.

Homogenity

Homogeneity test aims to determine whether the cream is made have a uniform composition or not. The absence of granules when the preparation is spread on clear glass indicates that all preparations pass the homogeneity test.

Cream Type Test

Cream type test aims to determine the type of cream made. Because the cream formulation under test can be dissolved in water or made homogeneous with it, it is classified as the oil in water (O/W) type. This can also be seen in the concentration used, namely the oil phase is smaller than the water phase.

Tabel 3. Cream Physical Test Result

Testing	Run 1	Run 2	Run 3	Run 4	Run 5	Run 6	Run 7	Run 8
pH	6,3	6,3	6,5	6,6	6,6	6,5	6,4	6,4
Viscosity	180	180	145	140	140	155	150	150
Spreadability	5,27	5,23	6,53	7,27	7,31	5,9	6,22	6,28
Adhesion	1,59	1,60	1,02	0,98	0,98	1,26	1,19	1,17

pH test

When cream is applied to the skin, it changes the pH of the skin. Scaly skin is a sign that the environment has a pH that is too high. While skin irritation occurs at acidic pH [16]. The safe pH of cream preparations when applied to the epidermis of the skin is 5-8 [10]. The following is the TEA and stearic acid curve for pH in Figure 1.

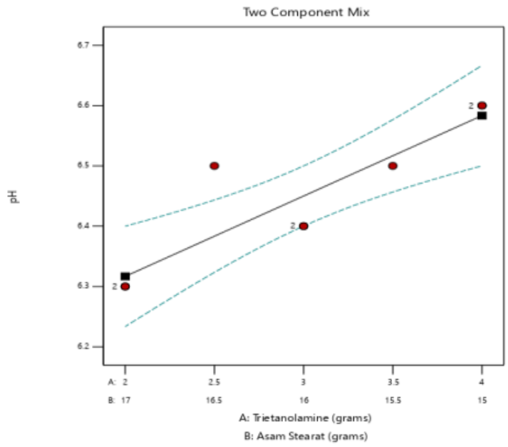

Figure 1. TEA and stearic acid curve for pH

In the pH plot, the correct linear form was selected to assess the pH response, which has the equation for the combination of TEA and stearic acid for the pH test using the simplex lattice design approach as follows:

Y = 6,58 (A) + 6,32 (B)………………….. (equation 1)

Information : Y = response received, A = TEA, B = stearic acid

In the equation 1, stearic acid and triethanolamine are used to raise the pH of the resulting cream product. ANOVA with a p-value of 0.0027 (<0.05) was generated from the simplex lattice design equation using the linear model, and thus was considered the most suitable for evaluating the pH response. However, the underfit analysis yielded a p-value of 0.5725 (> 0.05), indicating that the gap between the actual data and the model's predictions was not statistically significant. The alkaline nature of TEA allows it to raise the pH of the mixture.

Viscosity test

The purpose of the viscosity test is to establish a user-adjustable consistency of a creamy product. The ideal cream viscosity is between 50 and 200 dPas[13]. Figure 2 shows the effect of stearic acid and TEA on viscosity.

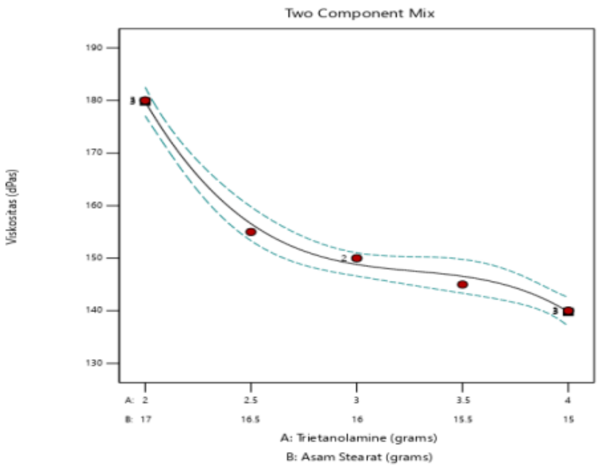

Figure 2. TEA and stearic acid curve for viscosity

In the viscosity plot, the cubic shape is considered appropriate for assessing the viscosity response which has the equation for the combination of TEA and stearic acid for the viscosity test using the simplex lattice design approach as follows :

