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Effectiveness of Cream Preparations Combination of Bay Leaf Extract (Syzygium polyanthum Wight) and Papaya Leaf (Carica Papaya L) as Anti-Inflammation

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ABSTRACT

Bay leaves (Sygyzium polyanthum Wight) and papaya leaves (Carica papaya L) are plants that have anti-inflammatory activity due to their flavonoid compounds. The purpose of this study was to determine the formulation of bay leaf and papaya leaf extracts into cream preparations. The treatment group consisted of 4 groups. The first group is the positive control (voltarene), the second group is the negative control (1% carrageenan). The third group was the group that was given the combination cream treatment of bay leaf and papaya leaf extract formula 2 and the fourth group was the group that was given the cream treatment combination of bay leaf and papaya leaf extract formula 3. The anti-inflammatory test was carried out based on observations for six hours by looking at edema volume and edema percentage. LSD test results showed that the cream formula 2 treatment (anionic) and the cream formula 3 treatment (nonionic) showed a significant difference with the negative control with a significance value of 0.000 ($p < 0.05$). This shows that formula 2 cream treatment (anionic) and formula 3 cream treatment (nonionic) can potentially reduce edema volume and can inhibit edema on the soles of rats induced with carrageenin.

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1. INTRODUCTION

Indonesia is one of the Asian countries where the potential users of medicinal plants are the largest in the world besides China and India [1]. In Indonesia alone, there are 90% of plant species that have medicinal properties and it is suspected that only around 9,000 plant species have medicinal properties (Salim and Munadi, 2017). Many people use various ingredients from roots, leaves, fruit and tubers to cure various diseases [3]. The use of drugs with natural ingredients is considered safer than the use of synthetic drugs, this is in accordance with the government's statement, namely the community to return to nature or back to nature and also because traditional medicines have relatively fewer side effects than synthetic drugs [4].

Palupi & Wardani, (2017) said that the non-steroidal anti-inflammatory drug (NSAID) that is often used by the public is dicofenac sodium, which has side effects such as nausea, gastritis, skin erythema and headache. There are side effects in using these drugs so another alternative source of treatment for inflammation is sought. Several types of plants have anti-inflammatory properties that are useful for maintaining a healthy body. One

of the plants that has these properties is bay leaf (Syzygium polyanthum Wight) which is rich in flavonoids [7]. In addition, papaya leaves (Carica papaya L) are also proven to have flavonoid compounds which have anti-inflammatory properties [8]. These two types of plants can be a natural alternative for those who want to relieve inflammation without adverse side effects.

Plants can be used as anti-inflammatory drugs in various dosage forms, such as a cream made from a combination of bay leaf extract (Syzygium polyanthum Wight) and papaya leaves (Carica papaya L). Topical use of drugs is generally the first choice in treating skin diseases because drugs work directly on the skin. One of the most commonly used topical drug dosage forms is cream, which is a semi-solid dosage form with one or more drug ingredients dissolved or dispersed in a suitable base [9]. Creams have the advantages of being easy to apply, comfortable to use, non-sticky, and easily washed off with water [10].

Until now, there have been no reports regarding the manufacture and research of cream preparations that combine extracts of bay leaves (Syzygium polyanthum Wight) and papaya leaves (Carica papaya L) as anti-inflammatories. Therefore, researchers are interested in conducting this research by making a cream preparation containing a combination of the two extracts as an anti-inflammatory drug.

2. METHODS

2.1. Tools and Materials

The tools used in this study were laboratory glassware, analytical scales, mortar, stamper, rotary evaporator, waterbath, and plestimograph. The materials used in this study were bay leaves and papaya leaves from Bojongsari Village, Kec. Bojongsari, Kab. Purbalingga Central Java Province, 70% ethanol, stearic acid, cetyl alcohol, glycerin, tween 80, span 80, methyl paraben, propyl paraben, TEA, and Aquadest.

2.2. Research Procedure

2.2.1 The simplification stage

Bay leaves and papaya leaves that have been collected are each cleaned of adhering dirt (wet sorting) and then washed with running water until clean, then drained to remove the remaining washing water. Bay leaves and papaya leaves that have been clean and free of washing water, then chopped and dried in the sun until dry, then cleaned again of dirt that may not have disappeared when conditions were dry. The dried simplicia was then crushed to become powdered simplicia and then sieved using a 40 mesh sieve and then weighed to obtain the final weight of the simplicia. Stored in a dry and clean container.

