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The Healing Effectiveness of Sesewanua Leaf Extract Cream (*Cleodenronsquamatum* VAHL.) against Rabbit Cuts Infected with Bacteria *Staphylococcus aureus*

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Abstract: ***Sesewanua plant (Clerodendronsquamatum Vahl.) is empirically used by people in several areas in North Sulawesi because it has several compounds that are thought to have antipyretic properties, one of which is flavonoids. This study aims to make the Formula of Sesewanua Leaf Extract Cream with concentrations of 1%, 3%, 5%, 7% and 9%, and determine the healing activity of Sesewanua leaf extract cream preparations on rabbit cuts infected with bacteria Staphylococcus aureus. The results of the physical properties test and stability test of the cream formula which included a stability test of 6 cycles met the requirements with test parameters namely organoleptic test, homogeneity test, pH test, spreadability test and adhesion test. The test results of the healing activity of the cream of sesewanua leaf extract on rabbit cuts smeared with bacteria Staphylococcus aureus showed that the preparation of 9% sesewanua leaf extract cream showed the most effective wound healing with a wound length of 0.1 cm. The ANOVA test results obtained a significant value of 0.788, meaning that 0.05, it can be concluded that there is no significant difference. Sesewanua leaf extract cream at a concentration of 9% has antibacterial activity that is more effective than other concentrations, as evidenced by a faster wound healing time.***

Keywords: Sesewanua leaf (*Clerodendronsquamatum* Vahl.), Cream, *Staphylococcus aureus*, rabbit

1. Introduction

The use of plants as medicinal ingredients has been widely used by the community. The Sesewanua plant (*Clerodendronsquamatum* Vahl.) has been empirically used by people in several areas in North Sulawesi to treat diseases such as fever, fractures, relieve pain and reduce swelling. Sasawanua Plant Khasiwa has been proven through research conducted by Sangi *et al*. (2008) Sesewanua leaves were analyzed to contain alkaloids and flavonoids. Flavonoids have strong anti - oxidants, stimulating the production of nitrite oxidation which can dilate blood vessels. Flavonoids can also inhibit the growth of fibroblasts, thus providing an advantage in the wound healing process. Excessive fibroblast activity can inhibit the wound healing process. Flavonoids can induce cell proliferation so that it can accelerate wound healing (Robinson, 1995). According to Huliselan et al., (2015) the ethyl acetate extract of Sesewanua leaves contains high antioxidant compounds with IC_{50} yields of 13.084 mg/L compared to the ethanol extract of Sesewanua leaves of 17.85 mg/L and the extract of *n* – hexane Sesewanua leaves of 23.737 mg. /L using themethod*1, 1 - diphenyl - 2 - picrylhydrazil* (DPPH), as well as research by Runtuwene (2019) showed that the sesewanua leaf gel has an antioxidant effect. Based on the research that has been done, it is developed into a pharmaceutical preparation, namely cream preparations.

2. Materials and Methods

2.1 Materials

Materials used are Sesewanua leaves, 96% Ethanol, Cetyl Alcohol, Glycerin, Triethanolamine, Liquid Paraffin, Stearic Acid, Aquades, *Nutrient Agar*, NaCl 0.9%solution *Mc Farland*, bacteria *Staphylococcus aureus*, Cinolon - N Cream.

2.2 Methods

Sesewanua leaf extract was made by maceration method. Sesewanua Leaf Powder as much as 500 g was put in a container and 2500 mL of 96% ethanol solvent was added and soaked for 3x24 hours while stirring occasionally. After 3 days it was filtered and produced filtrate 1 and debris 1. Debris 1 was remaceration with 1500 ml of 96% ethanol for 2x24 hours. Filtrate samples were filtered distillate 2. The filtrate 1 and filtrate 2 is mixed and vaporized by *an evaporator* to obtain viscous extract

