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Research Article

Anti-Inflammatory Activity Test of Ethanolic Extract of Transdermal Patch *Crinum asiaticum* L Against Male Wistar Rats Induced by Carrageenan

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ABSTRACT

Background:*Crinum asiaticum* leaves are recognized for their wound healing properties, particularly in treating abrasive or inflamed wounds. **Objective:** This study aims to evaluate the efficacy of a transdermal patch prepared from *Crinum asiaticum* leaf extracts in reducing inflammation. **Methods:** The preparation involved applying coconut oil to the fruit, roasting it, and then using it on the affected area. Leaf samples and extracts were utilized to formulate transdermal patches at three different concentrations (1%, 3%, and 5%). The patches were assessed organoleptically for thickness, weight uniformity, folding resistance, and pH. **Results:** The findings demonstrated that the 5% concentration transdermal patches exhibited superior anti-inflammatory effects compared to the 1% and 3% concentrations. This suggests that higher concentrations of *Crinum asiaticum* extracts enhance the therapeutic potential of transdermal applications. **Conclusion:** The study concludes that transdermal patches formulated with *Crinum asiaticum* leaves are effective in reducing inflammation, with 5% concentration offering the highest efficacy. Further research is recommended to explore the clinical applications of these patches in wound management.

Keywords: anti inflammation, *carrageenan*, *crinum asiaticum,* transdermal patch

1. Introduction

Indonesia is a developing country and it is known that there are many kinds of plants in Indonesia. Indonesian society uses a lot of plants that are empirically used to treat various diseases. Transdermal patch have a beneficial drug for long-term use because its side effects are small, easy to obtain, and do not have to be expensive [1, 2]. Due to the increasing demand for plant protection products, food supplements, and cosmetics, every traditionally widespread plant species deserves an opportunity to study its biological properties in a thorough and pharmacologically promising way like the leaves of a turkey. Cucumber leaves can heal bruising or swelling wounds by applying coconut oil and then drying it on a small fire and then applied to the sick part of the body, from the results of Harani 2015 study showed that a dose of 160 mg/200 grBB showed anti-inflammatory effects, as it can lower the level of C-Reactive Protein (CRP) in the blood serum of male white rats after induced 1% [1]. Flavonoids can have anti-inflammatory effects because they can inhibit various enzymes such as aldose reductase, Ca2+A TPase, lipoxygenase and cycloosigenase [2].

In addition, tannins also have anti-inflammatory effects as they prevent the release of prostaglandins in the arachidonate canal, which is an inflammatory mediator [3]. According to Harahap 2023 research, the leaves are also rich in alkaloids, and have been found to have a variety of pharmacological properties, such

as anti-cancer, antibacterial, antiviral, and anti-inflammatory properties. Anti-inflammation is the body's normal defence response to tissue damage caused by physical trauma, harmful chemicals or microbiological factors. Inflammatory responses are characterized by redness, heat, pain, tumor, and dysfunction. The use of anti-inflammatory drugs has therapeutic effects and inevitable side effects. In addition, the form of the preparation of the drug also affects the effectiveness and has side effects, so it is an innovative form of preparation to avoid the side effects of the so-called transdermal patch preparation [2, 4, 5]. The composition of patch preparations usually consists of synthetic ingredients, so this study uses natural ingredients to minimize side effects and increase the economic value of the plants. *Crinum asiaticum* is known to possess significant anti-inflammatory effects, which can be attributed to the presence of various bioactive compounds in its leaf extracts. Compounds such as flavonoids and alkaloids play a crucial role in alleviating inflammation by inhibiting pro-inflammatory pathways in the body. For instance, flavonoids can reduce the production of cytokines and other inflammatory mediators that contribute to the inflammatory response. Additionally, these compounds exhibit antioxidant properties that help protect cells from oxidative damage, which often occurs during inflammation. Research has shown that the use of *Crinum asiaticum* extracts can accelerate wound healing and reduce symptoms of inflammation, making it a promising natural option for anti-inflammatory therapy. Therefore, further exploration of the mechanisms of action and therapeutic potential of *Crinum asiaticum* is expected to contribute significantly to the management of inflammatory conditions [6].

2. Methods

2.1 Procedure for preparation and testing of extract quality parameters

Extraction by maceration method, with stages as follows [7, 8]. Fresh Simplisia from Crinum leaves (*Crinum asiaticum* L) is extracted by maceration by soaking simplisia in a 96% ethanol solvent for 3 repetitions within 3 days while complaining. Then we filter it with cylindrical paper. All Macerat gathered and put into in a vacuum rotary evaporator at 40°C, evaporation is continued over the waterbath at a wake-up temperature of 40°C until a thick extract is obtained to obtain gfood results and quality extracts, performed advanced tests, water content tests, seafood content, ethanol solution sulfur content. We conducted a thorough examination of phytochemicals like alkaloids, flavonoids, tannins, and saponins. Transdermal patch base design with extracts.

