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Research Article

Formulation of Cream Extract Kratom Leaf (*Mitragyna speciosa* Korth.) as Analgesic in Mice (*Mus musculus*)

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Abstract

Pain is an unpleasant sensation caused by tissue damage. One alternative pain management is the use of topical analgesics in the form of creams. Kratom leaves (Mitragyna speciosa Korth.) are known to contain alkaloids that have analgesic potential. This study aims to formulate a cream preparation of kratom leaf extract and evaluate its physical characteristics and analgesic activity. The cream preparations were made in three variations of extract concentrations: 10%, 25%, and 50%. Physical quality evaluation showed that all formulas met the organoleptic requirements, homogeneity, pH, viscosity, spreadability, and adhesiveness with an oil-in-water emulsion type. The pH value of the preparation was in the range of 4.56–5.50, viscosity 4,266–24,766 cPs, spreadability 5.05–5.66 cm, and adhesiveness 4.64–22.91 seconds. Increasing the extract concentration caused a color change in the preparation from light brown to dark brown. Analgesic activity testing using the hot plate method showed that all formulas had analgesic activity indicated by an increase in the pain threshold after administration of the preparation. The percentage increase in the pain threshold in Formula I (10%) was 14.35%, Formula II (25%) was 17.17%, and Formula III (50%) was 20.68%, while the positive control (counterpain cream) was 33.07% and the negative control (cream base) was 0%. This study concluded that cream formulated with kratom leaf extract exhibited analgesic activity as evidenced by the increase in pain threshold in mice.

Keywords: analgesic, cream, extract, hot plate, kratom leaf

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1 Introduction

Pain is a sensory and emotional experience that serves as a natural warning system of the body and can reduce an individual's quality of life [1]. Analgesics are drugs used to relieve pain without causing loss of consciousness and are classified into opioid and non-opioid groups. However, their use may lead to various side effects, including hypersensitivity reactions, gastrointestinal disorders, kidney damage, and potential hepatotoxicity, especially with long-term use [2]. Therefore, the development of alternative analgesics with fewer side effects is necessary. One potential alternative is the utilization of medicinal plants with analgesic activity, such as kratom (Mitragyna speciosa Korth.).

Mitragyna speciosa is a tropical plant native to Southeast Asia, including Indonesia, and has been traditionally used to relieve pain and treat various health conditions [3]. Although kratom is commonly administered orally, its effectiveness is limited due to low solubility, low bioavailability, and degradation in gastric conditions. In addition, oral use poses a risk of dependence. Therefore, topical delivery is considered a safer alternative, although the skin penetration of its active compounds remains a challenge due to their lipophilic nature and large molecular size [4].

The primary active compounds in kratom leaves are mitragynine and 7-hydroxymitragynine, which exhibit affinity for opioid receptors and show opioid-like analgesic activity [5]. Previous research by Anindita et al. (2023) demonstrated that kratom leaf ethanol extract formulated as a cream at concentrations of 0.26 g, 0.56 g, and 0.86 g produced antinociceptive effect, with the highest activity observed at the 0.86 g concentration [7]. A cream is a semi-solid preparation intended for topical use and contains one or more active ingredients dissolved in a suitable base [6]. Topical cream formulations offer several advantages including ease of application, good absorption, non-sticky properties, and ease of removal [6].

Based on the above description, research on topical formulations of kratom leaf extract remains limited, as most studies have focused only on its antinociceptive or analgesic activity. Therefore, this study aims to develop and evaluate the physically characteristics of a cream formulation containing kratom (Mitragyna speciosa Korth.) leaf extract as an analgesic agent in mice (Mus musculus).

2 Method

2.1 Tool and Materials

The tools used in this study were , homogenizer, brookfield viscometer, pH meter, analytical scales, weights, hot plates, adhesion test equipment, cream containers, and glass utensils (Pyrex).

The materials used in this study are daun kratom (*Mitragyna speciosa* Korth.), 96% ethanol, Stearic acid, Cetyl alcohol, Tween 80, Span 80, Propylene glycol, Ethoxydiglycol, phenoxyethanol, Triethanolamine, and aquadest.

