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FORMULATION OF YODIUM LEAF EXTRACT (*JATROPHA MULTIFIDA* L.) CREAM FOR CUTS HEALING IN WISTAR MALE RATS (*RATTUS NOVERGICUS)*

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Abstract: Yodium plant (*Jatropha multifida* L) has pharmacology effect as antibacterial, antioxidant, and anti-inflammatory. Yodium plant contain chemical compounds, namely alkaloids, flavonoids, phenols, and tannins which have benefits in helping the healing process of cuts. The aim of this study was to determine the difference in wound healing time in rats (Rattus norvegicus strain wistar) using Yodium leaf extract cream with concentrations of 5%, 10%, and 15%. This research is a true experiment. The cuts healing were carry out on Wistar male rats that smeared by yodium leaf extract cream and be observed its healing process. The cream preparations were tested for physical quality including organoleptic test, homogeneity, pH test, spreadability test, adhesion test, and viscosity test. The results of the organoleptic test of the three formulas have a green color, distinctive aroma, and semi-solid consistency. Test the homogeneity of the three homogeneous preparations. The pH test of the three cream preparations met the pH test requirements of 4-8. Spreadability test, the three cream preparations met the requirements of 4-7 cm. In the adhesion test, the three preparations met the requirements of 2-300 seconds. The cream was applied to the backs of 0.1-gram rats with use three times a day. Coral plant (Jatropha multifida L) has healing effectiveness againts cuts in white rats (Rattus novergicus strain wistar). The cream preparation with 15% concentration of yodium leaves extract concentration was more effective in the wound healing process for 9 days.
Keywords : Yodium leaf extract (*Jatropha multifida* L), Cream, Cuts, healing process

INTRODUCTION

Wounds are a form of tissue damage to the skin caused by contact with heat sources (such as chemicals, hot water, fire, radiation and electricity), the result of medical procedures, or changes in physiological conditions. Wounds cause disturbances in the function and structure of the body's anatomy (Purnama et al., 2017). Cuts are wounds caused by cuts from sharp objects. An incised wound is characterized by an elongated wound shape (the length of the wound is greater than the depth), with the edges of the wound being straight lines. The wound healing process is divided into three phases, namely the inflammatory phase, proliferation and termination which are tissue remodeling.

One of the plants that can be used as traditional medicine is yodium leaf or known as Chinese castor leaf (*Jatropha multifida* L). Yodium plants are known to have active ingredients of alkaloids, saponins, flavonoids and tannins. These substances play an important role in the wound healing process as antibacterial, antioxidant and anti-inflammatory. Yodium leaves also contain chemical compounds, namely the class of flavonoids, phenols and tannins.

Flavonoids are anti-inflammatory so they can reduce inflammation and help reduce pain, if there is bleeding or swelling of the wound. In addition, flavonoids are antibacterial and antioxidant and are able to enhance the work of the immune system because leukocytes as antigen-eaters produce faster and the lymphoid system is activated more quickly (Liana & Utama, 2018).

Tannin compounds contain antibacterial compounds where these compounds help shrink the cell wall or

cell membrane thereby inhibiting the permeability of bacteria to develop. Tannin compounds also play a role in the healing process of cuts, tannins are useful as an astringent where the astringent will cause mucosal permeability to decrease and the bonds between the mucosa become strong so that microorganisms and irritant chemicals cannot enter the wound (Liana & Utama, 2018)

Cream is a semi-solid dosage form containing one or more drug ingredients dissolved or dispersed in a suitable base material. This term has traditionally been used for semi-solid preparations having a relatively liquid consistency formulated as water-in-oil or oil-in-water emulsions (FI Edition VI). However, the use of the leaves of the plant as a wound healing has not been found. Therefore, researchers consider that research on "Formulation of yodium leaf extract cream (Jatropha multifida L) on wound healing in male Wistar rats (Rattus norvegicus strain wistar)" is necessary.

METHODS

Research Materials and Tools

Research materials included yodium leaves from Karangasem Village RT 29 / RW 08 Gondanglegi Malang, 25 male white Wistar rats, cetyl alcohol, TEA, glycerin, acetic acid, methyl paraben, propyl paraben, span 80, tween 80, liquid paraffin aquadest, ethyl chloride spray, ether, 96% ethanol, cotton, gloves, masks, cotton buds, flannel cloth.

The tools to be used in this study were rulers, markers, hair clippers, scalpels, brown bottles, porcelain cups, blenders, water baths (B-One), maceration vessels, ovens (Maspion), beaker glass (Pyrex), measuring cups. (Pyrex), 60 mesh sieve, pH stick, stamper, analytical balance, rotary evaporator (DLAB RE 100-Pro), viscometer.