Formulations preparation

Table 1: Sesewanua Leaf Extract Cream Preparation Ingredients

Name	*Formula (% b/v)*				
	F1	*F2*	*F3*	*F4*	*F5*
Sesewanua Leaf Extract	1 g	3 g	5 g	7 g	9 g
Stearic Acid	16 g	16 g	16 g	16 g	16 g
Liquid Paraffin	10 mL	10 mL	10 mL	10 mL	10 mL
Cetyl Alcohol	2 g	2 g	2 g	2 g	2 g
Glycerin	8, 5 mL	8, 5 mL	8, 5 mL	8, 5 mL	8, 5 mL
TEA	7 mL	7 mL	7 mL	7 mL	7 mL
Aquadest	*ad*100	ad100	ad100	ad100	ad100

Preparation of Sesewanua Leaf Ethanol Extract Cream

Sesewanualeaf extract cream was made with concentrations of FI 1%, F2 3% F3 5%, F4 7% and F5 9%. Each ingredient is weighed and separated. Cream manufacture begins with phase separation, namely the oil phase (stearic acid, liquid paraffin,) is put into a *glass beaker* while heated at a temperature of 70°C using a *hot plate.* The same was done for the aqueous phase (aquadest, glycerin and TEA). The melted oil phase is poured into a heated mortar, while stirring until homogeneous. Then, the water phase is added little by little while stirring slowly until a creamy mass is formed, then the thick extract of Sesewanua leaves is added into the cream mass little by little and stirred until homogeneous.

Physical Evaluation of Cream Preparations

a) Organoleptic Test

Organoleptictests were carried out by observing the color, smell, and shape of the cream (Sharon, *et al*., 2013). The resulting cream preparation should have a soft texture or form, a pleasant smell and an attractive color.

b) Homogeneity Test

Homogeneity test is carried out by using an object glass by applying a certain amount of preparation to a piece of glass or other suitable transparent material to produce a homogeneous preparation and no coarse grains are seen (Lubis, 2012)

c) pH Test

pH measurement is carried out using a pH meter. The trick is to weigh 1 gram of cream and dissolve it with 10 ml of distilled water. Then, use a pH - meter. The pH of the preparation that meets the skin pH criteria is around 4.5 – 6.5 (Tranggono and Latifa, 2007).

d) Spreadability Test

Each cream was weighed as much as 1 g, then placed on a pair of petri dishes and left for 1 minute, then placed a load of 50 g, the load was left for 1 minute and then the diameter of the spread was measured (Rahmawati, *et al*., 2010).

e) Adhesion Test

Weighed 0.5 grams of cream and smeared on *aplate* glass. The two glass plates are affixed until the plates are fused, given a load of 250 grams for 5 minutes after which they are released, then given the load of release. The time was recorded until the two plates separated from each other. Based on the requirements for good cream adhesion, which is more than 4 seconds (*Wasiaatmadja, 1997*).

f) Test Cycling

In this study, themethod was used *cycling test*. The cream was stored at 4°C for 24 hours and at 40°C for 24 hours, 6 cycles were carried out and the physical changes of the cream were observed (Dewi, 2010).

Preparation of Test Animals and Procedure for Making Infections

The test animals used in this study were 7 male rabbits aged about 2 - 3 months with a body weight of 1.2 - 1.5 kg. Prior to wound creation, rabbits were acclimatized for 4 days. The day before the wound was made, the test animals were shaved on the back until they were smooth and cleaned with 70% alcohol, then a 1.5 cm long cut was made on the rabbit's back using a *sterile surgical blade* to the subcutaneous area. bacteria suspension was *Staphylococcus aureus* given as much as 0.2 ml at each location. Observations were made after 24 hours to see the presence of infection in the wounds made, then the rabbit skin that had been infected withbacteria was *Staphylococcus aureus* given treatment.