2.2 Formulation of Cream Preparation

The cream is made in 3 formulas, each formula with weight 25 grams. Formula design in full can be seen at Table 1 below:

Table 1. Kratom Leaf Extract Cream Formula

Material	Concentration (%)				Function
	F0	F1	F2	F3	
Kratom Leaf Extract	-	10	25	50	Active Substances
Stearic acid	7	7	7	7	Ko emulsifier
Cetyl alcohol	4	4	4	4	Stiffening agent
Tween 80	3	3	3	3	Emulsifier
Span 80	2	2	2	2	Emulsifier
Propylene glycol	5	5	5	5	Humektan
Ethoxydiglycol	2	2	2	2	Enhancer

Phenoxyethanol	0,5	0,5	0,5	0,5	Preservatives
Triethanolamine	0,3	0,3	0,3	0,3	Alkalizing agent
Aquadest	Add 100	Add 100	Add 100	Add 100	Solvent

The necessary equipment and materials were prepared, and all ingredients were weighed according to their respective weights. The oil phase contained a mixture of stearic acid, cetyl alcohol, and Span 80, while the water phase contained propylene glycol, ethoxydiglycol, Tween 80, and distilled water. The oil and water phases, prepared in beakers, were heated to 70°C. The cream-making process was carried out using a homogenizer. The water phase was added little by little to the oil phase until a cream formed. After emulsification, triethanolamine was added and homogenized. The mixture was then allowed to cool to below 40–45°C before adding phenoxyethanol. Finally, the kratom leaf extract was incorporated and mixed until homogeneous.

2.3 Evaluation Parameters of Cream

2.3.1 Organolepti Test

The test method is conducted through visual observation to describe the color, aroma, and shape of the preparation. This test utilizes the human senses as the primary measurement tool [6].

2.3.2 Homogeneity Test

The test was performed by applying 0.5 g of cream to a glass slide and then covering it with another glass slide. Observed the arrangement of coarse particles or the inhomogeneity of the cream preparation. The requirement for cream preparation was considered homogeneous if it had an even texture and no lumps [7].

2.3.3 pH Test

pH testing is carried out using a pH meter. The good pH requirement for cream preparations is in the range of 4.5-6.5 according to the normal pH of the skin [8].

2.3.4 Viscosity Test

The test used a Brookfield spindle number 4 viscometer at a speed of 60 rpm. The viscosity value that meets the requirement is 2.000–50.000 cPs [9].

2.3.5 Spreadability Test

The test was performed by placing 0.5 g of cream on a glass plate, then covered with another glass plate and given a load of 150 g for 1 minute, then the distribution of the diameter of the preparation was observed. The good spreadability of topical formulations in the range of 5-7 cm [10].

2.3.6 Ahdesion Test

The test was carried out by placing 0.25 g of cream between two object glasses. The glass were pressed with a load of 250 g for 5 minutes, then attached to the adhesion test apparatus and pulled with a load of 80 g. The time required for the two glasses to separate was recorded. Good adhesion to cream preparation is in the range of >1 second [11].

2.3.7 Emulsion Type Test

The test was carried out using the dilution method. The prepared cream was placed in a beaker and then 10 mL of water was added. If the cream mixes well with the water, the resulting emulsion is oil-in-water (O/W) [12].

2.4 Analgesic Test

The analgesic activity of kratom leaf extract cream was evaluated using 25 healthy male Mus musculus mice, weighing 20–35 g, with normal activity levels. The animals were randomly divided into five groups. Prior to treatment, all animals were acclimatized for 7 days. On the day of testing, each group received different treatments: a negative control group (cream base), a positive control group (counterpain cream), and three test groups containing kratom leaf extract cream at concentrations of 10%, 25%, and 50%. A total of 100 mg of the respective cream was applied to the paw of each mouse

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and allowed to absorb for one minute. After the application period, each mouse was placed on a hot plate maintained at 50°C. The response latency, defined as the time (in seconds) from placement on the hot plate to the first sign of pain response (paw licking, hind limb withdrawal, or jumping), was recorded. Observations were conducted at 15-minute intervals for 120 minutes, with a cut-off time set at 15 seconds to prevent tissue damage [13], [14].

The analgesic activity was then calculated using the following formula:

$$\text{Percentage increase in pain inhibition} = \frac{\text{AUCp} - \text{AUCk}}{\text{AUCp}} \times 100\%$$

Description:
AUCp: AUC of the average response curve versus time of the treatment group.
AUCk: AUC of the average response curve versus time of the negative control group.