Preparation of yodium leaf extract (Jatropha multifida L.) by maceration method

660 grams of dry yodium leaf powder was macerated with 6000 ml of 96% ethanol for 3 days and constant stirring was carried out for 15 minutes every day. The filtrate is separated from the residue by filtering using a flannel cloth, then the filtrate is evaporated by rotary evaporator at 400 C, to obtain a thick extract.

Cream preparation

Table 1 Formula design of Yodium leaf extract cream (*Jatropha multifida* L.)

Ingredients	Formula 1 (g)	Formula 2 (g)	Formula 3 (g)
Yodium leaf extract	1	2	3
Stearic acid	1,4	1,4	1,4
TEA	0,2	0,2	0,2
Tweens 80	1	1	1
Span 80	1	1	1
Cetyl alcohol	1	1	1
Liquid paraffin	2	2	2
Glycerin	3	3	3
Methyl paraben	0,024	0,024	0,024
Propyl paraben	0,024	0,024	0,024
Aquadest ad	20	20	20

Materials are weighed according to the existing formula. Cream is prepared by separating the oil and water phases. Each oil phase and water phase were heated to 50^0C until all melted. Then the water phase was added to the oil phase, mixed and stirred constantly at room temperature and formed a cream base. The yodium leaf extract is mixed into the base and stirred until homogeneous. Cream is put in a container.

Evaluation of physical characteristic cream

In this study several tests were carried out to evaluate the **physical characteristic** of yodium leaf extract cream (*Jatropha multifida L.*), which consisted of:

1. Organoleptic test

   Organoleptic testing of yodium leaf extract cream was carried out by observing the shape, color change and

aroma of the cream formulation (Mardikasari et al., 2017) .

2. Homogeneity Test
   Homogenity testing of yodium leaf extract cream was carried out by taking a small sample of the cream formula, then placing a small amount of cream between the two glass slides. The arrangement of coarse or inhomogeneous particles was observed (Mardikasari et al., 2017).
3. Test of pH level
   The pH test was carried out by storing each sample of yodium leaf extract cream preparation. This is done by dipping the electrode into the cream until the pH meter shows a constant reading. Then the results of the scale reading are recorded (Mardikasari et al., 2017) .
4. Stickiness test
   As much as 0.5 gram of cream preparation is placed on an object glass that has been determined by its area (applying it on the smooth part) on the test equipment. Another glass object (a smooth surface) is placed on top of the cream, then a 500 gram load is placed for 5 minutes. The load weighing 80 grams is released so that it pulls the bottom glass object. Record the time required until the two glass objects are released.
5. Spreadability test
   The spreadability test was carried out by comparing the diameter of the spread of the cream preparation on the glass plate after being loaded. As much as 0.5 gram of base is placed in the middle of the glass plate, then the glass plate is placed on top of the preparation and left for 1 minute. The diameter of the cream spread is measured by taking the average length of the diameters of several sides. An additional load weighing 50 grams was placed on the glass, allowed to stand for 1 minute and the diameter of the spread of the cream was recorded. The experiment was continued until a constant spreadability was obtained (Shovyana & Zulkarnain, 2013).

Test of Cuts Healing in Rats

Mice were kept in plastic cages with woven wire as a cover, the bottom of the cage was covered with husks, and replaced every 3 days. 25 rats were adapted for 7 days, divided into 5 groups randomly. Before making an incision on the back of the rat anesthetized using ether. Mark the part of the rat's back where the wound will be made. Then shave the mouse fur on the back where the wound will be made. Then the part to be wound is cleaned with cotton containing alcohol. Make a wound by slashing the rat's back with a sterilized scalpel. Make cuts with a length of 1 cm. Mark the wound with a marker and measure it with a ruler. The animals used were 25 rats. In each group consisting of 5 rats, given the following treatment:

Table 2. The design of animal groups

Group	Treatment
I (Positive control group)	were smeared 0.1 gram of povidone yodium ointment
II (Negative control group)	were not given any treatment
III	Were smeared 0.1 gram of 5% yodium leaf extract cream.
IV	were smeared 0.1 gram of 10% yodium leaf extract cream
V	were smeared 0.1 gram of 15% yodium leaf extract cream

The treatment was carried out every day and Measuring the length of the incision using a ruler is carried out every day.

Data analysis

Univariate analysis of the data was carried out for describe the physical characteristic of yodium leaf extract cream and cuts healing process. The difference of cuts healing process in groups were analyzed by Anova statistical test followed by Post Hoc analysis used the SPSS program and $p < 0.05$ was chosen as the minimum level of significance.