Table 1. Composition modification of patch transdermal [9]

No	Composition	Formula			Function
		F1	F2	F3	
1	Leave extract *Crinum asiaticum*	0.5	1.5	2.5	Active compound
2	Glicerine	1.5	1.5	1.5	Skin moisture protect
3	Span 80	1.5	1.5	1.5	Oil phase emulgator
4	PEG40	2.5	2.5	2.5	Increase absorbation of medicine
5	HMPC	2.5	2.5	2.5	controls the release speed of the drug from the supply
6	Praben metyl	0.06	0.06	0.06	preserves
7	Vit E	0.5	0.5	0.5	Suplement, skin moisture
8	Aquadest	Ad50	Ad50	Ad50	Solvent

2.2 Patch preparation

Production of dermal patch preparation by following the procedure of Hope 2020[10] with a short procedure for the production of derman patch with the given composition: First, prepare all the necessary ingredients: leaf extract of *Crinum asiaticum*, glycerin, Span 80, PEG 40, HPMC, methyl parabens, vitamin E, and aquadest. Mix the leaf extracts of *Crinum asiaticum* with glycerine in a clean container and mix evenly [11]. To ensure good emulsification, slowly add Span 80 and PEG 40 while continuously mixing. After that, insert HPMC and mix until perfectly dissolved [12]. Next, add methyl parabens and vitamin E to maintain stability and provide additional benefits. Finally, dilute the mixture with aquadest until the desired consistency is achieved. Pour the mixture into the mold and let it harden at room temperature before using [13]. After a patch preparation test, an advanced test is carried out to evaluate the quality of the given dermal patch such as organoleptic tests, patch thickness and weight uniformity [14, 15].

2.3 Anti-inflammation analysis with in vivo study

In the anti-inflammatory trial using male white rats after obtaining animal ethics approval with number No. 0645/KEPH-FMIPA/2023 and carrying out a full study in Universitas Haji Sumatera Utara's pharmacological animal lab of as many as three for each treatment group. Previously, the mice were fed fast + 18 hours before the therapeutic test but still given drinking water, after which the rats were divided into five groups Negative control, F0, F1, F2, and F3.

After dividing into 5 groups before inducing the carragen solution sublantarily, the rat's volume of oedema was first measured and then treated with an agent of 0.1ml to increase the volume of the oedem, after being induced with the carragent then the rat was inhabited for 30 minutes before being treated. After 30 minutes of injection of the carragen solution, the patch was applied to the back of the mouse after being injected with carragen for 1 hour and the volume of the oedem was measured again and every 1 hour for 6 hours with a plastimometer [19, 20].

On the left foot of the mouse, markings were done using a black marker, this is intended to keep the mouse's foot in the rake water the same every time. And on the back of the mouse has been shaved in advance to facilitate in placing the patch [16,17]. Pre-measured mouse leg volume before inducing 0.1 ml of carragen solution subplantably [21]. After 30 minutes of induced carragen, each rat applied a patch to the back area. The first group as control negative was given a base patch. The second group as a positive control was given an anti-inflammatory patch that had circulated [22]. The third and fourth groups were given patches containing concentrations of 1%, 3%, 5%. Volume measurements of udern with a plastimometer were performed at 1st, 2nd, 3rd, 4th, 5th and 6th hours after induction with carragen [23].

Formula's evaluation :

Inflammations percentage (%) : (V0-V1) : V1 x 100%
Unhibitions inflammations percentage (%) : (V2-V3) : V3 x 100%

Formula's descriptions:
V0: Volume after injections carrageenan
V1: Volume before injections carrageenan
V2: Percentage of Control groups Mean
V2: Percentage of Interventions groups Mean [21]

2.4 Data analysis

Data analysis used is the standard deviation method and analyzed statistically using IBM SPSS Vers. 16.6 with *ANOVA (Analysis of Variance)* analysis with a 95% confidence rate. Then tested with Kruskal-Wallis and continued with post-hoc test analysis to find out the treatment groups were significantly different from the others.

3. Results

The results of the semplisia characterization examination obtained good results and met the requirements that have been set on MMI, and here are the results of examination of the quality of the extract samples used can be seen in Table 2.

