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Article

The Formulation of Transdermal Patch Ethanol Extract of Java Chili *(Piper retrofractum* Vahl.) Based and Its Analgesic Activity

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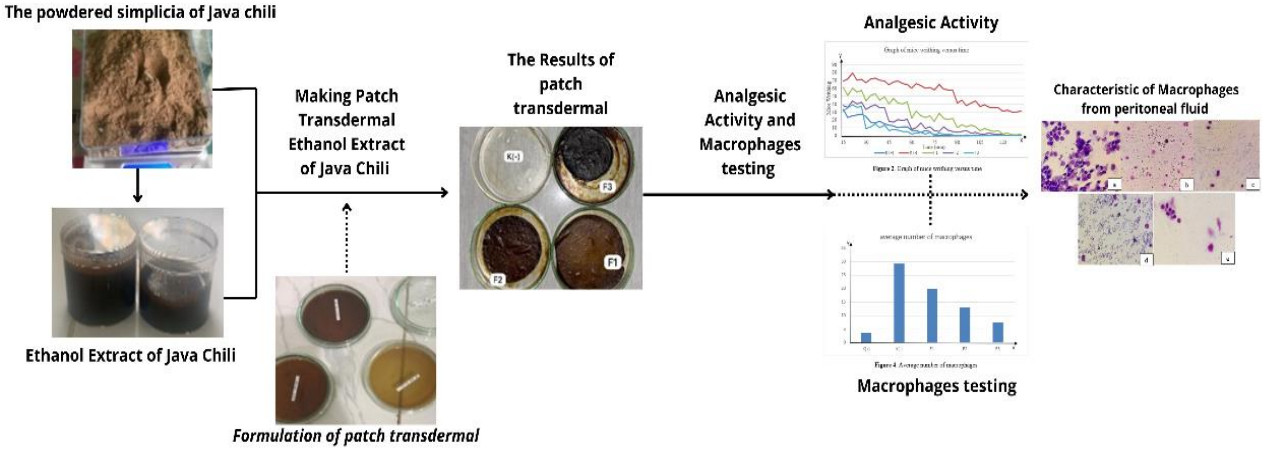
Abstract

Pain is an unpleasant sensory and emotional experience caused by actual or potential tissue damage. Java chili (*Piper retrofractum* Vahl.) is an Indonesian plant known for its secondary metabolites, including piperine, pipernonalin, guineensine, and essential oils. Among these, piperine is the primary compound with potential analgesic properties. This study evaluates the analgesic effects of transdermal patches containing ethanol extract of Java chili using the writhing test and macrophage count in acetic acid-induced mice. The patches were formulated with different concentrations of the active ingredient: F1 (1g extract), F2 (2g extract), and F3 (3g extract). The results show that increasing the ethanol extract concentration significantly alters the physical characteristics of the patches, including shape, thickness, color, and durability. In the analgesic test, the macrophage count in the negative control group was 29.33 ± 0.57. In contrast, the treatment groups showed a concentration-dependent reduction: F1 (20.00 ± 1.73), F2 (13.00 ± 3.00), and F3 (7.33 ± 1.15). The positive control group exhibited the lowest macrophage count (3.66 ± 1.15). These findings indicate that transdermal patches containing Java chili ethanol extract possess significant analgesic potential, with higher concentrations yielding stronger effects.

Keywords: *Analgesic; java chili; pain; transdermal patch*

Graphical Abstract



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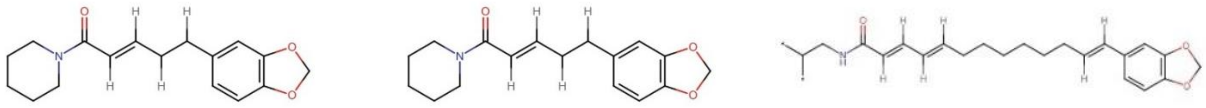
Introduction

Pain is an unpleasant sensory and emotional experience that results from actual or potential forms of tissue damage. Although pain is a sensation, it has cognitive and emotional components, which are described in terms of suffering. Pain stimuli are initially received by nociceptors, which are sensory neurons that function as pain receptors on the skin [1]. Pain can occur at high or low intensity when stretched or when the temperature increases due to tissue damage. Necrotic cells will release intracellular K+ and proteins. Increased extracellular K+ levels can cause depolarization of pain receptors or nociceptors allowing proteins to penetrate the microorganisms and cause inflammation. This results in the release of pain-inducing substances, such as leukotrienes, prostaglandin E2, and histamine, which stimulate pain receptors and cause pain (hyperalgesia or allodynia) in response to painful or innocuous stimuli [2].

