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Patch Formulation of Rambusa (Passiflora foetida) Leave Extract as Anti-Inflammatory Agent: An In Vitro and In Vivo Study

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ABSTRACT

Rambusa leaves are known to have health benefits, including anti-inflammatory, antitumor, anticancer, antihepatotoxicity and antimicrobial. Rambusa leaves contain active compounds including flavonoid, alkaloids, tannins, saponins, and steroids which have anti-inflammatory effects. So it was developed as a transdermal route preparation in the form of a patch to overcome the problem of side effects from using oral medications on the gastrointestinal tract. Rambusa leaves are formulated into additional ingredients in the form of HPMC, methyl paraben, propylene glycol, 96% ethanol, distilled water and made into ready-to-use patches. Furthermore, an evaluation of the physical quality of the formula was carried out and its anti-inflammatory effectiveness was determined through in vitro and in vivo tests. The results show that each formula produces physical properties that meet the requirements. Apart from that, the results of the in vitro test using sodium diclofenac as a standard show that formulas 100, 200 and 300 are able to penetrate the membrane from the results of the cumulative amount of active ingredients that have been tested, whereas in the in vivo test using wistar rat test, the results of % edema were analyzed using ANOVA and the results of % inhibition were carried out in a post hoc test with LSD. The highest effectiveness was obtained in formula 300, this shows that the formula is capable of inhibiting inflammation. From these results it can be concluded that rambusa leave extract can be developed into a transdermal patch formula for anti-inflammation.

Keyword: Anti-inflammatory, Rambusa Leave, Invitro, Invivo, Patch

ABSTRAK

Daun rambusa diketahui memiliki khasiat bagi Kesehatan, antara lain sebagi antiinflamasi, antitumor, antikanker, antihepatotoksik, antimikroba. Daun rambusa mengandung senyawa aktif antara lain flavonoid, alkaloid, tannin, saponin, dan steroid yang memiliki efek antifinlamasi. Sehingga dikembangkan sebagai sedian pada rute transdermal dalam bentuk patch untuk mengatasi maalah efek samping penggunaan antiinflamasi obat oral pada saluran cerna. Daun rambusa diformulasikan dengan bahan tambahan berupa HPMC, metil paraben, propilen glikol, etanol 96%, aquadest dan dibuat menjadi patch yang siap pakai. Selanjutnya dilakukan evaluai terhadap kualitas fisik formula dan ditentukan efektivitas antiinflamasinya melalui uji invitro dan invivo. Hasil penelitian menunjukkan bahwa setiap formula menghasilkan sifat fisik yang memenuhi persyaratan. Selain itu, hasil uji invivo dengan menggunakan natrium diklofenak sebagai standar menunjukkan bahwa formula 100,200, dan 300 mampu menembus membran berdasarkan hasil jumlah kumulatif bahan aktif yang telah diuji. Uji invivo menggunakan tikus wistar Dimana hasil persen edema dianalisis menggunakan ANOVA kemudian dikonversikan ke dalam persen inhibisi yang dilanjutkan dengan analisis post hoc menggunakan LSD. Efektivitas tertinggi diperoleh pada formula 300 dibandingkan formula yang lain, yang menunjukkan formula tersebut mampu menghambat peradangan. Dari hasil tersebut dapat disimpulkan bahwa ekstrak daun rambusa dapat dikembangkan menjadi formula transdermal patch untuk antifinflamasi.

Kata Kunci: : *antiinflamasi, daun rambusa, invitro, invivo, patch*

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Introduction:

Rambusa (Passiflora foetida L.) is a wild climbing plant commonly found in rice fields, beaches, and swamps. Rambusa is known for its beneficial in treating bone diseases, anemia, cancer, blood pressure, kidney disorders, and stress. Rambusa has the ability as an anti-inflammatory, anticancer, antitumor, and antimicrobial agent, as well as antihepatotoxicity (Novian, 2022). Rambusa leaves are known to contain active compounds including flavonoids, tannins, saponins, alkaloids, and steroids that exhibit anti-inflammatory activity (Mulyani et al., 2022). The community in Jember Regency utilizes Rambusa as feed for both cattle and goats. As a result, the use of Rambusa leaves in traditional medicine is known to be minimal, and there is a lack of awareness that Rambusa leaves have numerous health benefits.

