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The Anti-Inflammatory Activity of Cherry Leaf Extract (*Muntingia Calabura* L.) Balm Stick

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Abstract. In previous studies, cherry leaf extract has been shown to be anti-inflammatory. This means a preparation is needed to deliver the extract. Balm stick is an innovation in a stem-shaped balm that makes it easier to be used so that cherry leaf extract is made into a balm stick preparation. This study aims to determine the anti-inflammatory activity of the balsam stick of cherry leaf extract topically. The study was conducted by varying the concentration of cherry leaf extract at 2.5%, 5%, and 10% and tested its anti-inflammatory activity in male white rats induced by carrageenan. The experimental animals were divided into test groups, whereby the positive control group was given 2.5% hydrocortisone balm stick, the negative control group was given the balm stick preparation and the 3 test groups were given 2.5%, 5%, and 10%. The observations were made using a plethysmometer by looking at the volume of edema in the carrageenan-induced rat paws. Balm sticks with a concentration of 5% and 10% had an inhibitory power of more than 50% with a value of 72% and 95.83% while a concentration of 2.5% had an inhibitory power of 44.44%. Balm stick ethanol extract of cherry leaves has anti-inflammatory activity with concentrations of 5% and 10% and demonstrates an increase in anti-inflammatory activity, whereby the greater the concentration, the greater the anti-inflammatory activity produced.

1. Introduction

Advances in science and technology that are increasingly rapid and sophisticated do not shift the role of traditional medicine. In Indonesia, there are about 30,000 types of plants and more than 1,000 species have been known for their benefits as medical plants. One of the medical plants that can be used is cherry [1].

Kersen (*Muntingia calabura* L.) is a fruiting tree that can grow in less fertile soil and is able to tolerate acid, alkaline, and drought conditions. Cherry leaves have various pharmacological effects such as cardioprotective, antipyretic, antioxidant, anti-inflammatory, antidiabetic, antibacterial, and antiulcer [2]. Flavonoids, saponins, and tannins are the ingredients in cherry leaves. The flavonoids contained in cherries are flavones, flavanones, flavans, and biflavans. The content of flavonoids has received much attention as this group of compounds has many activities, one of which is anti-inflammatory [3].

Inflammation is a normal protective response to tissue injury caused by physical trauma, damaging chemical substances or microbiological substances. Broadly speaking, inflammation is divided into two basic patterns; namely acute inflammation and chronic inflammation [4]. Tissue damage due to trauma, microbial invasion, or harmful compounds can cause acute inflammation lasting several days characterized by sub-acute inflammation. Sub-acute inflammation is the period between acute and

chronic inflammations [5]. One of the most commonly used methods of Paw edema is based on its ability to inhibit the edema produced in the paws of mice after injection of carrageenan. The effect that can be measured is the volume of edema in the feet of the proinflammatory rats injected before and after using a plethysmometer[6].

The stick balm is an innovation from a stem-shaped balm to make it easier to be used and to avoid hand soiling, so cherry leaf extract is made in a balm stick preparation. The selection of the balm stick formula refers to the formulation carried out by Yati et al. with the concentration that can produce the balm stick with the best physical properties. The formulation of the balm stick consists of wax, fat, and oil[7]. The oil acts as an emollient to give a smooth and soft texture to the skin when applied.

The oil used as a base is olive oil. It is a fatty oil derived from ripe olives (*Olea europaea* L.). Olive oil has many benefits for body health, facial beauty, hair and skin protection, especially due to the high content of oleic acid in olive oil. [8]. The use of olive oil as a base has many advantages with an emollient effect and does not clog pores which makes it unable to cause irritation and is safe to use [9]. This study was conducted to determine the effect of the concentration of balsam sticks of cherry leaf ethanol extract on the inhibition of edema in the feet of male white rats induced by carrageenan.

2. Material and Methods

Materials

Cherry leaf extract (*Muntingia calabura* L.), which was obtained and identified by the Conservation Research Center and Botanical Garden, Indonesian Institute of Sciences in Bogor, Indonesia contains Cera alba (Merck), adeps lanae (Mercks), cetyl alcohol (Mercks), butyl hydroxytoluene (Mercks), olive oil (Bertolli), and carrageenan (Mercks). The comparison material used in this study was hydrocortisone (PT. Kimia Farma).

Mixture Test

This mixture test aims to determine the use of an appropriate surfactant in the formulation of balsam sticks of cherry leaf ethanol extract. The test is carried out with a ratio of 1:1 ethanol extract of cherry leaf and surfactant, which was followed by an observation of its mixability and stability [9].

Balm Stick Making

The balm stick is made with different concentrations of cherry leaf extract as shown in the table below.