Drugs that selectively relieve pain without significantly altering consciousness are called analgesics. Analgesic drugs are commonly used to relieve or reduce pain. Analgesics commonly used by the general public include non-opioid analgesic drugs such as aspirin, mefenamic acid, and paracetamol [3,4]. Unlike opioid analgesic drugs, these drugs are not addictive. Non-opioid analgesic drugs can cause side effects, especially gastrointestinal disorders, hypersensitivity reactions, kidney damage and too much consumption can also damage the liver. Although it can be cured with medication, cases of people suffering from drug poisoning are still common [5].

One of the Indonesian plants with high utilitarian value is Java chili (*Piper retrofractum* Vahl.) [6]. Javanese chili plant parts have several secondary metabolite compounds and the most are found in the fruit. Javanese chili fruit contains active compounds in the form of alkaloids, terpenoids and saponins. Meanwhile, Javanese chili leaves contain active compounds in the form of flavonoids, terpenoids saponins [7]. The main secondary metabolite compounds in chili plants are piperine, pipernonaline, guineensine and essential oils. Piperine has pharmacological activity as an antipyretic analgesic [8].

According to research conducted by Sari, et al. [10], piperine shows analgesic activity comparable to the analgesic standard drug indomethacin. Piperine at doses of 20 mg and 30 mg/kg body weight provides effects close to those of indomethacin. In another study, piperine was reported to act as a penetration enhancer in the transdermal delivery of curcumin. In addition to increasing curcumin flux, piperine flux in vitro permeation also increased with increasing piperine concentration as a penetration enhancer [11].



(a) (c) (c)

Figure 1. Structure of main secondary metabolite compounds of java chili: (a) piperine; (b) pipernonaline; (c) guineensine [9]

The piperine content in Java chili that is active as an analgesic can be innovatively formulated into a practical and effective transdermal patch with minimal side effects, which can be used for alleviating mild to moderate pain. The advantages of drug formulations in the form of transdermal patches include ease of use, reduced frequency of drug administration, maintained bioavailability, avoidance of the first-pass effect, and rapid metabolism, resulting in significantly reduced systemic circulation of the drug. Additionally, transdermal formulations can provide prolonged therapeutic effects with a single application, increasing patient comfort compared to other forms that require frequent dosing to achieve therapeutic doses [12]. Given these advantages, transdermal patches represent a good and effective form of herbal

drug delivery pharmacologically; therefore, research on innovative formulations of transdermal patches from Java chili extract to address pain is necessary.

Materials and Methods

Time and Place of Implementation

This research was conducted in the Laboratory of Technology and Formulation of Solid Preparations at the Faculty of Medicine and Health Sciences, Jambi University. The research lasted for 4 months from May to August 2024.

Materials and Instrumentations

The sample consisted of 400 mg of the powdered simplicia of Java chili (*Piper retrofractum* Vahl.) obtained from the Pharmacy Biology Department Laboratory, Faculty of Pharmacy, Gadjah Mada University, hydroxhypropyl metilylmetlulose (HPMC) (PT. Indo Sukses Pratama), polyvinylpyrrolidone (PVP) (PT. Chori Indonesia), sodium lauryl sulfate (SLS) (PT. Anugrah Putra Kencana), propylene glycol (PT Iniko Karya Persada), Giemsa (Merck) and water for injection (PT. Otsuka Indonesia). The Instrumentation used in this research are vacum rotary evaporator (*Scilogex*), measuring cup, beaker glass and test tube (*Pyrex*), petri dish (*OneMed*), filter paper and laboratory funnel (*Pyrex*), waterbath and oven (*Memmert*), animal scales and analytical scales (*Ohaus*), oral sonde and 1cc syringe (*OneMed*), microscope (*Euromex*), stopwatch and animal cages.