Inflammation often occurs in various parts of the body due to several factors, and in severe cases, it can lead to injuries. The mechanism of inflammation is caused by the increased presence of proinflammatory agents such as cytokines TNF-α, IL-1, and IL-6 found in the skin, which release mediators such as prostaglandin, bradykinin, histamine, and serotonin (Rahman et al., 2023). Currently, the administration of drugs is mostly done orally. However, this route has its drawbacks, such as passing through the first-pass metabolism in the liver. Additionally, it can cause reactions in the gastrointestinal tract (Manasadeepa, 2013). Therefore, there is a need to develop other routes, such as the transdermal route (Mauludiyah, 2018).

The delivery of drugs through the transdermal route is one of the developments aimed at addressing the issues caused by the factors mentioned above (Sudhanshu Mishra, 2022). One of the developed dosage forms is a patch that can penetrate the skin, allowing it to enter the bloodstream. However, this depends on the quantity and type of active substances, as well as the additives used. The composition of patch formulations is generally synthetic (Novita, 2021). In this research, a patch formulation will be developed using natural ingredients known for their anti-inflammatory effectiveness, making them safe for long-term use (Kusuma & Suparno, 2021).

A patch formulation can be developed through the delivery of active substances that can penetrate the skin membrane, namely by diffusing into the skin through the subcutaneous adipose tissue. In vitro testing, also known as penetration testing, is conducted to observe the transdermal penetration capability of Rambusa leave extract in delivering its active substances. This is done using a Franz diffusion cell apparatus, with rat skin membrane as the diffusion membrane (Novia & Noval, 2021). The development of polymers is used to support their role in controlling drug release (Fatmawaty et al., 2017).

The results of previous research indicate that the patch formula uses Hydroxypropyl Methylcellulose (HPMC) as a base, which has the ability to provide good physical stability based on the evaluation of each test. Higher concentrations of HPMC lead to increased weight, thickness, moisture absorption, and fold resistance (Wardani & Saryanti, 2021). Therefore, a formulation of a transdermal patch based on HPMC from Rambusa leave extract is being developed, and an evaluation of this formulation is underway. The expectation is that this patch formulation can penetrate the skin membrane, as indicated by the rate of penetration (flux), and can induce therapeutic effects as an anti-inflammatory. Following the selection of the preferred patch formula, in vivo testing is then conducted to assess the formulation's ability to be applied and its effectiveness as an anti-inflammatory.

Therefore, the development of Rambusa leaves as an anti-inflammatory agent in the production of patch formulations provides a solution to address issues related to long-term side effects of synthetic oral medications (Novia & Noval, 2021). Additionally, Rambusa leaves are utilized as an alternative for the active ingredient in innovative patch products that are safe, practical, economical, and efficient. It is known that there is no existing research on patch formulations developed from Rambusa leaves, especially for use as an anti-inflammatory. This has sparked the interest of researchers to develop patch formulations from Rambusa leaves that have anti-inflammatory effects.

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Methods:

Preparation of Simplisia

The prepared Rambusa leaves are then sorted and dried, not under direct sunlight. Subsequently, the Rambusa leaves are processed into powdered simplicia by being finely ground using a grinding machine (Wardani & Saryanti, 2021).

Extraction Process

The preparation of Rambusa leave extract using the maceration method involves weighing 2000 grams of the leaves, adding 96% ethanol (1:10), soaking for 2x24 hours with occasional stirring, filtering, evaporating the filtrate with an evaporator, and calculating the yield of the concentrated extract (Wardani & Saryanti, 2021).

Preparation of Formulation

The formulation is prepared with various weights of different active ingredients and additives in equal amounts, as shown in Table 1.

Table 1. Formulation of Rambusa Leave Extract Transdermal Patch

Materials	F1	F2	F3	Function
Rambusa Leave Extract	100gr 1gr 0.3gr	200gr 1gr 0.3gr	300gr 1gr 0.3gr	Active Substance Base
HPMC	10	10	10	Preservative
Methyl Paraben	40 47.7	40 46.7	40 45.7	Penetration Enhancer
Propylene Glycol				
96% Ethanol				Solvent
Aquadest				Solvent

Formula Evaluation Organoleptic test

This test includes visual observation of the form, color, and odor of each formula (Wardani & Saryanti, 2021).

