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FORMULATION AND CHARACTERIZATION OF ANTI-INFLAMMATORY TRANSDERMAL PATCH PREPARATIONS FROM THE EXTRACT OF PATAH TULANG (*Euphorbia tirucalli*)

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ABSTRACT

Transdermal patches are pharmaceutical preparations that aim to provide a drug delivery system across the surface of the skin and tissue, which is then delivered to the blood. is a plant that contains secondary metabolites with anti-inflammatory activity, such as alkaloids, flavonoids, polyphenols, tannins, steroids, and saponins. This study aimed to determine the characteristics of anti-inflammatory transdermal patch preparations prepared from *Euphorbia tirucalli* extract. The research method was laboratory experimental by preparing patches using varying concentrations of *Euphorbia tirucalli* extract, namely F1 (5%), F2 (10%), and F3 (15%). Next, an evaluation of patch preparation was carried out, including organoleptic tests, weight uniformity tests, thickness tests, fold durability tests, pH tests, and moisture tests. From the research results, it can be concluded that *Euphorbia tirucalli* extract at concentrations of 5%, 10%, and 15% can be made into patch preparations. The best characteristics of the patch preparation were F2 with an extract concentration of 10%, which had a smooth, flexible texture, folding durability >300 folds, pH 4.5, and moisture value of 7.30%.

Keywords: Anti-inflammatory, *Euphorbia tirucalli*, Transdermal patch

INTRODUCTION

Inflammation is the body's defense response to various stimuli. Inflammation is caused by a local reaction of tissues or cells to stimulate the release of chemicals such as histamine, serotonin, bradykinin, leukotrienes, and prostaglandins, which stimulate tissue changes in this reaction. Signs of inflammation include redness, heat, pain, and swelling (Sustiwa et al., 2023).

Anti-inflammatory drugs are divided into two groups: steroidal and non-steroidal anti-inflammatory drugs. However, both classes of drugs have several adverse effects. Steroid anti-inflammatory drugs can cause side effects including osteoporosis, glaucoma, and diabetes (Ifmaily et al., 2021). Nonsteroidal anti-inflammatory drugs are often used to relieve pain and reduce inflammation. Based on 2018 Riskesdas data, 19.8% of all households in Indonesia store non-steroidal anti-inflammatory drugs. However, this class of drugs can cause stomach ulcers, bleeding, kidney problems, and anemia. Based on this, many anti-inflammatory treatments have been developed using natural ingredients, especially plants (Nugroho, 2012).

Euphorbia tirucalli can be used to cure inflammation. In Indonesia, this plant grows well and is known as a type of plant that is commonly used by people as traditional medicine (Mamarimbing et al., 2022). Empirically, for Bitung people, a bone fracture plant is used to treat fractures caused by accidents or falls. The treatment was performed by gently crushing

the stem of the *Euphorbia tirucalli* plant, which was then applied to the affected area (Garakia et al., 2020). Flavonoids, tannins, and steroids are chemical ingredients with anti-inflammatory properties.

This study aimed to develop a drug delivery system in the form of an anti-inflammatory transdermal patch derived from natural ingredients, using *Euphorbia tirucalli* extract. Transdermal delivery is a systemic drug delivery system that applies a drug to the skin surface.

RESEARCH METHODS

Equipment and Materials

The equipments used in this research include macerator, chopper (Miiso), waterbath (LabTech), rotary evaporator (In Scien Pro EVA-700), desiccator (Dianrui 300 mm), vernier caliper (Trickle Brand 12 inch), pH meter (Mediatech P-2Z-B1900126), analytical balance (mrc ASB-220-C2-V2), and mortar and stamper (8 cm).

The materials used in this research include *Euphorbia tirucalli* extract, etanol 96% pharmaceutical grade PT. Bratachem, aquadest pharmaceutical grade, PT. Bratachem, HPMC pharmaceutical grade PT. Bratachem, PVP pharmaceutical grade PT. Bratachem, propylene glycol pharmaceutical grade PT. Bratachem, DMSO pharmaceutical grade PT. Bratachem, Mayer's reagent CV. DPPH, Dragendorff's reagent CV. DPPH, magnesium powder pharmaceutical grade PT. Bratachem, concentrated HCl, PT. Bratachem, $FeCl_3$ PT. Bratachem, gelatin 1%, glacial acetic acid, PT. Bratachem and H_2SO_4 PT. Bratachem.

Research Procedure

1. **Determination**

   Determination was performed at Siliwangi University, number 553/UN58.10.6/LL/2023.

2. **Sample Processing**

   Stem and twig samples from *Euphorbia tirucalli* were obtained from the TOGA garden of the Department of Pharmacy, Poltekkes Kemenkes Tasikmalaya, West Java. The stems and twigs of *Euphorbia tirucalli* collected were then sorted and washed thoroughly using running water. Then drained and dried. Subsequently, the fresh samples were ground using a chopper.