Treatment and observation

a) Each rabbit was given the following:
   Treatment A: Wound was given cream base (negative control); Treatment B: Wound was given Cinolon - N Cream (positive control); Treatment C: Wound was given cream with 1% Sesewanua leaf extract; Treatment D: Wound was given cream Sesewanua leaf extract 3%; Treatment E: Wounds were given Sesewanua leaf extract cream 5%; Treatment F: Wounds were given Sesewanua leaf extract cream 7%; Treatment G: Wounds were given Sesewanua leaf extract cream 9%
b) Then observations were made every day for 6 days, measuring the length of the wound closure.
c) Cream preparations are given by applying evenly to the wound area 2 times a day. Observations on the wound before administration and after treatment showed signs of healing by measuring the length of the wound using a cm scale ruler.

3. Results and Discussion

The maceration of 500 g of Sesewanua leaf simplicia produced a thick extract of 28.3 g. The extraction process by maceration and using 96% ethanol solvent this process was chosen because it can attract polar compounds present in Sesewanua leaves such as flavonoids and alkaloids.

The cream preparations made are o/w type cream. The advantages of this o/a cream are that it is easy to wash with water, is not sticky, does not leave stains on clothes and has good drug release properties because when the drug is applied to the skin there will be evaporation and an increase in the concentration of the drug which is soluble in water so that it can be absorbed into the skin. Encourage the absorption of medicinal ingredients through the skin tissue (Aulton & Taylor, 2013)

The results of testing the physical properties of the preparation of Sesewanua leaf cream

a) Organoleptic Test

This test include color, shape, and odor. Observations were made from week 0 to week 6. The observation of the organoleptic preparations cream with various concentrations can be seen in Table 2.

Table 2: Test Appearance (Cycles 0 - 6)

Formula	Observation		
	Odor	Form	Color
Basis	Base	Semi solid	White
F1	Typical extract	Semi solid	Green light
F2	Typical extract	Semi solid	Green Brownish
F3	Typical extract	Semi solid	Green Brownish
F4	Typical extract	Semi solid	Dark green
F5	Typical extract	Semi solid	Green

The results of organoleptic observations of Sesewanua leaf extract cream FI 1%, F2 3%, F3 5%, F4 7% and F5 9% from the 0th cycle to the 6th cycle, showed that the Sesewanua leaf extract cream had different colors from each concentration. The color change from each concentration indicated that the addition of Sesewanua leaf extract in the cream base affected the color of the cream preparation. The greater the concentration of extract contained in the cream, the more concentrated the color produced by the cream. The form of each concentration is the same. Semi solid and odor for the typical concentration of the extract. As for the cream base, it is white and smells like a cream base.

b) Homogeneity Test

Homogeneity Test was carried outaims to see and determine the mixing of the ingredients of the cream preparation so that there are no visible coarse grains. Observations were made from week 0 to week 6. The results of observations of cream preparations with various concentrations can be seen in Table 3.

Table 3: Homogeneity Test (Cycle 0 - 6)

Cycle	Homogeneity Test					
	Base	Concentration 1%	Concentration3%	Concentration5%	Concentration7%	Concentration9%
1	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
2	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
3	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
4	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
5	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
6	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous

The results of the homogeneity test showed that there was no change in the dosage during the 6 test cycles at the 5 concentrations. Based on the results of the homogeneity test on the preparation of Sesewanua leaf extract cream which was carried out before and after the storage *cycling test* at a temperature of ± 4°C for 24 hours then removed and placed at a temperature of ± 40°C for 24 hours (1 cycle), carried out until 6 cycles. All cream preparations did not show the presence of coarse grains when the preparation was applied to a transparent glass. The nature of the active substance from Sesewanua leaves is easy to mix with an W/A basis so that there is no clumping and phase separation. This shows that the preparations made have a homogeneous composition (Directorate General of POM, 1985). The cream is said to be homogeneous if there is an even color equation and no particles are found in the cream (Ida and Noer, 2012).

c) pH test

Testing was carried out to see the pH of the Sesewanua leaf extract cream preparation. Observations were made from week 0 to week 6. Based on the requirements of SNI 16 - 4954 - 1998 regarding the pH range of cream preparations that meet the requirements, namely 3.5 - 8.