Drying Shrinkage Test

The weight of the patch formula is measured after being stored in a desiccator for 24 hours, and the percentage of drying shrinkage is calculated (Wardani & Saryanti, 2021).

Thickness Test

To assess the thickness of the patch formula, a caliper is used to measure at three different points (Wardani & Saryanti, 2021).

Humidity absorption test

This test is conducted on the patch by storing it in a desiccator for 24 hours at room temperature, then weighing it. It is subsequently stored at 40°C for 24 hours and weighed again.

Fold Resistance test

To assess resistance to folding, the patch formula can be subjected to multiple folds in the same position. Resistance to folding is determined by examining the formulation, which should not easily break during storage (Wardani & Saryanti, 2021).

pH test

The pH test is conducted using a porcelain dish filled with 5 ml of distilled water with a pH of 6.5. The patch formula is placed in it and allowed to swell for 2 hours at room temperature. The pH is then observed using universal pH indicator paper (Wardani & Saryanti, 2021).

Invitro Penetration Test

According to Novia and Noval (2021) and Kaluku et al. (2022), the penetration test is conducted using a Franz diffusion cell. A phosphate buffer solution with a pH of 7.4 is used as the medium for soaking rat skin membranes. Transdermal patch formulations containing active ingredients with three different formulas are placed on both the donor and receptor compartments. A phosphate buffer with a pH of 7.4 is used to fill the receptor compartment while stirring is performed using a magnetic stirrer at a temperature of 37°C and a speed of 500 rpm. Samples from each formula in the receptor compartment are periodically collected in 3 ml aliquots at 0-180 minutes and analyzed using UV-Vis Spectroscopy.

Effectiveness Test In Vivo

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This research involved 15 wistar rats in total. The testing was conducted with 5 treatment groups, namely: the negative control group, the positive control group given Voltaren patches, and Treatment Groups I, II, and III with 3 different patch formulas. Measurements were taken using a plethysmometer on wistar rat that had been marked on their paws. All wistar rats were injected with 0.1 mL of 1% carrageenan subplantarly in their paws. Subsequently, the wistar rats were treated according to their respective treatment groups. Measurement of the percentage of inflammation inhibition began 30 minutes after 1% carrageenan injection. Measurements were taken every 30 minutes for a duration of 6 hours (Arum et al., 2022).

Results:

The physical quality evaluation results of the formulated patch from Rambusa leaves can be seen in Table 2.

Table 2. Results of the physical quality evaluation of the Rambusa leave patch formulation

Physical properties	Formula I	Formula II	Formula III	Requirement of formula
Organoleptic test	Brownish-yellow color, fine semi-solid texture, odor of rambusa leave	Brownish-yellow color, fine semi-solid texture, odor of rambusa leave	Dark brown color, fine semi-solid texture, odor of rambusa leave	Visually appropiated
Drying Shrinkage Test (%)	2,24	3,0	2,27	There is no absolute value (Wardani & Saryanti, 2021)
Thickness Test (mm)	0,81 mm	0,48 mm	0,98 mm	< 1 mm (Suryani, 2017)
Humidity absorption test (%)	0,91	3,58	0,61	≤10% (Arifin, 2019)
pH test	6	5	5	4-8 (Hartesi, 2021).
Fold Resistance test	>200x	>200x	>200x	300x (Nurahmanto, 2017)

Invitro Penetration Test

In vitro penetration testing of the patch formula was conducted to determine the extent to which the active ingredients could be released into the skin layers (Rahman et al., 2023). This was carried out by determining the optimum wavelength, and the obtained optimum wavelength was 275 nm for sodium diclofenac. Refer to Figure 1 below:

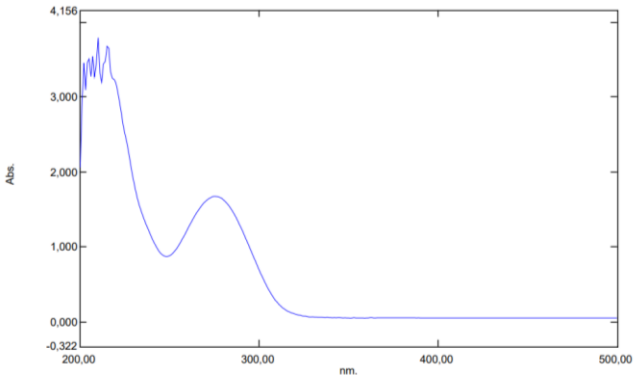

Figure 1. Wavelength of sodium diclofenac

Then, create a standard curve for sodium diclofenac to obtain the equation y = bx + a.