3 Result and Discussion

The results of the evaluation of the physical characteristics of the kratom (*Mitragyna speciosa* Korth.) leaf extract cream preparation are presented in Table 2. Organoleptic testing is a test that aims to describe the color, aroma, and appearance of the preparation. This is important to assess the characteristics of the preparation so that the resulting cream can provide comfort and good acceptance when used [15]. Cream base (F0) indicates a white preparation, has a cream base aroma that is not rancid, and has a semi-solid form. Formulas I, II, and III show the same aroma and form characteristics, namely having a distinctive aroma of kratom leaf extract and a semi-solid form. However, there are visible differences in the color of the resulting preparation, where each formula shows a different color intensity. This is based on the level of concentration of kratom leaf extract used in each formula. The higher the concentration of the extract used, the more intense the preparation will be [16]. The homogeneity test aims to assess the uniformity of mixing and detect the presence of coarse particles. The results showed all formulas were homogeneous, indicating the absence of coarse particles, making them comfortable to use [17].

Table 2. Physical Characteristics of Cream Formulated with Kratom Leaf Extract

Evaluation	Formula			
	F0	FI	FII	FIII
Organoleptic	White, non-rancid, semisolid	Light brown, typical odor of kratom leaf extract, semisolid	Brown, typical odor of kratom leaf extract, semisolid	Dark brown, typical odor of kratom leaf extract, semisolid
Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous
pH	6,31 ± 0,015	5,50 ± 0,015	5,02 ± 0,020	4,56 ± 0,055
Viscosity	6.542 cPs ± 0,325	4.266 cPs ± 0,281	4.871 cPs ± 0,222	24.766 cPs ± 0,351
Spreadability	6,05 cm ± 0,608	5,66 cm ± 0,104	5,13 cm ± 0.152	5,05 cm ± 0,05
Adhesion	1,31 s ± 0,190	4,64 s ± 0,124	14,29 s ± 0,584	22,91 s ± 0,266
Emulsion type	O/W	O/W	O/W	O/W

A pH test is performed to determine the acidity level of a preparation. This test is important because preparations with a pH that is too acidic or too basic can cause skin irritation. A preparation is considered to meet pH requirements if it is within the range of 4.5–6.5 [8]. The pH test results for the base of the kratom (Mitragyna speciosa Korth.) leaf extract cream showed results that met the test requirements with an average of 6.31. Furthermore, all three kratom leaf extract cream formulations also met the pH testing standards, ranging from 4.56 to 5.50. Stearic acid and kratom leaf extract have acidic properties that can

lower the pH value of the preparation, especially when used in high concentrations. Therefore, the addition of basic triethanolamine plays a role in neutralizing the acidic nature of the stearic acid and extract so that the pH of the preparation remains within the appropriate range [18].

Viscosity testing is a test that aims to determine the thickness of a preparation. This test is necessary because the viscosity of a preparation can affect the comfort of its use. Too high a viscosity makes the preparation difficult to remove from the packaging and uncomfortable, while too low a viscosity causes the preparation to be too runny and not adhere optimally to the skin [17]. The viscosity value of a cream preparation that meets the standards is 2,000-50,000 cPs [8]. The viscosity test results for the base cream preparation containing kratom (Mitragyna speciosa Korth.) leaf extract met the test requirements, namely 6,542 cPs. Furthermore, the three formulas of the kratom leaf extract cream preparation also met the viscosity test standards, namely in the range of 4,266-24,766 cPs. The addition of cetyl alcohol to the cream formulation can affect the viscosity of the preparation. This is due to cetyl alcohol's ability to absorb water and water vapor during the storage process. Furthermore, stearic acid can also act as a thickening agent in cream preparations [18], [19]. Furthermore, the higher the extract concentration in a formulation, the higher its viscosity. Formula III, with a 50% extract concentration, exhibited the highest viscosity compared to the other formulations. This is because the higher the extract concentration, the less water is added, thus increasing its viscosity [9].

Spreadability testing is a test carried out to evaluate how quickly a cream can spread when applied to the skin [8]. The spreadability of the preparation plays an important role in facilitating the application process to the skin, because the better the spreadability, the less energy is needed during use [17]. Topical preparations are said to meet the spreadability requirements if they are in the range of 5-7 cm [20]. The cream base and all three kratom leaf extract formulas met the requirements for spreadability testing. A product's spreadability is inversely proportional to its viscosity. The higher the spreadability, the lower the viscosity. This is because a lower viscosity means the product is thinner and has a higher spreadability. The thinner the product, the easier it will flow when applied, making it easier to spread. Furthermore, the smaller the bonds between particles, allowing for easier particle movement [8].