Preparation of Ethanol Extract of Java Chili

The preparation of Java chili extract was conducted using the maceration method with 70% ethanol as a solvent. A total of 400 g of Java chili powder was dissolved in 2L of 70% ethanol, ensuring that all the powder was submerged, and maceration was performed for 24 hr with 2 repetitions, stirring during the first 6 hr. The solvent mixed with the Java chili powder was filtered through a funnel lined with filter paper to obtain the filtrate (macerate) of Java chili extract. The macerate was then evaporated using a vacuum rotary evaporator at a temperature of 60°C to obtain a liquid extract. The yield of the extract was then calculated using formula 1[13]

$$\text{Yield (\%)} = \frac{\text{Weight of Extract Obtained } (g)}{\text{Initial Sample Weight}(g)} \text{ x } 100\% \qquad (1)$$

Formulation

The formulation of the ethanol extract was prepared in the form of a patch consisting of an active substance, namely the ethanol extract of Java chili (*Piper retrofractum* Vahl.) at various concentration levels, as well as positive control (K+), negative control (K-), and other additives. The formula for the transdermal patch of ethanol extract of Java chili (*Piper retrofractum* Vahl.) is shown in Table 1. Preparing of the Transdermal Patch of Ethanol Extract of Java Chili (*Piper retrofractum* Vahl.) according to Hendriati and Hamid (2021) [14].

Preparation of Transdermal Patch from Ethanol Extract of Java Chili

HPMC and PVP were dissolved in pre-heated water, then propylene glycol, Java chili extract, enhancer, and 96% ethanol were added sequentially until reaching 15 mL. The solution was poured into a petri dish and allowed to stand for 24 hr until all air bubbles were eliminated. The patch was then oven-dried at 40°C for 48 hr. The patch sheets were cut into 1 x 1 cm pieces for application on the abdomen of the mice.

Table 1. Composition transdermal patch of formula

Materials	K (-)	Formulas			Function
		F1	F2	F3	
Extract ethanol of java chili	-	1g	2g	3g	Active substance
HPMC	2%	2%	2%	2%	Polymer
PVP	2%	2%	2%	2%	Polymer
Na lauryl sulfate	-	5%	5%	5%	Surfactant
Propylen glycol	2mL	2mL	2Ml	2mL	Preservative

96% Ethanol	15mL	15mL	15mL	15mL	Solvent

Evaluation of Physical Quality of the Patch Preparation

The evaluation of the physical quality of the preparation included clarity, shape, color, odor, pH, thickness, and folding endurance [15].

Adaptation of Test Animals

A total of 25 male mice that have passed the ethical code test and obtained research ethics approval from Jambi University with certificate number 2006/UN21.8/PT.01.04/2024. These male mices have never been used at all in research and were randomly selected, healthy, and have normal activity.. Before being used in the study, the mice were adapted for 2 weeks under the same conditions as treatment. Mice were declared healthy and suitable for research if they showed no signs of illness and did not lose more than 10% of their initial body weight [16]. The mice were fasted for 12 hr while still being given drinking water before the experiment.

Analgesic Activity

Mice were induced with 0.1 mL of acetic acid intraperitoneally, leading to a motor response in the form of writhing. The patches according to the formula (F1-F3 and negative control) were applied to the shaved abdomen of the mice [14]. In the positive control group, mice received paracetamol orally. Mice were observed for 6 hr, and the number of writhes was counted every 15 min.

Collection of Peritoneal Fluid and Macrophage Samples The euthanized mice were placed in a supine position, the abdominal skin was opened and cleaned with 70% alcohol, then 1 mL of aquadest was injected into the peritoneal cavity. The abdomen was massaged, then the peritoneal cavity was opened, and the peritoneal fluid was collected. The obtained peritoneal fluid was used for macrophage smears for observation [14].