3. **Extraction Process**

   The finely ground stems and twigs of *Euphorbia tirucalli* were placed in a macerator and then remaceration using 96% ethanol solvent for 3 days. The ratio of one remaceration between plants and solvent was 100 g of fresh, ground stems, and twigs soaked in 500 mL of 96% ethanol for 2 × 24 h with occasional stirring, then filtered, and the residue was soaked again in 250 mL of 96% ethanol, stirred, and stored for 1 × 24 hours (Garakia et al., 2020). The maserate of the broken stems and twigs was then filtered and evaporated until a thick extract was obtained.

4. **Phytochemical Screening**

   a) **Alkaloids**

   The extract was put into a test tube, followed by the addition of a few drops of 2 N HCl and distilled water, heated in a water bath for 2 min, cooled, and filtered. The filtrate was then divided into 2. Three drops of filtrate were added to 2 drops of Mayer's reagent solution. The presence of white sediment or turbidity indicates the presence of alkaloid chemical compounds. Three drops of filtrate were added to 2 drops of Dragendorff's reagent solution, and the presence of orange-yellow sediment or turbidity indicated the presence of alkaloid chemical compounds (Harahap et al., 2021).

   b) **Flavonoid**

   The extract was taken with a spatula and then a spatula of Mg powder and four drops of 2% HCl were added. The presence of flavonoid compounds was indicated by a change in the color of the filtrate to orange-red (Harahap et al., 2021).

c) Polifenol

The filtrate was extracted in water, heated, filtered, and dripped with $FeCl_3$ reagent solution. The presence of blue to black indicates the presence of polyphenolic compounds (Harahap et al., 2021).

d) Tanin

The filtrate was extracted in water, heated, filtered, and dripped with $FeCl_3$ reagent solution. The presence of blue to black indicates the presence of polyphenolic compounds (Harahap et al., 2021).

e) Saponin

Samples were extracted in water, heated, and filtered. The filtrate was placed in a test tube and shaken vigorously for approximately 5 minutes. The formation of foam that is stable and does not disappear for 10 minutes with a minimum foam height of 1 cm indicates the presence of saponins (Harahap et al., 2021).

f) Steroid and Triterpenoid

Samples were extracted in water, heated, and filtered. The filtrate was placed in a test tube and shaken vigorously for approximately 5 minutes. The formation of foam that is stable and does not disappear for 10 minutes with a minimum foam height of 1 cm indicates the presence of saponins (Harahap et al., 2021).

5. Transdermal Patch Formulation

Transdermal patch formulations from *Euphorbia tirucalli* extract were prepared using three formulas with varying extract concentrations. The transdermal patch formula made can be seen in Table I.

Table I. Formula of Transdermal Patch

Materials	Weight (gram)		
	F1	F2	F3
Euphorbia tirucalli extract	0,75	1,50	2,25
HPMC	0,75	0,75	0,75
PVP	0,75	0,75	0,75
Propilen Glikol	0,75	0,75	0,75
DMSO	0,15	0,15	0,15
Aquadest	6	6	6
Etanol 96%	Up to 15	Up to 15	Up to 15

Note:
F 1: Transdermal patch formula containing 5% extract
F 2: Transdermal patch formula containing 10% extract
F 3: Transdermal patch formula containing 15% extract

Equipment and materials are prepared, then the materials are weighed first. PVP was finely ground in a mortar, and then finely crushed HPMC was added until homogeneous. Subsequently, crushed distilled water was added until it was homogeneous and a gel was formed. The gel that had been formed was placed in a beaker, and then a small amount of 96% ethanol was added and stirred until it was completely dissolved. Then, the ethanol extract of the broken stems and twigs was added and stirred until homogeneous, propylene glycol and DMSO were added, and the mixture was stirred until homogeneous. Subsequently, 96% ethanol up to 15 g was added, and then poured into a mold whose bottom had been covered with aluminum foil, left for ± 1 hour until there were no bubbles, and then dried at room temperature for ± 48 hours until dry. After the patch is dried, it is removed from the mold (Nitiariksa & Iskandar, 2021).