Table 2. Simplisia's characteristic

No	Parameter	Results (%)	MMI Crhiteria (%)	Interpretations
1	Evaluations water level	8.3	≥15.4%	Qualified
2	Evaluations of water-soluble level	15.66	≥4,4	Qualified
3	Evaluations of total ash content	5.66	≤7.2	Qualifed
4	Evaluations of ash not acid soluble	9.63	≤4	Not qualified

Ashes are residues of organic matter resulting from the combustion of an organic material. The content of ash and its composition depends on the type of material and the way it is made. The total ash level in each simplisia identifies that simplisia is rich in minerals. A low level of insoluble ash in acid indicates the presence of sand or other resin in a low level.

Phytochemical screening

Table 3. Phytochemical screening *Crinum asiaticum*

No	Phytochemical screening	Interpretations
1	Alkaloid	+
2	Flavonoid	+
3	Saponnins	+
4	Tannins	+

+ : Positive compound; -: Negative compound

3.1. Dermal Patch

A transdermal patch is prepared by mixing vitamin E with a surfacing agent (Span 80 and PEG 400) and extracting the leaves of the bacon inside the patch in a strain until homogeneous and isolated (patch 1). Then develop HPMC inside the aquadest that has been heated on another patch. Glycerin and methyl parabens are added and mixed to be homogeneous. Then put in the open for 24 hours at a temperature of 60 C (Fig. 1).

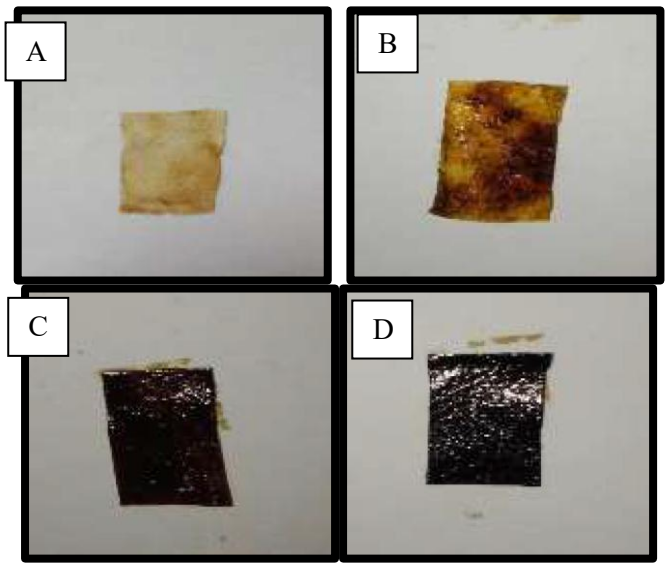

Figure 1. Dermal patch : (a) F0 (Formula 1); (b) F1 (Formula 2); (c) F2 (Formula 3); (d) F3 (Formula 4)

3.2. Evaluations of dermal patch

Table 4. Evaluations of dermal patch

No	Formula	Concictency	Patch multiple	Weight homogeneity(%)	pH
1	F0	Semi-solid	300	4.81	6.38
2	F1	Semi-solid	300	4.92	6.43
3	F2	Semi-solid	300	4.76	6.36
4	F3	Semi-solid	300	4.21	4.46

F0: Basis patch; F1: Patch 1% extract; F2: Patch 2% Extract; F3: Patch 3% Extract

Based on Table 4 of the four patch test formulas, the aim is to determine the thickness of the patch. The result of the patch thickness is 0.44 mm for F0, 0.33mm for F1, 0.24 mm for F2, and 0.12 mm for the F3. The result in the above table is in accordance with the standard of good patch requirements, i.e. it should not exceed 1 mm, and if it is too thick, it will be difficult to remove the active substance from it. A transdermal patch thickness test is performed to determine the patch density on the preparation made. The ideal patch has a thin thickness but does not quickly crack or break so it is convenient when applied or when used. The patch thickness is influenced by the technique of removing the patch solution into the mold and also by the weight of the patches formed from each formula.

The folding resistance of F0 is 300 times the fold resistance, of F1 is more than 300 times that of F1, of F2 is over 300 times, and of F3 is about 300 times. From formula 0 to formula 3, the result meets the standard of >200. The test results of the four formulas have good folding resistance and do not break despite

having been folded as many as 300 times. The weight uniformity of F0 is 4.81%, F1 is 4.92%, F2 is 4.76 and for F3 is 4.21%. The pH should not be too acidic as it can irritate the skin and should not also be too basic because it can cause skin to peel. The pH test results in obtaining a pH value ranging from 5-7 so that it still meets the pH that is safe for topical use because the pH range for topic use is between 4-8.