2.2.2 Extract manufacturing stage

Each 500 grams of papaya leaves and bay leaves were weighed and added to a separate container. Then, 70% ethanol solvent was added to each container until the leaves were completely submerged. Maceration was carried out for 3x24 hours while occasionally stirring, then kept at room temperature protected from light. After that, the filtrate was concentrated with a rotary evaporator to produce thick extracts of bay leaves and papaya leaves. The resulting extract weight is then weighed to calculate the yield [7].

2.2.3 Anti-Inflammatory Activity Test

1. Preparation of Test Animals
   The test animals used in this study were male Wistar rats with a body weight of 150-200 grams. The treatment group consisted of four groups. The first group was the positive control (voltarene), the second group was the negative control (1% carrageenan), the third group was the group that was given the combination cream treatment of bay leaf and papaya leaf extract formula 2, and the fourth group was the group that was given the combination cream treatment with leaf extract. salam and papaya leaf formula 3.
2. Preparation of Carrageenin Suspension
   Carrageenin solution used as an inflammatory agent was prepared by dissolving 1 gram of carrageenin in 0.9% physiological NaCl solution in a 100 ml measuring flask to obtain a carrageenin concentration of 1% (w/v).

3. Testing of Anti-Inflammatory Activity of Cream Preparations Combination of Bay Leaf Extract and Papaya Leaf

   The stages of testing the anti-inflammatory activity of a cream combination of bay leaf and papaya leaf extracts are as follows:

   a) Prior to treatment, the animals were acclimatized for 7 days and fed. Animals are considered healthy if they do not experience significant changes in body weight and visually do not show signs of illness.
   b) Rats were fasted for ± 18 hours before testing, but drinking water was still given.
   c) With the help of a marker, each rat's hind left leg was marked on the lateral malleus so that the insertion of the foot into the mercury on the plethismometer was correct.
   d) On the test day, rats were randomly divided into 4 groups. Each group consisted of 6 rats, then each group was weighed and the volume of their legs was measured, and expressed as the initial volume (Vo).
   e) The left legs of all rats were injected subplantarly with 0.1 mL of 1% NaCl carrageenan suspension
   f) One hour after injection of carrageenan suspension, each group was treated topically as follows:
      - The first group (negative control) was given 1% carrageenin solution.
      - The second group (positive control) was given Voltaren® Emulgel.
      - The third group was treated with anionic formula 2 cream.
      - The fourth group was treated with nonionic formula 3 cream.
   g) One hour after administration of the preparation, the volume of the rat's feet was measured by dipping the rat's foot into the plestimometer and expressed as Vt (foot volume at hour t). Measurements were carried out for 6 hours.
   h) The percentage of inflammation of each rat was calculated by the following equation:

$$\%\, radang = \frac{Vt - V0}{V0} X100\% \quad (1)$$

3. RESULTS AND DISCUSSION

The research on the formulation of cream preparations of bay leaf extract (Syzygium polyanthum Wight) and papaya leaf (Carica papaya L) aims to determine the anti-inflammatory effect of cream preparations containing bay leaf and papaya leaf extracts in cream preparations. The method of measuring the anti-inflammatory effect used in this study was to use a plestimometer and carrageenan as inducers. This method was chosen because it is a method of testing anti-inflammatory activity that is simple, easy to perform and frequently used. The use of carrageenan as an inflammation inducer has several advantages, including not leaving scars, not causing tissue damage and providing a more sensitive response to anti-inflammatory drugs [11].

Carrageenan as an irritant compound induces cell injury through the release of mediators that initiate the inflammatory process. At the time of the release of inflammatory mediators there is maximal inflammation and lasts several hours. Inflammation induced by carrageenan is characterized by increased pain, swelling. Inflammation caused by carrageenan induction lasted for 6 hours and gradually reduced within 24 hours [12].

In this study inflammation was created by inducing the soles of rats' feet with 1% carrageenan suspension with an injection volume of 0.1 mL. Measurement of anti-inflammatory power was carried out by observing the ability of a combination cream of bay leaf and papaya leaf extract to reduce the swelling of the legs of experimental animals due to injection of 1% carrageenan suspension. After being injected with carrageenan, the rats showed swelling and redness on the rat's feet. Measuring the volume of inflammation on the soles of rats using a plestimometer can be influenced by several factors, including the difficulty in codifying the test animals and the clarity when reading the scale. This can be reduced by calming the test animal, giving clear

boundaries with a permanent marker on the ankles of the rats, the volume of mercury must be the same each time the measurement, the rat's feet must remain submerged to the mark [13].

In this study, a voltarene emulgel was used as a positive control. Voltaren emulgel is used because voltaren emulgel is included in the class of non-steroidal anti-inflammatory drugs (NSAIDs) which have a mechanism of inhibiting prostaglandin synthesis by inhibiting the cyclooxygenase enzyme. In addition, Voltaren Emulgel was used as a positive control based on topical anti-inflammatory products that are already on the market. By using a positive control that has been circulating in the market, it can later be used as a comparison for cream extracts of bay leaves and papaya leaves.