Y = +139,80 (A) + 179,80 (B) – 43,92 (AB) + 53,33 (AB(A-B))……………………(equation 2)

Information : Y = response received, A = TEA, B = stearic acid, AB = combination of TEA dan stearic acid

From the equation 2 it can be said that the presence of TEA and stearic acid can increase the viscosity of duku leaf ethanol extract cream preparations. While the combination of stearic acid and triethanolamine can reduce the viscosity of the cream preparation. From the simplex lattice design equation, significant significance is obtained in the ANOVA with a p-value of 0.0001 (<0.05) and is considered the most appropriate for assessing the pH response. On the other hand, the p-value of 0.7846 (> 0.05) obtained from the mismatch analysis indicates that the cubic model is not significant to pure error; that is, there is no difference between the observed and predicted data. Stearic acid can affect the viscosity of the preparation because stearic acid is a fatty acid which will make the preparation thicker[10].

Spreadability test

When applied to the skin, how quickly the cream spreads is measured by the spreadability test. Easily spreadable to a depth of 5–7 cm, ideal for semi-solid formulation [13]. Figure 3 shows the spreadability curve for TEA and stearic acid.

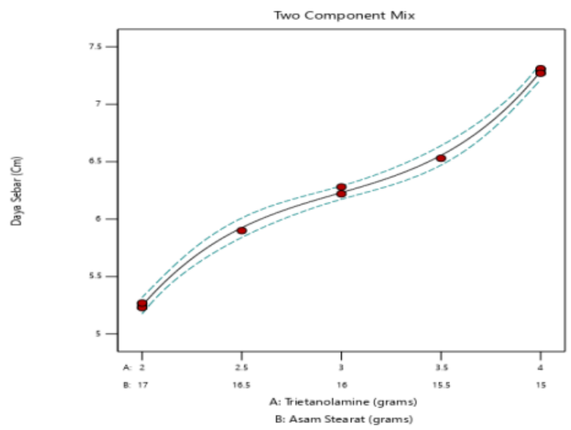

Figure 3. TEA and stearic acid curve for spreadability

In the scatter plot the cubic shape is considered appropriate for assessing the spreadability response and has the equation for the combination of TEA and stearic acid for the spreadability test using the simplex lattice design approach as follows :

$Y = +7{,}29\ (A) + 5{,}25\ (B) - 0{,}1427\ (AB) - 2{,}08\ (AB(A-B))$…………………………(equation 3)

Information: Y = response received, A = TEA, B = stearic acid, AB = combination of stearic acid dan TEA.

From equation 3 it can be said that stearic acid and triethanolamine can increase the spreadability of cream preparations. While the combination of stearic acid and triethanolamine can reduce the spreadability of the cream preparation. Anova, with a p-value of 0.0001 (<0.05) from the simplex lattice design equation, is considered the most acceptable for evaluating the pH response. Comparatively, the lack of fit analysis yielded a p-value of 0.2753 (> 0.05), indicating that the cubic model was not statistically significant due to pure error and that there was no difference between the observed and expected data. TEA can affect the spreadability of the preparation because TEA is in the form of a solution that can increase the spreadability.

Adhesion test

The adhesion test aims to evaluate how well a semi-solid preparation adheres to human skin. Excellent adhesion for cream formulations, lasts more than a second[14]. The following shows the TEA and stearic acid curves for adhesion in Figure 4.