3.3. Inflammations analysis with in vivo study

In the test of anti-inflammatory activity, the first data obtained from this test was data on the volume of the oedema palm of the mouse both before induced and after inducted with the agent.

Table 5. Mean of Oedemas volume on paw rats

Hours	Control groups	F0	F1	F2	F3
0	3.5	2.92	2.15	2.19	2.24
1	4.05	3.94	4.5	3.98	4.5
2	3.78	3.89	3.77	3.39	4.4
3	3.77	3.34	3.31	3.1	3.36
4	3.74	3.2	3.2	3.09	3.22
5	3.71	3.01	2.66	3.02	3.19
6	3.62	2.79	2.09	2.2	2.55

Based on the Table 5 described increase on the volume of the oedema differently in each group. The increase in the volume of the oedema on the positive control differs from the other trial groups.

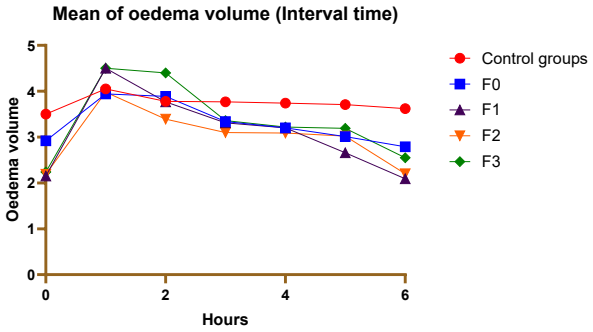

Figure 2. Graphic scheme of increased oedema volume

A positive control group is a group that is given the supply of patches that are available on the market. The volume of the positive control group's oedema increased in the 1st hour and decreased at the 2nd, 3rd and 4th hours and so on. How graphic of increased oedema volume can see on (Fig. 2).

Table 6. Mean of Percentage inhibitions

Hours	Control groups	F0	F1	F2	F3
1	90	65	95	97	99
2	75.65	66	82	86	89
3	70.14	35	70	74	77.17
4	42.54	33	55	63	66.81
5	9	8	10.4	13.84	45.66
6	5	4	6.94	7.34	12

The highest volume of oedema and the size of the percentage value of the formed oedema, comparable to the ability of the test compound in inhibiting the formation of the oedema (inflammations). The percentage of inflammatory inhibition is calculated using the formula: (a-b)/a x 100, where a: percentages of oedema (inflammation) of the negative control group and b: percentases of oedem (inflammation) of the test substance group (Fig 3).

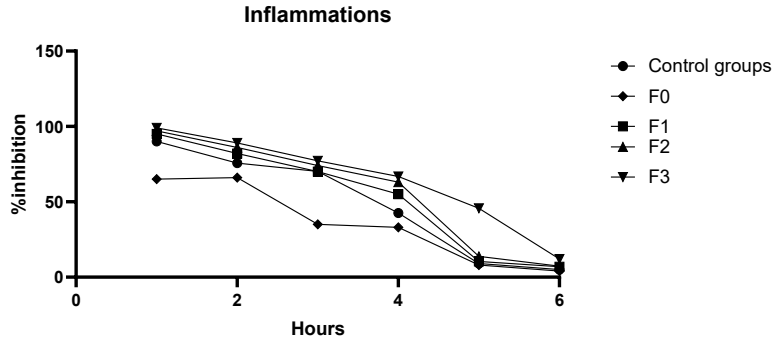

Figure 3. Percentage inflammation inhibitions

This indicates that F3 starts to give anti-inflammatory effect at 2 - 6 hours. On table 6 it can be seen that at 2 hours the percentage of mouse palm oedema begins to experience a decrease in oedema that occurs at 2 hour. This is related to the duration of the agent's work in inducing oedema. According to Morris (2003). Oedema caused by carragenan can last for 5-6 hours, so it can be concluded that the decrease of oedema occurring at 5 o'clock is due to the reduction of the effect of cargenan in inducing oedema and affecting the magnitude of the percentage of inhibition of the produced oedema (Fig. 4).

Table 7. Percentage of oedema

Hours	Control groups	F1	F2	F3
1	7	98	97	99
2	8	82	86	89
3	9	76	74	77.17
4	10	60	63	57
5	9	34	28	16
6	9	26	20	8

The increase in the percentage of the whole trial group's oedema from 1st to 5th hours varies significantly ($p \leq 0.05$). At control F3 the oedema forms maximum at 2nd hours and decreases at 3.4,5 and 6th hours. This suggests that 1% concentration carragen with an injection volume of 0.1 ml is a good oedema-inducing agent and can cause significant inflammation.