Table 4: pH test (Cycle 0 - 6)

Cycle	Average pH value					
	Base	Concentration 1%	Concentration 3%	Concentration5%	Concentration7%	Concentration9%
0	4, 94	5, 50	7, 36	7, 74	6, 81	5, 93
1	5, 20	4, 97	4, 90	7, 69	6, 63	6, 52
2	5, 81	7, 17	5, 91	6, 69	6, 62	8, 32
3	6, 71	5, 81	6, 24	8, 21	7, 92	7, 81
4	6.11	7, 41	6, 32	8, 95	11, 57	11, 87
5	7, 18	6, 78	6, 60	12	10, 38	9, 08
6	7, 36	6, 49	7, 14	10	9, 55	8, 84
Average	6, 19	6, 30	6, 35	8, 75	8, 49	8, 83

The result of measuring the pH of cream using a pH meter, shows that at a concentration of 1%, the average pH value is 6.30. At a concentration of 5%, the average pH value was 6.35. At a concentration of 7%, the average pH value was 8.75. The difference is caused by differences in the acidity of the active ingredients added to the cream preparation. The decrease in pH also occurs with increasing storage time but still shows a pH range that is in accordance with skin pH and pH according to SNI 16 - 4954 - 1998 the pH value of good skin moisturizing preparations ranges from 4.5 - 8. This indicates that the pH is safe for cream preparations.

The results of the pH test at week 4 showed that the graph tends to increase in the 5% formulation, 7% formulation and 9% formulation. The more the amount of stearic acid given, the pH tends to be low because of the acid group contained

in stearic acid. The emulsion is unstable due to the release of triethanolamine during storage. Triethanolamine is a strong base so that it increases the pH at each concentration of the preparation. Changes in pH are also caused by environmental factors such as temperature, poor storage, combinations of extracts that are less stable in preparations due to oxidation (Young et al 2002).

Based on the results of the one – waytest *ANOVA* that has been This study was conducted to compare the pH of the cream of Sesewanua leaf extract from cycle 0 to cycle 6. The results of the statistical data of the pH test obtained a significant value of 0.019 or 0.05. it can be concluded that the cream pH test before and after the *cycling test* had a significant difference. The significant difference was caused by the unstable temperature factor so that it could affect the pH of each formula.

d) Spreadability

Spreadabilitytest was carried out to determine the ability of the base to spread on the skin surface when applied. Good base spreading ability will provide ease of application on the skin surface. Observations were made from week 0 to week 6. The test results can be seen in table 5

Table 5: Spreadability Test (Cycle 0 - 6)

Cycle	Value Spread (cm)					
	Base	Concentration1%	Concentration3%	Concentration5%	Concentration 7%	Concentration 9%
0	4, 5	5, 3	6, 4	5, 4	4, 9	5, 3
1	3, 2	6.8	6.7	5.3	5.6	6
2	3, 1	6.8	6.6	5.3	5.6	5.6
3	3, 1	6.4	6.7	5	5.5	5.8
4	3, 1	6.8	6.1	5.4	5	5.9
5	3, 5	6.4	6.8	5.4	5.6	5.6
6	2, 9	6	6.3	5.8	5.9	6.15
Average	3, 34	6, 3	6, 5	5, 3	5, 4	5, 7

The test results showed that the preparation of Sesewanua leaf extract cream from cycle 0 to cycle 6 had different mean values. The change in the diameter of the spread of cream preparations with various concentrations indicates that the addition of variations in the concentration of the extract has an effect on the spread of cream preparations. Cream preparations with a large dispersion diameter will make it easier for the cream to spread on the skin surface, so that the absorption of the compounds contained in the cream will increase.