6. Characterization of Transdermal Patch Preparation

a) Organoleptic Test

This is done by observing color, smell, and texture (Novia, 2021).

b) Weight Uniformity Test

The weight uniformity test was carried out by weighing 3 patches one by one and then calculating the average patch weight and standard deviation from each formula (Novia, 2021).

c) Thickness Test

The thickness test was carried out by measuring the thickness at 3 different points, namely, the top, left, and right of each patch preparation using a micrometer. This test was performed in 3 patches (Novia 2021).

d) Fold Durability Test

The fold durability test was carried out by folding the transdermal patch repeatedly in the same place until the preparation broke or cracked. The maximum number of folds was 300 times. The number of times the preparation can be folded in the same place is the fold durability value of the transdermal patch (Novia, 2021).

e) pH Test

The pH test was carried out by cutting a 1 × 1 cm^2 patch, placing it in a beaker containing 5 mL of distilled water, allowing it to swell for 2 hours at room temperature, and measuring the pH using a pH meter (Wardani & Saryanti, 2021).

f) Moisture Test

The moisture test was performed by weighing each patch (initial weight), which was then placed in a desiccator containing silica gel and stored at room temperature for 24 hours. After 24 hours, the patch was removed from the desiccator and weighed (final weight) to calculate moisture content. A good transdermal patch moisture percentage is < 10% (Novia, 2021).

Data Analysis

The results were statistically analyzed using descriptive analysis methods.

RESULTS AND DISCUSSION

Determination

Based on the results of the plant sample determination carried out at Siliwangi University, the plant was found to be a Patah Tulang plant with the scientific name *Euphorbia tirucalli*.

Extraction

1600 grams of fresh simplicia from *Euphorbia tirucalli* was extracted using the remaceration method with 12 liters of 96% ethanol solvent which was soaked for 3 days. The resulting thick extract of broken stems and twigs was dark brown in color, amounting to 18 grams with a yield of 1.12%.

Phytochemical Screening

Phytochemical screening was performed to determine the secondary metabolites contained in the extract. The results of the phytochemical screening of *the Euphorbia tirucalli* extracts are shown in Table II.

Table II. The Results of the Phytochemical Screening of *Euphorbia tirucalli* Extracts

Secondary metabolite compounds	Results description
Alkaloid	Reagent Mayer's (+) Reagent Dragendorff's (+)
Flavonoid	(+)
Polifenol	(+)
Tanin	(+)
Saponin	(+)
Steroid/Triterpenoid	(+)

Note :
(+) : proven to contain secondary metabolite compounds
(-) : proven not to contain secondary metabolite compounds

Mayer's reagent showed white turbidity. The white color formed was due to the formation of a complex compound between the alkaloid and the K ion from Mayer's reagent. The nitrogen atom in the alkaloid ring bonds covalently in coordination with the K ion of Mayer's reagent (Aristina et al., 2019). Dragendorff's reagent resulted in a color change to orange yellow. The K+ metal ion from the Dragendorff reagent forms a bond with the nitrogen in the alkaloid to form a light brown to yellow potassium-alkaloid complex that precipitates (Kayaputri et al., 2014). Alkaloids exert anti-inflammatory activity by regulating histamine production by mast cells and reducing the secretion of interleukin-1 released by monocytes (Yuda et al., 2022).

Examination of the flavonoids of *the Euphorbia tirucalli* extract showed positive results with an orange color change. The addition of magnesium powder and hydrochloric acid to the flavonoid test caused a reduction in the existing flavonoid compounds, giving rise to a red reaction, which is a characteristic of the presence of flavonoids. The addition of concentrated HCl in the flavonoid test was intended to hydrolyze flavonoids into their aglycones by hydrolyzing O-glycosyl. Glycosyl is replaced by H+ in the acid because of its electrophilic nature. Reduction with Mg and concentrated HCl produces complex compounds that are red or orange in color. If the color is red to orange, it is provided by the flavone compounds (Abidin et al., 2020). Flavonoids from the flavonol, flavon, and isoflavone groups have anti-inflammatory activity by inhibiting COX-2 (cyclooxygenase-2 enzyme) which plays a role in mediating inflammation and thus can provide good anti-inflammatory activity (Hermanto et al., 2019).

The results of testing for polyphenolic compounds in *Euphorbia tirucalli* extract were positive for these compounds. The reaction of $FeCl_3$ with the sample creates color in this test, the role of which is that the Fe^{3+} ion undergoes hybridization (blackish in color) (Harahap et al., 2021). Tannin test results were positive for the formation of a white precipitate. The formation of a white precipitate when reacted with gelatin solution indicated the presence of tannins in the sample. This is related to the nature of tannins, which allows them to bind and precipitate proteins (Kayaputri et al., 2014). Polyphenolic compounds regulate immunity by influencing immune system regulation, including by controlling the formation of cytokines (Garakia et al., 2020), and act as anti-inflammatory agents by inhibiting the production of oxidants (O_2) by neutrophils, monocytes, and macrophages (Anisa et al., 2019).

Testing for steroid/triterpenoid compounds in *Euphorbia tirucalli* extract showed positive results for triterpenoid compounds, namely a purplish red color change. The color formed was caused by the reaction of the extract with glacial CH_3COOH and concentrated H_2SO_4. Triterpenoids are secondary metabolites derived from terpenoids. These compounds are cyclic or acyclic and often contain alcohol, aldehyde, or carboxylic acid groups (Yuda et al., 2022). This compound has anti-inflammatory activity, which works by inhibiting phospholipase via the arachidonic acid pathway. Inhibition of phospholipase also inhibits the formation of arachidonic acid from phospholipids (Maifitrianti et al., 2019).