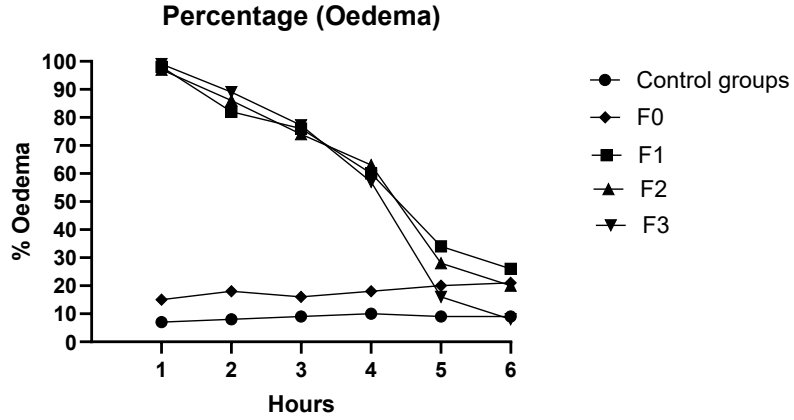

Figure 4. Percentage of oedema

4. Discussion

The role of the agent in inducing the onset of oedema is by stimulating inflammation mediators such as histamine, prostaglandins, other inflammatory mediators. The release of the mediator by the agent is divided into two phases. The first phase, the agent will stimulate the release of serotonin and histamine during the first hour [12].

Crinum asiaticum leaves have been recognized for their wound healing properties, particularly in the treatment of abrasive or inflamed wounds. This study aimed to evaluate the efficacy of transdermal patches formulated from *Crinum asiaticum* leaf extracts in reducing inflammation. The preparation process involved applying coconut oil to the fruit, roasting it, and subsequently using it on the affected area. Leaf samples and extracts were utilized to create transdermal patches at three different concentrations: 1%, 3%, and 5%. These patches were assessed organoleptically for parameters such as thickness, weight uniformity, folding resistance, and pH levels. The findings indicated that the transdermal patches at a 5% concentration exhibited superior anti-inflammatory effects compared to those at 1% and 3% concentrations. This suggests that higher concentrations of *Crinum asiaticum* extracts enhance the therapeutic potential of transdermal applications. The study concludes that transdermal patches formulated with *Crinum asiaticum* leaves are effective in reducing inflammation, with the 5% concentration demonstrating the highest efficacy. Further research is recommended to explore the clinical applications of these patches in wound management.

In recent years, the use of natural compounds for therapeutic purposes has gained significant attention due to their potential efficacy and fewer side effects compared to synthetic drugs. *Crinum asiaticum*, a plant commonly found in tropical regions, contains bioactive compounds that contribute to its medicinal properties. These compounds, particularly flavonoids and alkaloids, are known for their anti-inflammatory and antioxidant effects, which play a crucial role in wound healing [20, 23]. The incorporation of such natural extracts into transdermal delivery systems offers an innovative approach to enhance the therapeutic effects while minimizing adverse reactions.

Moreover, the findings of this study highlight the importance of optimizing the concentration of active ingredients in transdermal formulations. The superior performance of the 5% concentration patch suggests a dose-dependent relationship between the concentration of *Crinum asiaticum* extracts and their anti-inflammatory effects [19]. This insight not only paves the way for further research into the mechanisms behind these effects but also encourages the exploration of other natural sources that may offer similar benefits. Future studies should focus on clinical trials to validate these findings and assess the long-term efficacy and safety of *Crinum asiaticum*-based transdermal patches in diverse wound management scenarios [20].

5. Conclusion

Crinum asiaticum leaf extract can be formulated in the form of a patch preparation and a transdermal patch of *Crinum asiaticum* leaves.

6. Data Availability Statement

The datasets generated and analyzed during the current study are not publicly available due to privacy and ethical considerations but are available from the corresponding author upon reasonable request.

7. Ethical Statement

This study was conducted in accordance with ethical guidelines for animal research. The anti-inflammatory trial was performed using male white rats after obtaining approval from the Animal Ethics Committee, with approval number No. 0645/KEPH-FMIPA/2023.

8. Author Contributions

Each author has made substantial contributions to this study, including conceptualization, study design, implementation, data collection, analysis, and interpretation. All authors have participated in drafting, revising, and critically reviewing the manuscript. They have provided final approval of the version to be published and have been involved in the decision regarding the journal for submission. Furthermore, all authors agree to take full responsibility for every aspect of the work.

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11. Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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