RESULT AND DISCUSSION

The extract was prepared using the maceration method. The 96% ethanol solvent was chosen because

of its semi-polar nature, which is expected to attract polar and non-polar compounds. 96% ethanol has a polarity index of 5.2 so it is categorized as a semi-polar solvent (Sadek, 2002). 96% ethanol is an organic compound that has constituent elements such as carbon, oxygen and hydrogen so that it can mix with water which is considered polar and can be non-polar because ethanol contains aliphatic hydrocarbon groups. Therefore, the nature of 96% ethanol can dissolve secondary metabolites such as alkaloids, flavonoids, saponins, tannins, terpenoids and anthraquinones (Fadillah, 2014). Extraction results from 600 g of yodium leaf powder give a91 g viscous extract or 13,78% rendemen. . The resulting viscous extract weight shows a yield percentage of 13.78%.

The results of organoleptic observations of cream preparations were green in color, had a distinctive odor and the consistency of semi-solid preparations. In the physical test results of homogeneous cream preparations, there are no coarse grains in the cream which indicates that the preparation is homogeneous.

Table 3. Result of pH level test

Formula	pH Level							required value range
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
1	6	6	6	6	6	6	6	4-8
2	6	6	6	6	6	6	6	
3	6	6	6	6	6	6	6	

The pH test obtained a stable pH value for the 3 formulas from the first to the 7th day, namely 6. This value met the required range of pH values, namely 4-8. If the pH value is too low it can cause scaly skin and if the pH is too high it can cause skin irritation (Mailana et al., 2016) .

Table 4. Stickiness and spreadability of Yodium leaf extract cream

Formula	Stickiness value (seconds)	Required value range (seconds)
F1	4,1	2-300
F2	4,3	
F3	4,5	

Table 5. Spreadability of Yodium leaf extract cream

Formula	**Load weight (g)**	**Spreadability (cm)**							**Average (cm)**	Required value range **(cm)**
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7		
F1	0 g	4,5	4,8	5,0	5,1	5,1	5,2	5,2	4,2	4 – 7
	50 g	5,0	5,4	5,2	5,5	5,6	5,8	5,1	5,3	
	100 g	5,5	5,8	5,5	5,5	5,7	5,9	5,9	5,6	
	150 g	5,8	6,2	6,0	5,7	5,9	6,2	6,2	6,0	
	200 g	6,1	6,3	6,3	6,3	6,4	6,4	6,5	6,3	
F2	0 g	4,0	4,5	4,8	5,2	5,4	5,5	5,5	4,9	4 – 7
	50 g	4.5	5,6	5,1	5,3	5,5	5,5	5,7	5,3	
	100 g	5,5	5,3	5,6	5,7	5,8	5,8	5,9	5,6	
	150 g	5,8	6,0	5,7	6,1	6,1	5,8	6,3	5,9	
	200 g	6,4	6,0	6,0	6,3	6,2	6,4	6,4	6,2	
F3	0 g	4,0	4,6	4,7	5,1	5,1	5,5	5,3	4,9	4 – 7
	50 g	5,2	5,1	5,3	5,5	5,4	5,5	5,6	5,3	
	100 g	5,7	5,8	6,0	5,9	6,1	6,3	6,4	6,0	
	150 g	6,0	5,9	6,2	6,3	6,5	6,5	6,3	6,2	
	200 g	6,2	6,0	6,3	6,4	6,3	6,5	6,5	6,3	

The results of the spreadability test of the three formulations met the requirements. The results can be seen in table 5. The spreadability test is responsible for the ease of use of the cream preparation. The greater the scattering value, the greater the spreading ability, and the smaller the spreading power value, the smaller the spreading ability (Sari et al., 2015). The results of the spreadability test for the cream extract met the requirements, namely > 4 seconds (Hapsari, 2016).

This study used 25 wistar strain white rats as test animals which were divided into 5 treatment groups for 9 days. The first group was a positive control that was given povidone yodium ointment. The second group was given 5% yodium leaf extract cream, the third group was given 10% yodium leaf extract cream, the fourth group was given 15% yodium leaf extract cream and the fifth negative control group was not given any treatment. The reason for using povidone yodium ointment in positive controls is because it is an antiseptic for wounds containing 10% povidone yodium extract which can help the wound healing process and trigger the formation of new tissue, and can prevent or treat germs that cause wound infections on the skin.

From the results of research conducted on the healing effect of cuts of yodium leaf extract cream (*Jatropha multifida* L.) on the backs of rats with several concentrations, where observations were made after the rats were slashed. Treatment of the wound was carried out using povidone yodium ointment and yodium leaf extract cream (*Jatropha multifida* L.) with different concentrations, carried out topically by administering the drug three times a day, with measurement times every day.

Measurement of wound length on day 1 to day 9 experienced a change in wound length. Which on the first day the incision was still open with a length of 10 mm on the day and the wound healed on the 9th day (wound closure).