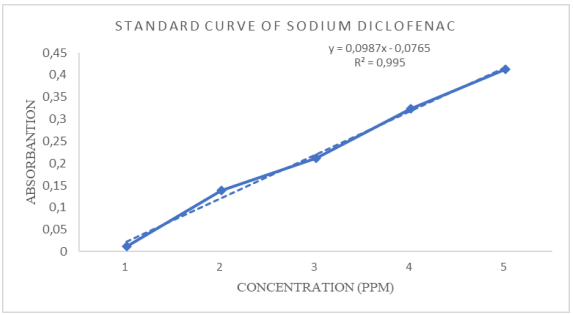

Figure 2. Calibration curve of sodium diclofenac

From the above equation, calculations were performed to determine the cumulative amount of the active ingredient in the Rambusa leave extract. This resulted in the cumulative amount of the active ingredient that penetrated the formulation with various formulas, with the order 1 < 2 < 3 apparent from Table 3, where the cumulative amount is measured per unit area within a specified time, namely a maximum of 180 minutes.

Table 3. Cumulative amount of active ingredient vs time

Time (min)	Cumulative amount of active ingredient (μg/cm²)		
	Formula 100	Formula 200	Formula 300

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Time (min)	Cumulative amount of active ingredient (µg/cm²)		
	Formula 100	Formula 200	Formula 300
0	0	0	0
15	13.933	13.34	15.711
30	19.086	18.342	22.03
60	22.702	22.275	26.159
120	26.197	26.608	32.585
180	28.943	30.762	46.998

The results from the data in the above table were then used to create a curve of the cumulative amount of the active ingredient versus time.

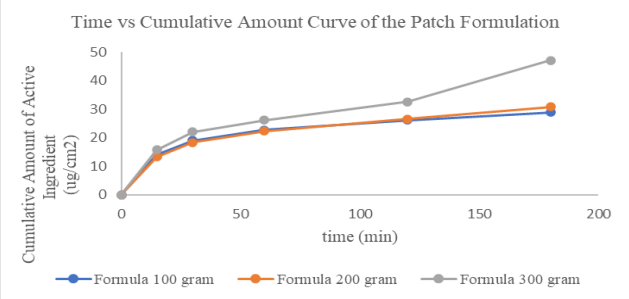

Figure 3. Time vs Cumulative Amount Curve of the Patch Formulation

In Vivo Effectiveness Test

The results of the effectiveness test of anti-inflammatory properties in the patch formulation on test animals can be found in Table 4. Calculate the percentage increase in edema volume (Sentat 2018).

Percentage of inflammation = (Vt−Vo/Vo) x 100%

Information:

Vt = Volume after carrageenan injection.

Vo = Volume before carrageenan injection

Table 4. Percentage of Edema: Results of Anti-inflammatory Test

Treatment Group	Test Animals	% Edema	Average
Carboxymethyl cellulose sodium	1	29,16	46,10
	2	34,16	
	3	75	
Diklofenak sodium	1	9	8,83
	2	6,3	
	3	11,2	
Formula 100	1	25	28,93
	2	31,9	
	3	29,9	
Formula 200	1	26,5	28,5
	2	29,5	
	3	29,9	
Formula 300	1	18	15,1
	2	12,5	
	3	13,8	

From the % edema data, the percentage of inhibition was calculated, as shown in Table 5 below. The percent of inflammation inhibition is calculated by the formula (Sentat 2018)

Percentage of inflammatory inhibition = (Vt−Vo/Vo) x 100%

Information:

Vt = Percent average of the control group.

Vo = Average percent of the treatment group.