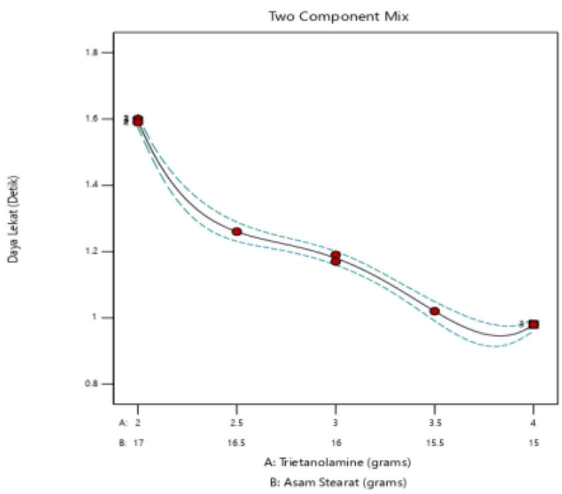

Figure 4. TEA and stearic acid curve for adhesion

The adhesion plot is in the form of a quadric which is considered appropriate for assessing the adhesive response and has the equivalent combination of TEA and stearic acid for the adhesion test using the simplex lattice design approach as follows :

$Y = +0,98000\ (A) + 1,59\ (B) - 0,4300\ (AB) +$

$0,3600\ (AB(A-B)) - 1,43\ (AB(A-B)^2)$…….(equation 4)

Information: Y = response received, A = TEA, B = stearic acid, AB = combination of stearic acid dan TEA.

From the equation 4 it can be said that triethanolamine and stearic acid can increase the adhesion. While the combination of stearic acid and triethanolamine can reduce the stickiness of the cream preparations. Anova, with a p-value of 0.0001 (<0.05) from the simplex lattice design equation, is considered the most acceptable for evaluating the pH response. Meanwhile, the p-value of 0.2430 (> 0.05) obtained from the lack of fit analysis shows that the quadratic model is not significant for pure error, that is, there is no difference between the observed data and the projected data. Stearic acid can affect the adhesion of preparations because stearic acid is a fatty acid which will produce thicker preparations so that the spreadability is greater.

Determination of Optimal Formula Based on Simplex Lattice Design

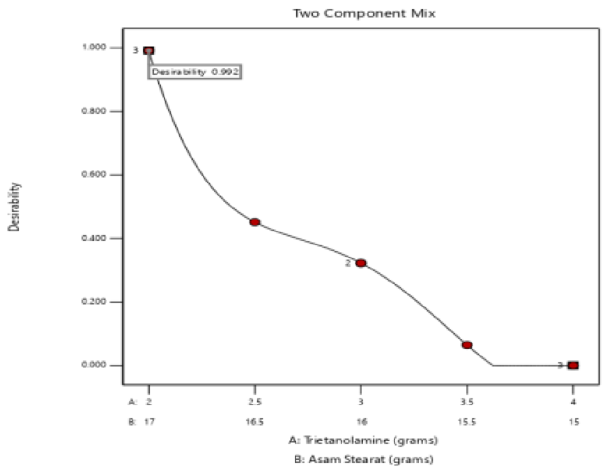

Figure 5. Curve for optimal formula

The optimal formula using the simplex lattice design approach was obtained with a weight of 2g TEA and 17g stearic acid. with the desirability value obtained is 0.992. The desirability value is the value for knowing the program's ability to make predictions and fulfill according to the specified criteria and is the target value achieved, which is expressed in the range 0-1[10].

Optimal Formula Verification Test Results of Duku Leaf Ethanol Extract Cream

Table 4. Verification Optimal Formula

Parameter	Prediction	Test Result ± SD	Significance	Interpretation
Viscosity (dPas)	179.804	179.67 ± 0.333	0.720	not significantly different
Spreadability (cm)	5.247	5.133 ± 0.044	0.123	not significantly different
Adhesion (detik)	1.595	1.377 ± 0.038	0.028	Significant different
pH	6.317	6.33 ± 0.033	0.673	not significantly different

Table 4 shows the verification findings, which revealed that the viscosity, spreadability and pH did not change much, but the adhesion did not change significantly.