Based on the results of the one – way test *Anova* this study was conducted to compare the spreadability of the cream of Sesewanua leaf extract from cycle 0 to cycle 6. The results of the statistical data of the pH test obtained a significant value of 1, 000 or 0.05. it can be concluded cream before and after the *spreadability test cycling test* that there was no significant difference between them.

In accordance with the requirements of a good cream will produce a spread of 5 - 7 cm (Wasiaatmadja, 1997). Good dispersion causes the contact between the drug and the skin to be broad, so that the absorption of the drug into the skin takes place quickly

e) Adhesion Test

This test is carried out to see the ability of the preparation to adhere or stick to the surface of the skin when used. Observations were made from week 0 to week 6. The test results can be seen in table 6.

Table 6: Adhesion Test (Cycle 0 - 6)

Cycle	Average Adhesive Value (seconds)					
	Base	Concentration1%	Concentration3%	Concentration5%	Concentration7%	Concentration9%
0	63, 6	68, 3	41, 6	36	18	21, 6
1	6	14	41	18	38	20
2	80	22	47	15	43	22
3	126	83	23	26	33	22
4	24	4	15	21	19	18
5	87	18	38	26	26	21
6	77	18	48	12	23	27
Average	66, 22	32, 47	36, 22	22	28, 57	21, 65

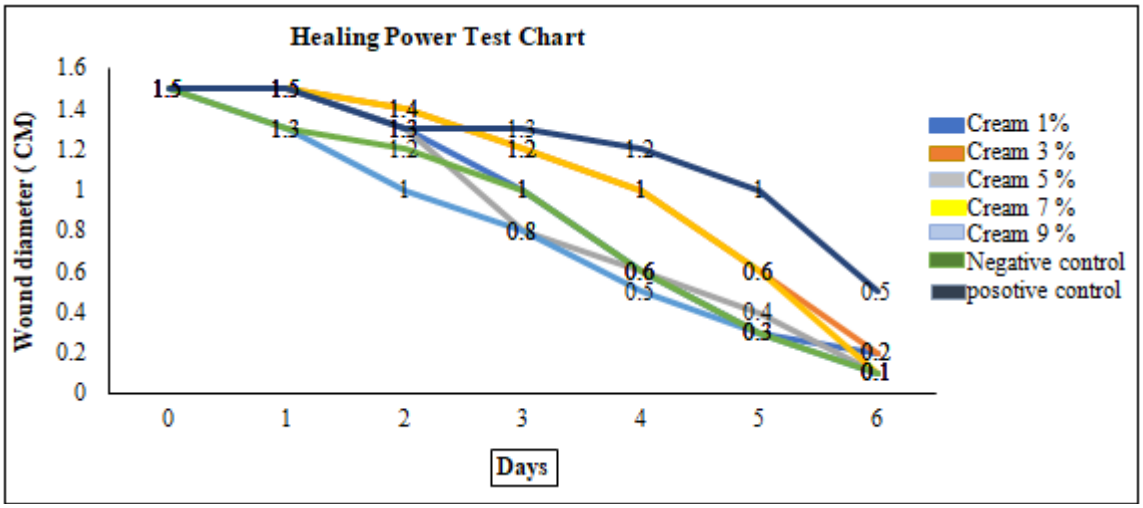
The results of the adhesion test before and after storage for 6 cycles. At a concentration of 1%, the average adhesion value was 32.47. At a concentration of 3%, the average adhesion value was 36.22. At a concentration of 5%, the average value of adhesion was 22. The concentration of 7% showed a value of 28.57 and a concentration of 9% showed an average value of 21.65%. the 2% formula is longer than the 1%, 3%, 4% and 5% formulas. The longer the time it takes for the two glass objects to come off, the better the stickiness of the cream preparation. The longer the cream is attached to the skin, the greater the effect. The results of table 6 testing the stickiness of the cream of Sesewanua leaf extract showed that all concentrations met the good requirements of more than 4 seconds (Wasiaatmadja, 1997).