In this anti-inflammatory test, 2 cream formulas with different emulsifiers were used. The anionic emulsifier used formula 2 and the nonionic emulsifier used formula 3. The choice of formula 2 and formula 3 was because in testing the physical properties of the cream preparations the two formulas showed the best results than the other formulas.

Table 1. The results of edema volume for cream preparations combined with bay leaf and papaya leaf extracts

Group	Observation time (hours)						
	0	1	2	3	4	5	6
Group 1 (negative control)	0,01 ml	0,03 ml	0,033 ml	0,035 ml	0,033 ml	0,035 ml	0,03 ml
Group 2 (positive control)	0,01 ml	0,028 ml	0,026 ml	0,025 ml	0,025 ml	0,023 ml	0,023 ml
Group 3 (FA2 Cream)	0,01 ml	0,028 ml	0,026 ml	0,026 ml	0,026 ml	0,025 ml	0,025 ml
Group 4 (FN3 Cream)	0,01 ml	0,028 ml	0,026 ml	0,026 ml	0,026 ml	0,025 ml	0,025 ml

The results of edema volume in table 1 show that edema was seen in all treatment groups compared to the soles of the rats' feet before injection of carrageenan. This is because carrageenin works by inducing phospholipids (mast cell membranes) found in the soles of rats' feet. Inflammation caused by carrageenan is local and will gradually decrease within 24 hours. In the negative control group, carrageenin injection showed the highest increase in edema. This shows that carrageenin actually causes inflammation. The positive control group, the formula 2 cream treatment group (anionic) and the formula 3 cream treatment group (nonionic) showed a significant difference in edema volume with the negative control. This shows that the voltaren emulgel as a positive control and cream treatment in formula 2 and formula 3 had the effect of reducing edema in rat feet [12]. The positive control group showed edema at 1 hour. After 1 hour, the edema volume decreased. This decrease in edema volume is due to the inhibition of cyclooxygenase by diclofenac sodium, which is an NSAID non-steroidal anti-inflammatory drug (Hidayati et al, 2008). Diclofenac sodium is usually used to treat inflammation in rheumatoid arthritis, osteoarthritis and gout. Diclofenac sodium given orally will be absorbed quickly and almost completely, namely ± 99% in the digestive tract [14].

In the cream treatment group formula 2 (anionic) and formula 3 (nonionic) also showed an effect of reducing edema volume. The combination cream of bay leaf and papaya leaf extract has an anti-inflammatory effect topically because it contains flavonoids based on a qualitative flavonoid test. Flavonoids are compounds that play a role in inhibiting the inflammatory process by inhibiting the cyclooxygenase enzyme which plays a role in the synthesis of prostaglandins.

The edema volume data for the control group and the treatment group were then calculated by the percent edema value. The results of this edema percentage are then used to calculate the AUC value and anti-inflammatory power (% DAI). The following results of edema percentage from each treatment group are shown in Table 2.

The results of table 2 show that the negative control has the largest percentage of edema compared to the other test groups. In the negative control, edema formed maximally at 5 hours and decreased at 6 hours. This shows that 1% carrageenan is a good edema-inducing agent and can cause significant inflammation. Meanwhile, the positive control group had the smallest percentage of inflammation followed by the cream

formula 2 (anionic emulsifier) and formula 3 (nonionic emulsifier) treatment groups. In group 2, group 3 and group 4 the percentage of inflammation increased from 1 hour and showed a decrease from 2 to 6 hours [12].

The first hour there was an increase in edema in all treatment groups. According to Singh (2014) states that in the first hour after injection of carrageenan there will be an increase in edema because carrageenin will induce cell injury so that these cells will release mediators such as histamine, serotonin and bradykinin as well as excess prostaglandin production in the tissues. These mediators will later trigger inflammation and the appearance of edema.