Table 1. Formula for Making Balm Stick Preparations

Materials	Functions	Amount			
		F I(%)	F II(%)	F III(%)	F IV(%)
Cherry extract	Active substance	2,5	5	10	-
Cera alba	Hardener	30	30	30	30
Adeps lanae	Fastener	10	10	10	10
Cherry extract	Plasticizer	10	10	10	10
Butyl Hydroxytoluene	Antioxidant	0.1	0.1	0.1	0.1
Span 80	Emulsifier	5	5	5	-
Olive oil	Emollient	Ad 100	Ad 100	Ad 100	Ad 100

The Manufacturing of Anti-Inflammatory Test Materials

As a comparison material (positive control), hydrocortisone powder from Kimia Farma, which was made of 2.5% Stick Balm, was used. 1g of carrageenan powder was then dissolved with 0.9% NaCl to 100 ml in a Beaker glass. It was then stirred until it was dissolved completely so that the concentration obtained is 1% w/v [6].

Grouping and Treatment of Test Animals

The study was conducted experimentally with a completely randomized design, using 25 male white rats which were divided into 5 groups consisting of 5 rats. The division of the groups of rats was as follows: Group I (positive control) was given 2.5% of hydrocortisone stick balm; Group II (negative control) was given a balm stick base (F4); Group III (F1) was given 2.5% of cherry leaf extract balm stick; Group IV(F2) was given 5% of cherry leaf extract balm stick; and Group V (F3) was given 10% of cherry leaf extract balm stick.

After acclimatization for 7 days, the right hind leg of the rats was marked and measured using a plethysmometer as the initial volume. One hour before the induction of carrageenan, the right leg of the rat was smeared with the test preparation for each group 50 times to help penetrate the test preparation through the skin [7]. An hour after the administration of the test preparation, each group was induced by 0.1 ml of 1% w/v carrageenan subplantarly the paws of the rats that had been marked. Measurements were made every 1 hour for 5 hours. Changes in the level of inflammation that occurred were recorded as the volume of the rats' paws. From the data obtained, the percentage of inflammation inhibition can be determined [6].

The data obtained were tested statistically by using one-way analysis method (One Way ANOVA), to see the effect of the treatment. If it meets the requirements for the ANOVA test and if there is a treatment effect, then it is continued with the Tukey HSD test. If it does not meet the requirements of the ANOVA test, then it is continued with the Kruskall-Wallis test. Meanwhile, if there is an effect of treatment then it is followed by the Mann-Whitney test.

3. Results and Discussion

In this study, the cherry leaves used were obtained from the Research Institute for Spices and Medicinal Plants (BALITRO). The plant determination carried out by the BALITRO laboratory showed that the plant to be used in this study was cherry leaf (*Muntingia Calabura* L.). The yield of cherry leaf extract was 17.92%, with water content of 20.69%, and ash content 2%. In addition, the results of the phytochemical screening of extracts were positive for alkaloids, flavonoids, tannins, and saponins [10].

The results of the admixture test showed that both surfactants were mixed with the extract and span 80 was more mixed than tween 80. Therefore, span 80 was used for the formulation. This took place because cherry leaf extract had an HLB that was close to span 80.

The results of the organoleptic test in this study of the three formulations of the balm stick obtained the results of the texture and smell that were not much different from one formula to another. The color had a difference that F3 was more concentrated than F2 and F2 was more concentrated than F1. This shows that the concentration of the extract has no effect on the texture and smell. However, the difference in the concentration of the extract shows that the more concentration of extract used, the more concentrated the color produced on the balm stick preparation.

The results of the homogeneity test in this study of the three balm stick preparations in the three formulas showed a homogeneous arrangement. This demonstrates that all the components used in the balm stick preparation are mixed homogeneously during melting and grinding which means that after printing there are no coarse grains. It can be concluded that there is no effect of the concentration of the extract on the homogeneity of the balm stick preparation.

The pH test aimed to see whether the preparation had a pH suitable for the skin or not. The pH test was carried out using a pH meter. The test results obtained were the pH of the preparation according to a normal skin pH of 4-6 [11]. Therefore, the difference in concentration of cherry leaf extract did not affect the pH of the balsam stick preparations made.

In this melting point test, the results obtained met the requirements of the SNI 16-4769-1998 standard, namely 50-70ºC and a good balm stick preparation had a melting point of more than 50% [3]. Each of these formulas had a very high melting point because the formulation of the balm stick had a high melting point and the olive oil base contained oleic acid which was an unsaturated fatty acid composed of 18 C atoms with one double bond [12]. There was an effect of different concentrations of cherry leaf extract on the melting point shown by the one-way ANOVA test ($p<0.05$). This is because the more concentration of cherry leaf extract used, the greater the molecular weight which can affect the higher melting point (Muchson, 2013). Tukey test results showed that formula 1 was comparable to formula 2 and formula 4 ($P>0.05$). Meanwhile, formula 3 was comparable to formula 2 ($P>0.05$) and formula 3 was significantly different from formulas 1 and 4 ($P<0.05$).