Based on the results of the one – way test *ANOVA* that has been This study was conducted to compare the spreadability of the cream of Sesewanua leaf extract from cycle 0 to cycle 6. The statistical data of the adhesion test obtained a significant value of 0.273 or 0.05. it can be concluded cream before and after the *stickiness testcycling test* that there was no significant difference between the longer the time the

cream is attached to the skin, the better the cream produced because the active substances contained in the cream preparation are longer attached to the skin and have an effect. good adhesion for topical preparations not less than 4 seconds (Ulaen *et al.*, 2012).

Cut wound healing test

The process of wound healing was carried out by observing the inflammation phase, proliferation phase, remodeling phase and the diameter of the cut every day for 6 days and measuring the length of the wound every day. The results of the healing can be seen in Graph 1.



Graph 1: Healing Power Test

In this study, the test animals were slashed using a *sterile surgical blade* and the length of the incision was 1.5 cm. Measurement of wound length from all treatment groups from day 1 to day 6 where the length of the wound gradually healed up to day 6.

The first day the wounds for all treatments were still open and on day 2 the concentration of 9% and the positive control began to narrow the edges of the wound with a length of 1.3 cm, changes on day 6 showed concentrations of 5%, 7% and 9% began to narrow the wound with The same length as the positive control. The results of the observation of wound length for positive control of Cinolon N still healed faster than wounds that were given a cream base. This is because Cinolon - N contains the active substances *fluocinolone acetonide* and *neomycin sulfate* for skin infections such as dermatitis caused by bacteria. For cream of 1% Sesewanua leaf extract and 3% Sesewanua leaf cream, it was not completely covered and there were still scabs. A scab that forms on the surface establishes homeostasis and prevents contamination of the wound by microorganisms. The rate of scab formation in the five treatment groups indicated the speed of wound healing. The formation of a scab is the initial process of the inflammatory phase of the wound healing process (Klokke, 1980). The ineffectiveness of Sesewanua leaf extract cream at concentrations of 1% and 3% in healing wounds is thought to be because the release from the base is influenced by physico - chemical factors of the drug, either from the base or the drug ingredient, solubility factor and concentration of the active ingredient. Wounds that were treated with a cream base even though the edges of the wound had narrowed but there was still pus in the middle, this was because the cream base did not contain an active substance for antibacterial but experienced wound healing which was marked by a decrease in the length of the wound in rabbits, meaning that a healthy rabbit's body had natural abilities. to protect and restore the body.

Based on observations, it is known that the cream of Sesewanua leaf extract 5%, 7% and 9% contains active substances that are able to heal infected wounds. The healing process of skin infections on the rabbit's back is due to the presence of flavonoid compounds and those contained in the Sesewanua leaf extract cream which act as antibacterial. Flavonoids function as antibacterials by binding to bacterial proteins so that they inhibit enzyme activity which ultimately interferes with the bacterial metabolic process. Moreover, the nature of the lipophilic of flavonoids cause memran bacterial cells were damaged due to cell membranes containing lipid thus allowing these compounds pass through the membrane (Robinson, 1995).

The observations were obtained followed by analysis using statistical test ANOVA, to see if there are any effects of the seven treatment on wound healing. The results of the ANOVA test obtained a significant value of 0.788, meaning 0.05, it can be concluded that there is no significant difference. Sesewanua leaf cream at a concentration of 9% has antibacterial activity that is more effective than other concentrations, as evidenced by a faster wound healing time. The healing process of skin infections is also influenced by the physiological state of the test animals, because the skin is a physical barrier that can defend the body from pathogenic agents. If there is skin damage, the skin will defend the body with a rapid immunologic process against these pathogenic agents and remove these microorganisms from the epidermis and dermis. A good cream preparation is a cream preparation that has stable adhesion and spreadability and there is no change in homogeneity, odor and color pH and viscosity of the preparation.

4. Conclusion

Sesewanua leaf extract cream with a concentration of 9% has an effect as a healer of cuts infected with bacteria *Staphylococcus aureus* in rabbits.

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