Test the Effectiveness of the Optimal Formula of Duku Leaf Extract Cream

Table 5. Effectiveness of the Optimal Formula of Duku Leaf Extract Cream Result

Formulas	Inhibition Zone Diameter (mm) ± SD	Category
Negative Control	0	-
Positive Control	16,64 ± 0,009	Strong
Duku Leaf Extract Cream	6,62 ± 0,007	Moderate

The radical zone surrounding the well indicates that the cream is effective against *Staphylococcus aureus*, and this is what the antibacterial activity test looks for. The average inhibition zone produced by the optimal formulation of duku leaf ethanol extract cream was 6.62 ± 0.007 mm, while the inhibition zone produced by the positive control was 16.64 ± 0.009 mm, and the inhibited zone produced by the negative control was 0 mm.

DISCUSSION

Selection of emulgator in cream preparation is important factor because emulsifier can influenced of quality and stability an emulsion[18]. Stearic acid and triethanolamine is used an emulsifier widely. By reacting with stearic acid, the anionic emulsifier triethanolamine forms stearate TEA, which increases the stability of O/W emulsions [12]. The high content of stearic acid creates a thick base and changes the viscosity of the cream. The optimal formula of cream was obtained with a weight of 2g TEA and 17g stearic acid.

In the verification of the optimal formula, there is no significant in viscosity, spreadability and pH. There is significant difference in adhesion influenced by the difference in the testing time of the eight runs with the optimal formula which affects the stability of the preparation. This variation is still included in the adhesiveness criteria of the preparation, therefore the simplex lattice design approach is suitable for finding the best combination of stearic acid and triethanolamine in cream [17]. The optimal formulation includes the organoleptic properties of the cream, including a brownish-green hue, a strong distinctive odor of duku leaf extract, and a smooth feel when applied topically. The resulting cream does not meet the preparation quality requirements in terms of color of cream, the brownish-green hue color and strong odor can cause discomfort when used on skin.

In the cream formulation of legetan leaves extract found the optimal stearic acid and trietanolamin is 1,824% stearic acid and 2,176% trietanolamin. Cream formulation was stable in the storage. Viscosity, viscosity shift, and spreadability of cream that occurs between optimum formula for prediction results and results trials did not significantly different (18). The optimal formula of rice cream (*Oryza sativa* L) type O/A is variety stearic acid 2.5%, cetyl alcohol 2.5-3.0% and TEA 1.0-1.2% (19). This cream was stable and according to quality requirements.

The inhibition zone of the optimal formula was greater than the negative control because the optimal formula contained duku leaf ethanol extract of 8%, which meant that the optimal formula had antibacterial activity against Staphylococcus aureus. The inhibition zone of the optimal formula for duku leaf ethanol extract cream is smaller than the positive control because the positive control contains gentamicin which is a chemical ingredient as an active substance which has antibacterial properties, while the duku leaf ethanol extract cream contains the active substance duku leaf extract derived from nature, so it has a smaller inhibition zone compared to gentamicin which is included in chemicals.

Natural materials have less antibacterial power than chemicals because of the low content of a compound and also the complexity of the chemical compounds contained in natural products as basic ingredients for traditional medicines. The optimal duku leaf ethanol extract cream formulation was tested for its antibacterial effect on *Staphylococcus aureus* bacteria, the average diameter of the inhibition zone was included in the moderate inhibition response. In contrast, the average diameter of the inhibition zone in the positive control was included in the strong growth inhibition response [6].

CONCLUSION

The optimal formula of duku leaf ethanol extract cream with the simplex lattice design method is 2 grams of triethanolamine with 17 grams of stearic acid and has an average inhibition zone of 6.62 ± 0.007 mm which is included in the moderate category.

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CONFLICT OF INTEREST

No conflict of interest in this research

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