Table 5. Percentage Inhibition Data of Rat's Paw at the 8th Hour

Treatment Group	Test Animals	% inhibition	Average
Na Diklofenac	1	0.80	0.80
	2	0.86	
	3	0.75	
Formula 100	1	0.45	0.36
	2	0.30	
	3	0.35	
Formula 200	1	0.42	0.39
	2	0.36	
	3	0.35	
Formula 300	1	0.72	0.66
	2	0.75	
	3	0.70	

In Table 5, it is indicated that all groups of the patch formula with Rambusa leave extract are capable of inhibiting inflammation, although to a lesser extent compared to sodium diclofenac, which serves as the positive control. Formula 300 exhibits the best anti-inflammatory capability with an average percentage inhibition of 0.66%.

In the above test results, an analysis was conducted using the one-way ANOVA method. The analysis results indicate differences between

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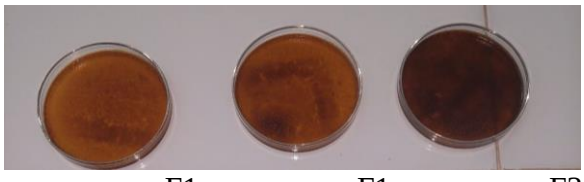
the test groups (p< 0.05). To determine the differences between the test groups, a post hoc LSD test was conducted.

The test results for various treatments above indicate that the positive control group shows the lowest percentage of edema. This suggests that Sodium Diclofenac has the ability to inhibit inflammation. Meanwhile, the group with formula 300 demonstrates anti-inflammatory capabilities compared to the other two formulas, as evidenced by the smallest percentage of edema among the three formulas. The test results indicate that the CMC-Na group (negative control), the formula 100 group, and the formula 200 group differ from the sodium diclofenac group (positive control). This implies that the CMC-Na group, as well as the formula 100 and formula 200 groups, do not exhibit anti-inflammatory effects (Hartesi, 2021).

The sodium diclofenac group (positive control) is not different from the formula 300 group with a significance value (p > 0.05) of 0.098 compared to the other 2 formulas of the LSD test. This means that the formula 300 group is capable of inhibiting inflammation. Additionally, the formula 300 group shows no significant difference, indicating its consistent ability to inhibit inflammation.

Discussion:

The organoleptic testing of the transdermal patch formulation reveals a brown color, smooth texture, and an extract scent. HPMC, as the polymer, also contributes to a physical appearance that is free from aeration and wrinkles, resulting in a smooth semi-solid texture. From the three formulas, F3 produces a darker color, which is the typical color of concentrated brown extract due to the presence of a greater amount of extract.



F1 F1 F3

Figure 2. The organoleptic testing of the transdermal patch formulation, F1 with 100 g of extract, F2 with 200 g of extract, F3 with 300 g of extract

Drying loss testing aims to determine the drying shrinkage, moisture content in the patch after storage 1x24 hours in the desiccator. The amount of drying loss value can be influenced by the regulation of moist content (Wardani & Saryanti, 2021). There is no absolute value of what amount of drying shrinkage is required (Patel DP, 2009).

Patch thickness testing aims to determine the thickness of the patch obtained from each formula in accordance with the requirements, which is no more than 1 mm. If the patch is too thick, it will be difficult to remove the active substance from the patch (Suryani, 2017). The result obtained is no more than 1 mm.

The transdermal patch moisture test aims to determine the water content in the patch preparation and the ability of the patch preparation to absorb moisture (Ermawati, 2019). The lower the percent moisture value, the resulting patch is also more stable because of the little water content and protected from microbial contamination. Conversely, if the percent moisture value is greater, it will affect the stability of the preparation and be susceptible to microbes (Nurahmanto, 2017). The percent moisture requirement is ≤10% (Arifin, 2019) and all formulas meet the requirements.

pH testing aims to determine the safety of the preparation. The pH should not be too acidic because it can irritate the skin and also should not be too alkaline because it can cause scaly skin. The test results in the pH test obtained a pH value ranging from 5-6 so that it still meets a pH that is safe for topical use because the pH range for topical use is between 4-8 (Hartesi, 2021).

The folding resistance test is conducted manually by folding the patch repeatedly on the same line until the patch breaks or folds as much as 300x. A good patch has a folding resistance of up to 300x (Nurahmanto, 2017). And the whole formula has met the requirements.