The adhesion test is a test performed to assess how firmly a cream adheres to the skin's surface. This test measures how long the cream remains on the adhesion tester [8]. The test conditions for a preparation will be said to be good if it has an adhesive strength of more than 1 second [11]. The adhesion strength of the cream base and the three kratom leaf extract formulas met the test requirements. Theoretically, the adhesion strength of the cream is related to the spreadability of the preparation. Creams with low spreadability tend to have longer adhesion times, while creams with higher spreadability show shorter adhesion times [9]. The higher the adhesive strength of a preparation, the longer it can remain on the skin's surface. High adhesive strength indicates the preparation's ability to adhere for longer, allowing the active ingredient to be fully absorbed [8].

Emulsion type testing is a test conducted to determine the emulsion type of a cream preparation. This test is performed by diluting the cream with water [12]. The results of the emulsion type test that has been carried out on the base formula, Formula I, Formula II, and Formula III show that all formulas have an O/W type. This is because the water phase is more dominant or more than the oil phase, thus forming an O/W type. These results are also supported by the calculation of the HLB value of the emulsifier used, Tween 80 has an HLB value of 15 which is more hydrophilic, while Span 80 has an HLB value of 4.3 which is more lipophilic. The combination of Tween 80 and Span 80 produces a mixed HLB value of 9.65. The HLB value is in the range of 8–18, so the emulsion system formed is included in the oil-in-water (O/W) type [21].

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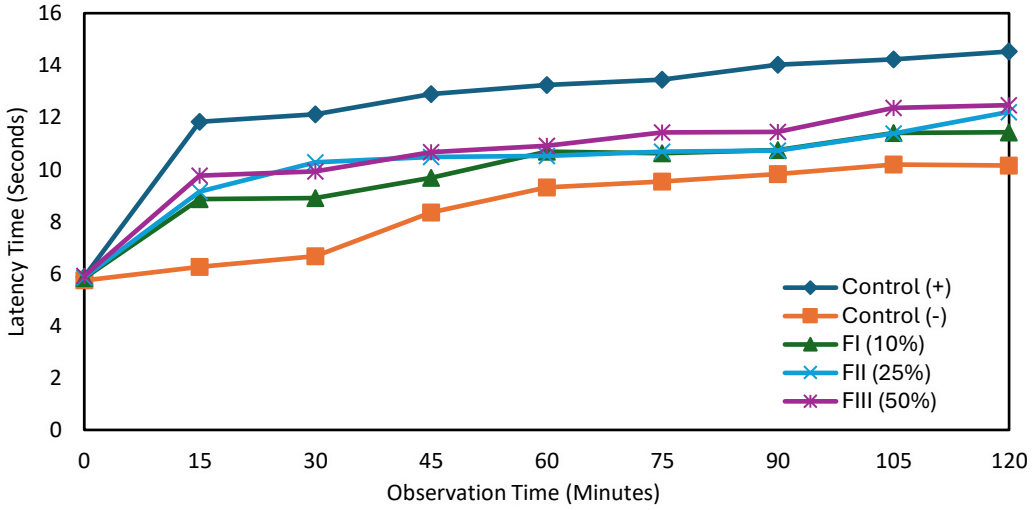

Figure 1. Average Latency Time Improvement Graph

The analgesic activity of kratom leaf extract cream was evaluated using the hot plate method by measuring the response latency as an indicator of pain threshold. The pain threshold percentage describes the ability of the test compound to increase tolerance to pain stimuli, where the higher the percentage value, the greater the analgesic activity produced [22]. The analgesic activity of kratom leaf extract cream is associated with its active alkaloid compounds, which act through both opioid and non-opioid pathways. Kratom leaves contain at least 66% alkaloid compounds [3]. The main alkaloids contained in kratom are mitragynine and 7-hydroxymitragynine. The primary mechanism involves the opioid system, where mitragynine acts as a partial agonist of μ-opioid receptors, while 7-hydroxymitragynine exhibits stronger analgesic potency. Activation of these receptors inhibits pain transmission at both peripheral and central levels by reducing the release of pain-related neurotransmitters [23]