Table 2. The percent yield of the cream preparation is a combination of bay leaf and papaya leaf extracts

Group	Percent edema (%)					
	1st hour	2nd hour	3rd hour	4th hour	5th hour	6th hour
Group 1 negative control (carrageenin)	200% ± 0.0000	233% ± 0.5164	250% ± 0.5477	233% ± 0.5164	250% ± 0.5477	200% ± 0.0000
Group 2 positive control (voltarene emulgel)	183% ± 0.4082	167% ± 0.5164	150% ± 0.5477	150% ± 0.5477	133% ± 0.5164	133% ± 0.5164
Group 3 FA2 cream treatment$_2$	183% ± 0.4082	167% ± 0.5164	167% ± 0.5164	167% ± 0.5164	150% ± 0.5477	150% ± 0.5477
Group 4 FN cream treatment $_3$	183% ± 0.4082	167% ± 0.5164	167% ± 0.5164	167% ± 0.5164	150% ± 0.5477	150% ± 0.5477

Table 3. Anti-inflammatory anova results

Tests of Normality

		Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Treatment	Statistic	df	Sig.	Statistic	df	Sig.
Volume udem	Negative group	.259	6	.200*	.825	6	.098
	Positive group	.221	6	.200*	.909	6	.427
	F2	.262	6	.200*	.866	6	.211
	F3	.262	6	.200*	.866	6	.211

*. This is a lower bound of the true significance.
a. Lilliefors Significance Correction

Test of Homogeneity of Variances

		Levene Statistic	df1	df2	Sig.
Volume udem	Based on Mean	1.464	3	20	.254
	Based on Median	.777	3	20	.520
	Based on Median and with adjusted df	.777	3	17.056	.523
	Based on trimmed mean	1.355	3	20	.285

ANOVA

Volume udem

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	20983.167	3	6994.389	23.089	.000
Within Groups	6058.667	20	302.933		
Total	27041.833	23			

The data obtained were then analyzed using the Kolmogorov Sminov statistical test to determine the normality of the data. The Kolmogrov sminov test in the negative control group (1% carrageenan) yielded a significance value of 0.098 (p > 0.05), the positive control treatment group (voltarene emulgel) yielded a significance value of 0.427 (p > 0.05), the cream formula 2 treatment group (anionic) yielded a significance value of 0.211 (p > 0.05), the formula 3 treatment group (nonionic) yielded a significance value of 0.211 (p > 0.05), it is known that the test data population meets the normality test requirements. Furthermore, a test of homogeneity of variance level was carried out to determine whether the data population tested had a homogeneous variant or not. The results of this test showed that the data of the negative control treatment group, the positive control group, the cream formula 2 (anionic) treatment group and the cream formula 3 (nonionic) treatment group had homogeneous variants, so that it could be continued with the one-way ANOVA test. Furthermore, the data were analyzed using the Post Hoc Test with the LSD test to determine whether there was a significant difference or not.

Table 4. LSD test results

Multiple Comparisons

Dependent Variable: Volume udem
LSD

(I) Treatment	(J) Treatment	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Negative group	Positive group	75.000*	10.049	.000	54.04	95.96
	F2	63.667*	10.049	.000	42.71	84.63
	F3	63.667*	10.049	.000	42.71	84.63
Positive group	Negative group	-75.000*	10.049	.000	-95.96	-54.04
	F2	-11.333	10.049	.273	-32.29	9.63
	F3	-11.333	10.049	.273	-32.29	9.63
F2	Negative Group	-63.667*	10.049	.000	-84.63	-42.71
	Positive Group	11.333	10.049	.273	-9.63	32.29
	F3	.000	10.049	1.000	-20.96	20.96
F3	Negative Group	-63.667*	10.049	.000	-84.63	-42.71
	Positive Group	11.333	10.049	.273	-9.63	32.29
	F2	.000	10.049	1.000	-20.96	20.96

*. The mean difference is significant at the 0.05 level.

LSD test results showed that the cream formula 2 treatment (anionic) and the cream formula 3 treatment (nonionic) showed a significant difference with the negative control with a significance value of 0.000 (p <0.05). This shows that formula 2 cream treatment (anionic) and formula 3 cream treatment (nonionic) can potentially reduce edema volume and can inhibit edema on the soles of rats induced with carrageenin. While the cream formula 2 treatment (anionic) and the cream formula 3 treatment (nonionic) showed no significant difference with the positive control group (voltarene emulgel). This shows that formula 2 cream treatment (anionic) and formula 3 cream treatment (nonionic) have the ability to inhibit edema. This is because the extracts of bay leaves and papaya leaves contain flavonoids based on the qualitative tests that have been carried out. The anti-inflammatory activity in bay leaves and papaya leaves is due to the presence of flavonoid compounds whose mechanism of action inhibits the cyclooxygenase pathway in the arachidonic acid metabolic pathway [7].