Determination of the Number of Macrophages

The determination of the number of macrophages was carried out by making a smear of the peritoneal fluid, staining the preparation with giemsa solution, and observing it under a microscope at 400x magnification, followed by counting the macrophages [14].

Data Analysis of Research

The analysis of the physical quality test data of the patch was performed descriptively, while the data obtained from the observation of the number of writhes and macrophages were tested using parametric statistical methods. Data analysis was conducted using analysis of variance (ANOVA) followed by Fisher's test. If significant differences were found ($p \leq 0.05$), further testing was conducted using Duncan's multiple range test. Data analysis was carried out using SPSS version 20.0.

Results and Discussion

Ethanol Extract of Java Chili

The powdered simplicia of Java chili *(Piper retrofractum* Vahl.) weighing 400 g was extracted using the maceration method for 24 hr, followed by two remaceration. The resulting ethanol extract of Java chili weighed 67 g. The ethanol extract of Java chili appeared as a thick brown liquid with a characteristic aroma of Java chili, the result obtained in the following Figure 2. The yield percentage of the ethanol extract of Java chili was calculated to be 16.75%, according to the Indonesian Herbal Pharmacopoeia, a good extract should have a yield percentage above 7.5%, it meets the required standard [17].

(a) (b)

Figure 2. (a) Powdered simplicia of Java chili; (b) ethanol extract of Java chili

Physical Properties of the Transdermal Patch

The physical properties of the transdermal patch formulated with the ethanol extract of Java chili (Piper retrofractum Vahl.) were assessed to determine its suitability for application. The evaluation covered clarity, form, color, odor, pH, thickness, and fold resistance [18]. The results of the transdermal patch formulation of Java chili ethanol extract can be seen in the Figure 3.

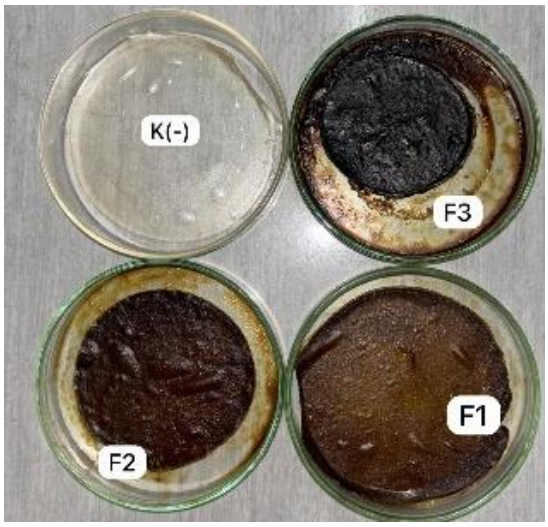


Figure 3. Result of transdermal patch formulation: (K-) Transdermal Patch (0g extract); (F1) Transdermal Patch (1g extract); (F2) Transdermal Patch (2g extract); (F3) Transdermal Patch (3g extract)

The evaluation of the physical properties of the transdermal patches prepared with ethanol extract of Java chili (*Piper retrofractum* Vahl.) revealed notable variations across the tested parameters. The clarity of the patches decreased with increasing extract concentration, as the control was clear, Formula 1 (F1) was transparent, and both Formula 2 (F2) and Formula 3 (F3) were translucent. The form of the patches showed that the control, F1, and F2 were elastic, whereas F3 was slightly elastic, indicating reduced flexibility likely due to the higher concentration of the extract. The color of the patches also changed with increasing extract concentration, ranging from colorless in the control to light brown in F1, brown in F2, and dark brown in F3. Additionally, the odor of the patches was influenced by the Java chili extract, with F1, F2, and F3 exhibiting its characteristic aroma, while the control remained odorless.