In addition to the opioid pathway, kratom also demonstrates analgesic effects through non-opioid mechanisms. Certain alkaloids, such as speciogynine and paynantheine, have been reported to reduce inflammation by inhibiting COX-2 expression and the NF-κB pathway [24]. This is supported by findings from Prasetya et al. (2025), which showed that kratom leaf extract significantly inhibited COX-2 activity (74.38%) with minimal effect on COX-1 (2.47%) [25]. These results suggest that the analgesic activity of kratom involves both opioid receptor modulation and selective COX-2 inhibition.

Table 3. AUC Data and Percentage Increase in Pain Threshold

No.	Formula	AUC	Percentage Increase in Pain Threshold
1	Control +	1529,38 ± 49, 726	33,07% ± 3,563[a]
2	Control -	1022,14 ± 23, 732	0% ± 0[b]
3	FI (10%)	1193, 50 ± 14, 953	14,35% ± 1,306[c]
4	FII (25%)	1234, 45 ± 12,769	17,17% ± 2,494[cd]
5	FIII (50%)	1282,99 ± 18,214	20,68% ± 2,974[d]

Description: Different superscript letters within the same column indicate significant differences ($p \leq 0.05$), while values sharing at least one common letter are not significantly different.

The Shapiro–Wilk normality test for pain relief data confirmed a normal distribution, with a significance value greater than 0.05. However, homogeneity testing showed that the data were not homogeneous, as indicated by a significance value ($p < 0.05$). The Kruskal–Wallis test yielded a significant value ($p < 0.05$), indicating a difference in analgesic activity between treatment groups. Further Mann–Whitney tests showed that the positive control was significantly different ($p < 0.05$) from the negative control and all test formulas, indicating a stronger analgesic effect. The negative control also differed significantly from all formulas, concluding that all formulas possess analgesic activity.

Formula I (10%) showed a significant difference compared to Formula III (50%), indicating a dose-response relationship, where increasing the extract concentration increases analgesic activity. However, there was no significant difference between Formula I (10%) and Formula II (25%), or between Formula II (25%) and Formula III (50%). This indicates that increasing concentration does not always result in a proportional increase in biological activity, which may be influenced by interactions between compounds in the extract [26].

The absence of a significant difference between Formula II (25%) and Formula III (50%) indicates that increasing the concentration does not significantly increase the analgesic effect. This is thought to be due to receptor saturation, where the response has reached its maximum effect (Emax) [27]. Furthermore, mitragynine, as a partial agonist of the μ-opioid receptor, has limitations in producing a maximum response, and there is also the possibility of interactions with other alkaloid compounds in kratom leaves, such as speciogynine and speciociliatine, which are known to be weak antagonists. This condition can cause a ceiling effect, where increasing the dose no longer significantly increases the pharmacological effect [28], [29]. Furthermore, the physical characteristics of the preparation, particularly viscosity, affect the release and diffusion of active ingredients. Excessive viscosity can inhibit the release of active ingredients. Therefore, optimizing the concentration of the extract and cream base is necessary to achieve a balance between effectiveness and the physical characteristics of the preparation[30], [31].

4. Conclusion

Based on the results of the physical characteristics test of the cream preparation, it was found that all formulas met the requirements of a good cream, as evidenced by successful organoleptic, homogeneity, viscosity, pH, spreadibility, adhesion, and type emulsi tests. The analgesic efficacy of kratom leaf extract cream at three different concentrations was evaluated using the hot plate method. The formulation containing 50% extract showed the highest analgesic activity, with a pain threshold increase of 20.68%, followed by the 25% formulation (17.17%) and the 10% formulation (14.35%). These findings suggest that increasing the concentration of kratom leaf extract enhances its analgesic effect, highlighting its potential as a topical analgesic agent.

5. Declarations

5.1 Acknowledgements

All authors contributed to the writing of this article.

5.2 Author contributions

All authors contributed to the writing of this article.

5.3 Ethics

Ethical approval for this study was obtained from the Ethics Committee of the Faculty of Pharmacy, Universitas Mulawarman, with approval number No.127/KEPK-FFUNMUL/EC/EXE/09/2025.

5.4 Conflict of Interest
No conflicts of interest have been declared by the authors.

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