Table 4. The results of the AUC value of cream preparations combined with bay leaf and papaya leaf extracts

Group	AUC (mm.hour)
Group 1 negative control (carrageenin)	0,03
Group 2 positive control (voltarene emulgel)	0,02
Group 3 treatment cream formula 2 (anionic)	0,02
Group 4 treatment cream formula 3 (nonionic)	0,02

The results of the AUC value (table 4.11) show that the AUC value of the negative control group with a value of 0.03 is much greater when compared to the positive group and the cream treatment group of formula 2 and formula 3. This shows that the negative control group, namely carrageenin, can indeed induce edema characterized by an increase in rat foot edema volume. The function of the cream treatment, both formula 2 and formula 3, is to see whether there is an anti-inflammatory effect in the cream preparation. There was a significant difference in the average AUC value between the cream-treated control group and the negative control group. This shows that the cream treatment group has an anti-inflammatory effect. In the positive control group, there was a significant decrease in edema volume when compared to the negative control group and the cream treatment group. This shows that the positive control, namely Voltaren Emulgel, really has the ability as an anti-inflammatory agent. The AUC data obtained is then used in calculating the percentage of anti-inflammatory power (% DAI). The following results of the percent anti-inflammatory power of each treatment group are shown in Figure 1.

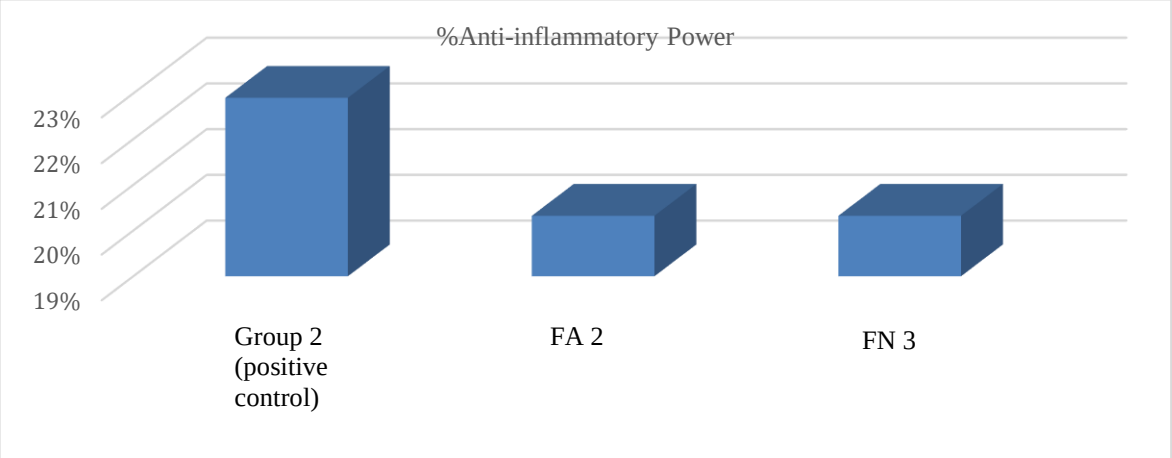

Fig. 1. Percent of the anti-inflammatory power of a cream combination of bay leaf and papaya leaf extracts

The results of calculating the average total AUC for each group (Table 4.11) that have been obtained are used to calculate the percent inhibition of inflammation. The percentage of inflammation inhibition is used to see how much the ability of a compound to inhibit the inflammatory process in percent (%). Based on the results of statistical analysis, it was found that the positive control had greater anti-inflammatory power compared to the formula 2 and formula 3 treatment groups. This was because the positive control used the drug Voltaren Emulgel, which Voltaren Emulgel is a class of steroidal anti-inflammatory drugs (NSAIDs) which has a mechanism of inhibiting the synthesis of prostaglandins by inhibiting cyclooxygenase enzymes. In addition, the use of Voltaren Emulgel as a positive control is based on topical anti-inflammatory products that are already on the market. By using a positive control that has been circulating in the market, it can later be used as a comparison for cream extracts of bay leaves and papaya leaves (Tomas, 2014).

The combination cream of bay leaf and papaya leaf extracts has an anti-inflammatory effect with an average percentage of inhibition in group 3 treatment of formula 2 (anionic) cream and group 4 of treatment of formula 3 cream (nonionic) is 20.3225%. The combination cream of bay leaf and papaya leaf extract has an anti-inflammatory effect topically because it contains flavonoids based on a qualitative flavonoid test. According to Mohamad et al (2014) as anti-inflammatories, several types of flavonoids can inhibit the cyclooxygenase and lipooxygenase pathways. Flavonoids are more likely to inhibit COX-2 so that they can be good anti-inflammatory drugs because they can reduce side effects on the gastrointestinal tract [15].

4. CONCLUSION

Provide a statement that what is expected as stated in the "Introduction" chapter can ultimately result in the "Results and Discussion" chapter, so there is compatibility. Moreover, the authors can elaborate on the prospect of the development of research results and inspire further studies (based on results and discussion).

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