The pH of all patches was within a skin-compatible range, with the control at 5 and the formulations ranging from 5.5 to 6. According to standard for a qualified pH value is 4.5-6.5 which aims to prevent the patch from irritating the skin [19]. Thickness increased slightly with the addition of the extract, from 0.12 mm in the control to 0.15 mm in F1 and 0.16 mm in F2 and F3. The thickness results for each formula have met the thickness requirements which should not exceed 1 mm, because if the patch is too thick it will be difficult to release the active substance from the patch [20]. Lastly, fold resistance, which reflects the durability of the patches, was excellent (>300 folds) for the control, F1, and F2 but decreased (<300 folds) in F3, likely due to reduced elasticity or increased stiffness at higher extract concentrations. For patch fold resistance, it has not fully met the requirements because the requirement for patch fold resistance is more than 300 folds [21]. For K(-), F1, and F2, the folding resistance can be said to be good, while F3 does not meet the folding resistance requirements. For transdermal patches of Javanese chili ethanol extract, it can be said that it meets the applicable requirements, it's just that the folding resistance test on F3 does not meet the requirements. The results of the evaluation of the physical properties of the transdermal patch of ethanol extract of Java chili can be seen in the Table 2.

Analgesic Test in Mice

The analgesic test was conducted to determine the analgesic effects caused by the use of Java chili ethanol extract on the abdomen of mice. The writhing test was chosen because it is the most widely used test to measure the response of analgesic activity on peripheral nerves using a chemical stimulus in the form of intraperitoneal acetic acid injection [22]. Mice induced with 0.1 mL of acetic acid intraperitoneally were then observed for writhing over a period of 6 hr, with the number of writhing counted every 15 min.

The results of the analgesic test of the ethanol extract patch of Java chili can be seen in the table 3. At the 15th minute, which is the initial point of

writhing in the mice after being induced with acetic acid, the positive control mice had received oral paracetamol, while F1, F2, and F3 contained the ethanol extract of Java chili. The greatest decrease in activity occurred in the positive control treatment group (oral administration of paracetamol). Paracetamol, as the positive control, is capable of reducing pain and inflammation. The analgesic and antipyretic compounds decrease pain and inflammation by inhibiting the cyclooxygenase enzyme, which plays a role in the synthesis of prostaglandins. The decrease in activity began to be noticeable at minute 35. This is because peak serum levels of paracetamol are reached within 30-60 min [23]. Formulas 1, 2, and 3 also exhibited analgesic effects, with a decrease in activity observed from minute 30 to minute 120. From the table 3, it can be seen that the effectiveness of the ethanol extract of Java chili with increased concentration can provide more effective effects than the negative control.

Table 2. Evaluation of the physical properties of the transdermal patch of ethanol extract of Java chili (*Piper retrofractum* Vahl.)

Parameter Test	**Formulas**			
	Control (-)	**F1**	**F2**	**F3**
Clarity	Clear	Transparant	Translucent	Translucent
Form	Elastic	Elastic	Elastic	Slightly Elastic
Color	Colorless	Light Brown	Brown	Dark Brown
Odor	Odorless	Java Chili Aroma	Java Chili Aroma	Java Chili Aroma
pH	5	5.5	6	6
Thickness (mm)	0.12	0.15	0.16	0.16
Fold Resistance	>300	>300	>300	<300

Table 3. Writhing count of mice

Time (Min)	**Mice Writhing (mean ± SD)**				
	K (+)	**K (-)**	**F1**	**F2**	**F3**
15	26.8 ± 3.77	72.2 ± 3.96	56.8 ± 4.20	40.00 ± 3.16	35.6 ± 2.97
30	18.00 ± 3.54	70.20 ± 2.39	48.4 ± 3.85	35.80 ± 2.28	11.60 ± 2.41
45	11.40 ± 1.14	66.40 ± 2.07	42.2± 2.95	19.00 ± 1.58	6.20 ± 1.30
60	5.60 ± 1.14	62 ± 2.55	25.20 ± 3.49	10.80 ± 3.11	3.00 ± 1.00
75	00.00 ± 00.00	59.60 ± 3.05	22.00 ± 3.74	6.80 ± 2.49	1.8 ± 0.84
90	00.00 ± 00.00	41.80 ± 2.77	11.80 ± 1.64	4.4 ± 1.14	0.40± 0.55
105	00.00 ± 00.00	36.60 ± 1.52	6.60 ± 1.52	2.20 ± 0.45	00.00 ± 00.00
120	00.00 ± 00.00	30.8 ± 0.84	1.8 ± 0.84	0.40 ± 0.55	00.00 ± 00.00