Table 6. Length of cuts day 1 until day 9

Group	Length of cuts (mm)									
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Decrease of cuts length
Positive control	10	9	8.1	7.1	6.2	4.8	3	1.4	0.4	9.6
P1 (5%)	10	9	8.2	7.3	6.2	4.7	3.2	1.4	0.8	9.2
P2 (10%)	10	8.4	7.7	6.4	5.3	4.4	3.4	2.2	0.8	9.2
P3 (15%)	10	8.4	7.3	6.0	4.2	2.6	1.3	0.2	0	10
Negative control	10	9	8.1	7.1	6.2	4.8	3	1.4	1.4	8.6

Measuring the length of the wound in each group of cream preparations of yodium leaf extract (*Jatropha multifida* L) on the first day, the length of the wound was 10 mm. on day 8 the wound length was 2-0.2 mm, and on day 9 the wound had not completely healed except for the F3 group with a wound length of 0 mm completely healed on day 9. The results can be seen in Table 6. Based on the average presentation of the results of reducing the length of the incision, the highest reduction was found in 15% yodium leaf extract cream. The graphic results show that 15% yodium leaf extract cream applied topically heals cuts faster than the positive control using a branded ointment containing 10% povidone yodium. The function of the positive control is to compare whether the test substance can have the same effect as or more than the cut drug used as a positive control.

According to Agramula, the wound process closes after the wound undergoes the process of removing the scab. This indicates that the growth of new cells has occurred by concluding the edges of the wound. The scab is released where the underlying tissue is dry and the edges of the wound are starting to pull towards the middle.

Based on the results of research for closed wounds on the use of each formula also shows that there is no significant difference between each concentration. According to Yunitasari et al (2016) in natural medicine there is often a decrease in activity with increasing dose or concentration, this happens because the compound

components they contain are not single but consist of various chemical compounds where these components work together to cause effects, but increasing the dose of the number of chemical compounds contained more and more so that adverse interactions occur which cause a decrease in the effect.

A number of previous studies have shown that the presence of alkaloids, flavonoids, saponins and tannins in various plants has a healing effect on wounds. In the process of healing cuts, tannins help speed up the wound healing process, this is because tannins function as an astringent where astrigen is a drug that has the ability to precipitate proteins on the surface of cells that have low permeability, which can cause closing of skin pores, hardening the skin. , stop light exudate and bleeding According to Ifora et al (2017). Mixed compounds in the form of flavonoids have a role as an antibacterial by means of protein denaturation which causes disturbances in cell formation, thereby changing the composition of the protein components, when the function of the cell membrane is disrupted, it causes an increase in cell permeability resulting in damage to bacterial cells and bacterial cells will die (Ifora et al, 2017).

The content of saponins, is able to accelerate the process of re-epithelialization of the epidermal tissue and infiltration of inflammatory cells in the wound area (Izzati, 2015). Saponins are called growth factors because the mechanism of action of saponins can stimulate the formation of new cells by the multiplication and growth of vascular endothelial cells, vascular smooth muscle cells and fibroblasts, causing cellular growth which can eventually repair damaged blood vessel walls. Saponins can increase the number of macrophages that migrate to the wound area, thereby increasing the production of cytokines which will activate fibroblasts in the wound tissue, then trigger the formation of collagen which has a role in the wound healing process. Saponin compounds are known to be used to stop bleeding which has precipitating and coagulating properties of red blood cells and can stimulate collagen growth in the wound healing process (Igbinosa et al., 2009) .

The difference in the decrease in the length of the incision between groups was analyzed using the ANOVA statistical test. The results of the normality test with Shapiro-Wilk obtained a p value > 0.05, which means that the data is normally distributed. The results of the homogeneity test showed that the data were homogeneous with a value of p = 0.409 (> 0.05) which indicated that the data came from the same population. In the Oneway ANOVA test results, a significance value of 0.336 was obtained, so p> 0.05 which stated that there was no significant difference or no difference in the decrease in the length of the incision between groups. From the results there were differences in wound healing between formulas where the 15% extract formula could close the incision faster than the 5% and 10% formulations but the differences in the groups that occurred were not significant.

CONCLUSION

Based on the results of the study, it can be concluded that cream preparation of yodium leaf extract (Jatropha multifida L) has effectiveness on wound healing in rats for 9 days. At a concentration of 15% yodium leaf extract cream (*Jatropha multifida* L) it was more effective in healing cuts in rats for 9 days.

AUTHOR CONTRIBUTION

ELS and NDD carried out study concept, design and drafting of the manuscript. ELS provide treatment to animal subject and prepared the extract. NDD participated in statistical analysis. All authors read and approved the final manuscript

CONFLIC OF INTEREST

This research was conducted purely as a research project for the development of pharmaceutical sciences, without any conflicts of interest and finances with any party.

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