The cumulative amount of the active ingredient that penetrates the formulation with various formulas is obtained, with the order 1 < 2 < 3 observed from Table 3. This phenomenon is

attributed to the patch formulation containing an HPMC base, which makes the affinity of the active ingredient in the formulation weak. Consequently, the active ingredient is easily released from the formulation, leading to an increase in the cumulative amount. Additionally, HPMC in the gel formulation can enhance the effect of propylene glycol as a penetration enhancer by reducing the barrier properties of the stratum corneum, facilitating the easy penetration and membrane traversal of the active ingredient (Chandra, 2019).

Inflammation is a normal protective response to tissue injury caused by physical trauma, harmful chemicals, or microbiological agents. The effectiveness of the transdermal patch with Rambusa leave extract demonstrates anti-inflammatory efficacy in male white rat test subjects. Transdermal patches are drug delivery systems with adhesive properties, characterized by a soft texture. They contain drug compounds that are released in a controlled manner through the skin at specific doses (Arum et al., 2022).

The aim of this research is to determine the activity and effective dose of ethanol extract from the Rambusa leave as an anti-inflammatory agent in rats. The study utilizes the Rat Hind Paw Edema method, which is based on the ability of a substance to inhibit inflammation in the hind paw of rats that have been injected with an inflammation-inducing agent (Rahman et al., 2023).

Based on the results of the anti-inflammatory testing using the rat hind paw edema method, it is evident that the transdermal patch formulation with Rambusa leave extract possesses anti-inflammatory activity, and the most effective dose is formula 300 (F3). The anti-inflammatory activity is associated with the presence of flavonoids, alkaloids, tannins, saponins, and steroids in Rambusa leaves (Mulyani, 2019).

The mechanism of flavonoids in inhibiting inflammation can occur through several pathways. They can inhibit the activity of cyclooxygenase (COX) and lipoxygenase, directly hindering the biosynthesis of prostaglandins and leukotrienes. Flavonoids also reduce leukocyte adhesion to endothelial cells by decreasing the mRNA levels induced by TNF-α, thereby reducing the expression of ICAM-1, E-selectin, and VCAM-1 on endothelial cells. Additionally, flavonoids can inhibit histamine release by mast cells by inhibiting the enzyme cAMP phosphodiesterase, leading to an increase in cAMP levels within cells. This results in calcium being unable to enter the cells, inhibiting the release of histamine (Febrianti & Musiam, 2019). Alkaloid anti-inflammatory mechanisms include stimulating the pituitary adrenal cortex axis, promoting the release of adrenal cortex hormones, inhibiting the release of inflammatory mediators, interleukins, and tumor necrosis factors, and regulating the level of nitric oxide, the ex pression of cytokine mRNA, and so on (Li S, 2020). Tannin has anti-inflammatory activity by inhibiting NO and prostaglandin (PGE2), by mediating the expression of cytokines, reduce nitric oxide (NO) induced by lipopolysaccharide (LPS), tannin can form a gastroprotective barrier to improve gastritis symptoms based on their antioxidant activity (Tong et al., 2022). The anti-inflammatory activity of saponin can reduce the oxidative stress caused by nerve damage, could restrain the translocation of the glucocorticoid receptor to the mitochondria, and decrease the H2O2-induced phosphorylation of extracellular-regulated kinase (ERK), c-Jun N-terminal kinase (c-JNK), and p38MAPK to down regulate the activity of neuronal PC12 cells (Tan, 2022). Steroid mechanisms by inhibiting inflammation by blocking the activity of inflammatory mediators (transrepression) or by inducing anti-inflammatory mediators (transactivation) (Suryana, 2017).

Conclusions:

From testing the transdermal patch formula with Rambusa leave extract, it can be seen that the formula meets the requirements as an anti-inflammatory. Based on physical quality tests including organoleptic test, drying shrinkage test, patch thickness test, patch moisture test, pH test, and folding resistance test. In vitro tests are performed to obtain the cumulative amount of the active ingredient that penetrates the formulation with various formulas is obtained. The results of in vitro testing show that all three formulas have the ability to penetrate and cross membranes

easily. The in vivo anti-inflammatory testing conducted on experimental rats showed that among F1, F2, and F3, it was found that the effectiveness of F3 was able to inhibit inflammation, as can be seen from the p value which was not significantly different from the positive control.

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