According to Hariningsih (2017), the higher the adhesive power of the lipstick, the better the ability of the lipstick to adhere which makes it difficult to be removed. Moreover, the longer the stickiness of a food preparation, the more drugs that can be absorbed into the body. The results of the adhesion test in this study met the requirements of more than 4 seconds (Puspitasari et al., 2018). The results of the one-way ANOVA test showed that there was a significant difference between groups ($P<0.05$), which means that the concentration of cherry leaf extract affected the stickiness. In the Tukey test, F1 was significantly different from F2, F3 and F4 ($P<0.05$).

In the hardness test according to Balsam [3], the preparation is said to be soft if the depth of penetration of the needle is 9-10.5 with a load of 50g. The deeper the needle penetrates, the softer the preparation is. The results of the hardness test obtained from the formulation of the balm stick made from the four formulas met the requirements and were not too soft. The one-way ANOVA test showed that there was a significant difference between groups ($P>0.05$) and the results of the Tukey F1 test were comparable to F4 ($P>0.05$). Nonetheless, F1 was significantly different from F2 and F3 ($P<0.05$). In the meantime, F2 was significantly different from F3 and F4, and F3 was different from F4 ($P<0.05$).

The results of the hardness test are used to find the yield value, namely the pressure required for the preparation to spread. The yield value is inversely proportional to the needle penetration depth. According to Kadu, the greater the needle penetration depth, the smaller the required yield value. This means that the softer the preparation was made, the less effort to apply the preparation which makes it able to spread over the skin [13]. The results obtained by the yield value met the requirements of 100-1000 dyne/cm². Hence, itcan be concluded that the preparations made had good dispersion [7].

Table 2. Percentage of Udem Inhibition

Groups		Observation Time Hours				
		T60	T120	T180	T240	T300
		(%)				
Group 1 Positive Control	±	24,04 ±	69,17 ±	76,66 ±	100 ±	100 ±
	SD	32,03	41,21	23,13	0	0
Group 3 (2,5%)	±	18,33 ±	46,10 ±	-13,33 ±	27,78 ±	44,44 ±
	SD	23,86	24,66	77,36	32,15	44,27
Group 4 (5%)	±	16,67 ±	25,00 ±	10,84 ±	56,10 ±	70,27 ±
	SD	20,41	58,46	58,74	11,36	30,27
	±	23,33 ±	35,00 ±	27,50 ±	84,16 ±	95,83 ±

Group 5 (10%)	SD	34,05	57,38	40,14	25,42	9,32

Notes :

$\bar{x}$: average inhibition of edema each time

SD : standard deviation of edema inhibition over time

According to Amdeekar, anti-inflammatory treatment is successful if there is a 50% inhibition of inflammation [14]. From the average percent of edema inhibition obtained, it showed anti-inflammatory activity in each group. The anti-inflammatory activity obtained from the test group that had more than 50% anti-inflammatory activity occurred in group 4 (F2 5%) and group 5 (F3 10%). The anti-inflammatory activity in these groups was seen at the 240th and 300th minute observations.

In this study, the concentration of ethanol extract of cherry leaves could provide an anti-inflammatory effect of more than 50%, namely 5% (group 4) and 10% (group 5), by reducing the volume of edema in the feet of rats induced by carrageenan. According to Kuo [12], cherry leaves have anti-inflammatory properties because they contain flavonoids. According to Triswaningsih [10], flavonoids have a benzopyran ring structure that can bind to the cyclooxygenase and lipoxygenase enzymes which makes them able to inhibit the formation of arachidonic acid turning into prostaglandins and leukotrienes which play a role in the inflammatory process. When the formation of arachidonic acid is inhibited by binding to the cyclooxygenase enzyme, inflammation can be thwarted.

The anti-inflammatory activity produced by this cherry leaf extract balm stick is possible by way of the drug being absorbed from the outer layer of the skin by diffusion through the skin barrier, namely 3 skin compartments consisting of the outer surface of the skin, the stratum corneum, and the living tissue beneath. After being applied to the outer surface of the skin, the drug will undergo changes in structure and composition which would determine the bioavailability of the drug. The three main routes of penetration of topical drugs in the intact stratum corneum are the transcellular pathway (through the stratum corneum), the intracellular pathway (diffusion through the lipid matrix between cells), as well as the hair follicle and sweat gland pathway [15].

4. Conclusion

In this study, balsam sticks with ethanol extract of cherry leaves had anti-inflammatory activity at concentrations of 5% and 10%. They showed an increase in anti-inflammatory activity, whereby the greater the concentration, the greater the anti-inflammatory activity produced. This means that the cherry leaf extract balm stick can be used as one of the newest anti-inflammatory drug delivery systems.

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