Based on Figure 2, increasing the concentration of the ethanol extract patch formulation of Java chili significantly enhanced the analgesic effect in male mice. In the F3 treatment group, which contained 3 g of Java chili ethanol extract, the analgesic response was comparable to that of the positive control group treated with oral paracetamol. In contrast, the negative control group (untreated) exhibited no nociceptive response after the 60th minute. Meanwhile, in the F3 treatment group, the absence of nociceptive activity was observed between the 90th and 120th min.

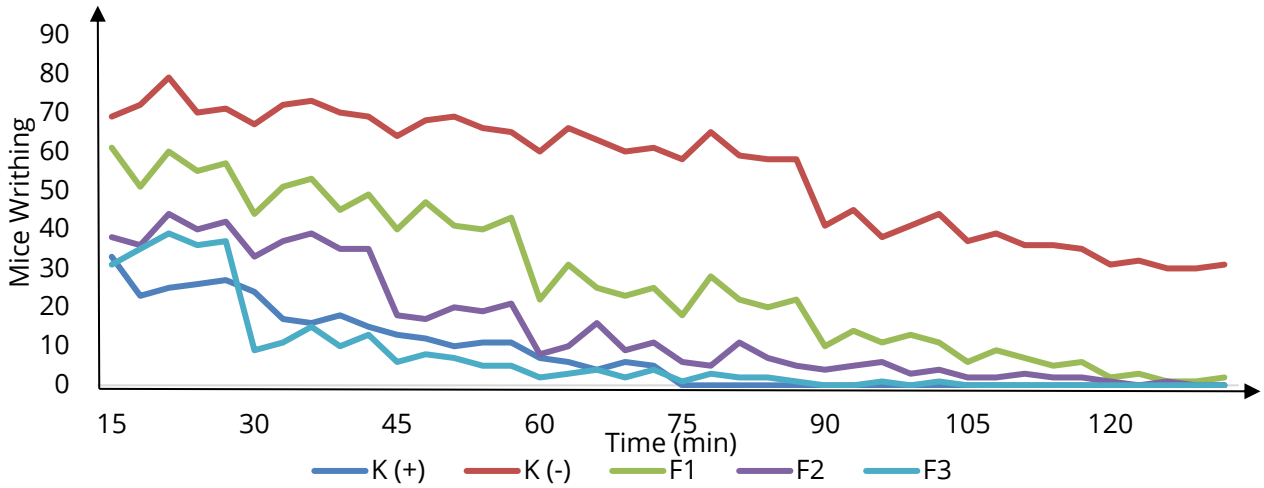


Figure 2. Graph of mice writhing versus time

Macrophage test and calculation of peritoneal macrophages in mice

Macrophage testing is conducted to see how infection affects the immune response through changes in the number of macrophages. The number of macrophages was observed using a microscope with a magnification of 400x [14]. The characteristics of macrophages from the peritoneal fluid of mice can be seen in figure 3. The average number of macrophages in mice induced with 1% acetic acid and given treatments can be seen in the figure 3. Based on the observations of the number of macrophages after 120 min, the highest number was found in the peritoneal fluid sample from the negative control group, followed by the transdermal patches F1, F2, F3 and positive control. Compared to the negative control, the administration of the ethanol extract of Java chili can reduce the number of macrophages in mice induced with acetic acid.

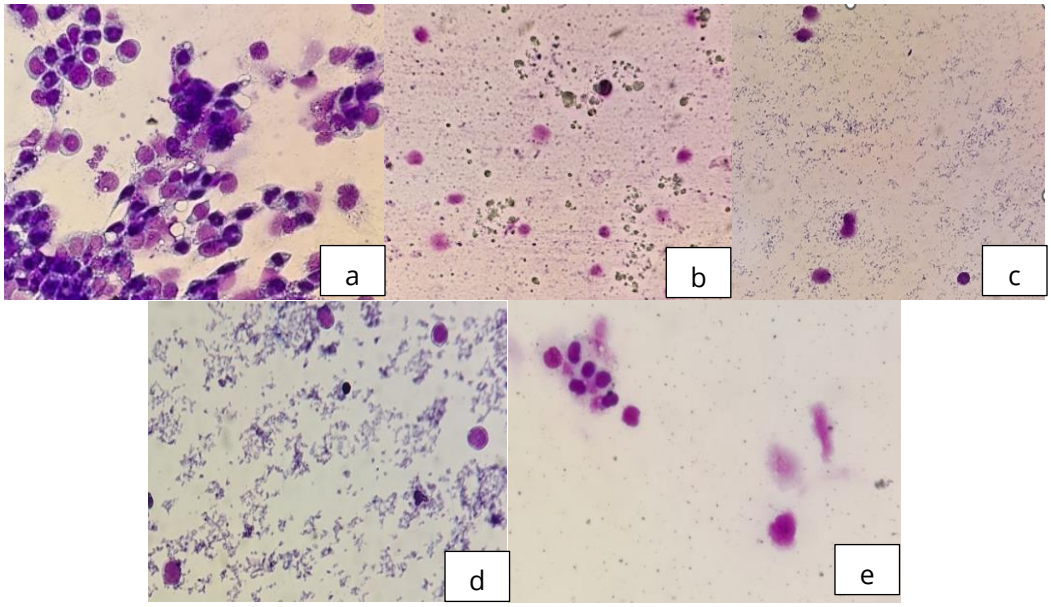


Figure 3. Characteristic of Macrophages from peritoneal fluid (a) negative control; (b) positive control; (c) Formula 1; (d) Formula 2; (e) Formula 3

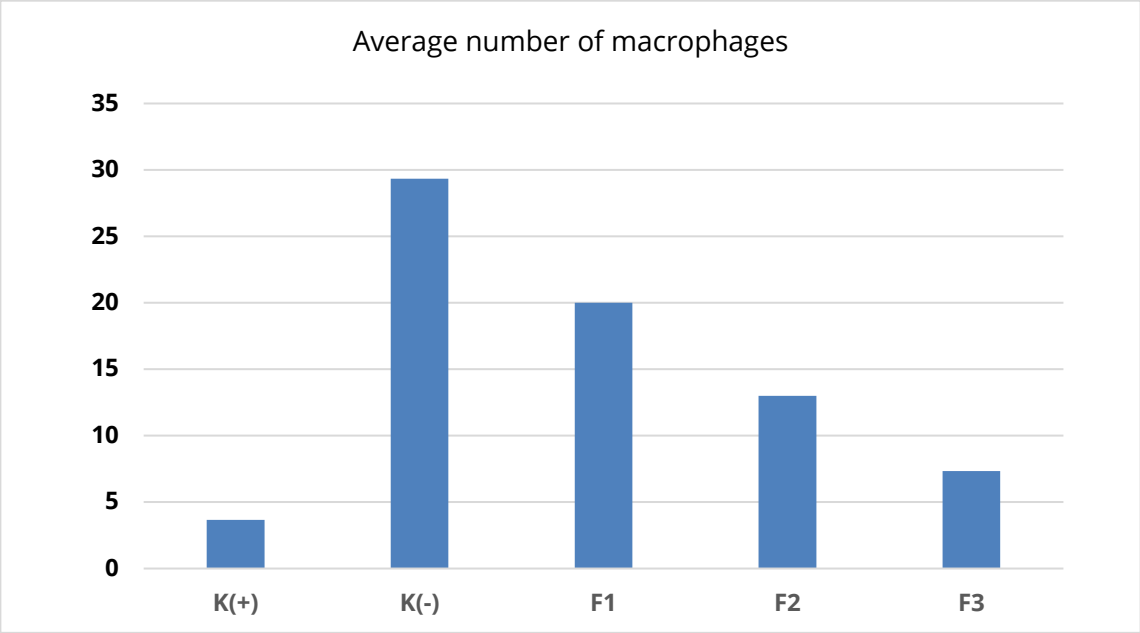


Figure 4. Average number of macrophages

The macrophage test results demonstrated that transdermal patches containing Java chili ethanol extract significantly decreased the quantity of macrophages in the inflammatory area when administered to mice. According to figure 4, in comparison to the negative control group (K-), this decline was noted in the treatment groups F1, F2, and F3. The average number of macrophages in the negative control group was 29.33, but the treatment groups—F1 had 20.00, F2 had 13.00, and F3 had 7.33—showed a progressive decline. The reduction in macrophages suggests that the immunological response involved in the analgesic process can be suppressed by the transdermal patch of Java chili ethanol extract.

Based on research conducted by Malik [24], the negative control does not have the same effect as that given to the positive control. This is because mice in the negative control are induced without treatment in the form of active substances that can increase the immune system in test animals. According to previous research [25], it shows that macrophage cells in the treatment group are less than in the control group. While it can also be seen that the higher the concentration of noni leaf extract given, the number of macrophage cells will decrease. Consequently, it can be seen that the higher the amount of extract given, the fewer the number of macrophage cells in the rat mandibular socket tissue. Which is in accordance with the results obtained, namely the increase in the concentration of ethanol extract of Java chili can reduce the number of macrophages in mice.

The decrease in the number of macrophages in the treatment group compared to the negative control (K-) is strongly related to the analgesic and anti-inflammatory activity of the ethanol extract of Java chili, which contains piperine. Piperine, as the main active compound in Java chili, is known to have mechanisms that inhibit inflammatory mediators, including pro-inflammatory cytokines such as TNF-α and IL-6, as well as the enzyme cyclooxygenase-2 (COX-2). Additionally, piperine is also capable of inhibiting the activation of the transcription factor NF-κB, which plays an important role in regulating the genes that trigger the inflammatory response.

The decrease in macrophages following the administration of the transdermal patch also indicates that the extract effectively reduces inflammation in mice. This anti-inflammatory activity can be attributed to piperine, a bioactive component in Java chili. Previous research has demonstrated that piperine possesses analgesic and anti-inflammatory properties by inhibiting cyclooxygenase (COX) and 5-lipoxygenase activity, reducing prostaglandin production. The

observed reductions in COX-2 expression and PGE2 levels further support the conclusion that the ethanol extract of Java chili can modulate inflammatory pathways, providing a potential therapeutic approach for inflammatory pain management [26].

Transdermal delivery allows the active compounds in Java chili to be absorbed slowly through the skin, resulting in stable levels of the compounds in the blood and providing sustained therapeutic effects. This method also reduces the risk of fluctuations in drug concentration that commonly occur with oral or injection routes [27]

Conclusion

Based on the research results obtained, it was found that the ethanol extract of Java chili with increased concentrations provides more effective effects compared to the negative control (-). The decrease in the number of macrophages following the administration of the transdermal patch of ethanol extract of Java chili also indicates that the extract can reduce inflammation and pain in mice. In the patch evaluation for organoleptic tests, the best results were observed in formula 2. The folding endurance evaluation was best in formulas 1 and 2, which was >300 folds. For the pH evaluation, all three formulas had a good pH of 5

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Author Contributions

Conceptualization, A.L., E., U.L; Methodology, U.L., N.N,P., Software, A.I., N.NP; Validation, A.L., U.L., J.H.N; Formal Analysis, E, U.L., A.T.Y; Investigation, A.L., I.P.S.; Resources, A.L., E., U.L; Data Curation, A.L.; Writing – Original Draft Preparation, U.L, N.N.P.; Writing – Review & Editing, A.L, E., A.T.Y; Visualization, N.N.P., I.P.S.; Supervision, J.H.N; Project Administration, A.L.; Funding Acquisition, A.L".

Conflict of Interest

The authors declare no conflict of interest

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