Testing the saponin compounds in *the Euphorbia tirucalli* extract showed positive results with the formation of foam. The formation of foam is caused by saponins containing compounds that are partially soluble in polar or hydrophilic solvents and compounds that are soluble in non-polar or hydrophobic solvents. Compounds that have polar and non-polar groups are surface active, so when saponins are shaken with a solvent, it can form micelles. The micelle structure occurs because the polar groups face outward, while the non-polar groups face inward; therefore, they look like foam (Qomariah et al., 2014). This compound has anti-inflammatory activity which works by inhibiting the formation of exudates and inhibiting vascular permeability (Audina et al., 2018).

Formulation and Evaluation of Transdermal Patch Preparations from Extract

The patch was prepared by mixing the PVP and HPMC polymers as a matrix. Both polymers are hydrophilic polymers that allow the active substance to dissolve quickly, allowing the drug to be easily released. PVP has water-soluble properties and functions as an agent to increase drug solubility in the matrix. PVP can produce a good film shape and is easily soluble in solvents that are safe for skin. Meanwhile, HPMC is a good stabilizing agent. HPMC can produce a patch matrix that is strong, not brittle, and flexible (Fuziyanti et al., 2022). The active substance was then added to a thick extract of Patah Tulang. After that, propylene glycol was added as plasticizer. The use of plasticizers adds flexibility to the patch preparation. Propylene glycol was chosen as a plasticizer because it has a milder irritating effect than other plasticizers (Zakaria et al., 2021). After mixing, DMSO was added as a penetration enhancer because DMSO works quickly as a penetration enhancer into the skin and then stirred again until homogeneous. Once homogeneous, 96% ethanol was added as a solvent until the preparation weighed 15 grams and was mixed. The solution was allowed to stand until no bubbles were formed. Next, the solution was poured into the mold and dried at room temperature for 2 days until dry. The dry patch preparation was evaluated using several tests, and the following are the evaluation results from testing the transdermal patch preparation.

Organoleptic Test

The organoleptic test results of the patch preparation have a sticky and wet texture, which can be caused by the hygroscopic characteristics of the PVP polymer, making it sticky and wet because it absorbs moisture from the environment (Rahayuningdyah et al., 2020). The organoleptic test results are presented in Table III.

Table III. Result of Organoleptic Test

Organoleptic	F1	F2	F3
Color	Dark brown	Dark brown	Dark brown
Smell	specific	specific	Specific
Texture	Sticky, flexible, slightly wet, and smooth	Sticky, flexible, wet and smooth	Slightly wet, flexible and rough
Transdermal patch display			

Note:
F 1: Transdermal patch formula containing 5% extract
F 2: Transdermal patch formula containing 10% extract
F 3: Transdermal patch formula containing 15% extract

Weight Uniformity Test

This test was performed to determine the weight of each patch. The weight of a patch affects its ingredients. A small standard deviation (SD) value indicates uniformity in the weights of the created patches. The same formula weight indicates that the patch formulation has the same number of components, or is not significantly different. If the number of components weighed in the formula is the same, one formula is expected to have a uniform weight, which indicates the uniformity of the active substance content. A good standard deviation of ≤ 0.05 (Nitiariksa & Iskandar, 2021).

The results of the weight uniformity test showed that the weights for F1 (2.38 grams ± 0.53), F2 (4.61 grams ± 0.76), F3 (2.72 grams ± 0.88). The patch preparation has a large weight because PVP is a hydrophilic polymer which is able to absorb water molecules, thereby influencing the weight of the patch to be of greater value (Zakaria et al., 2021). Polymers that have more water-attracting properties mean that when making patches, water

is easily retained in the patches during the drying process, which results in an increase in the weight of the resulting patches. In addition, differences in patch weight can also arise because of the manner in which the patch solution is poured into the mold. This can cause the patch solution to remain in the glass beaker. In addition, it can also be caused by the mass of patches left on the mold (Fuziyanti et al., 2022). The results of the weight uniformity tests for the three formulas are listed in Table IV.

Table IV. Result of Weight Uniformity Test

	Weight Uniformity Patch (gram)		
	F1	**F2**	**F3**
Mean±SD	2,38±0,53	4,61±0,76	2,72±0,88
Standard Deviation ≤ 0.05 (Nitiariksa & Iskandar, 2021)			

Note:
F 1: Transdermal patch formula containing 5% extract
F 2: Transdermal patch formula containing 10% extract
F 3: Transdermal patch formula containing 15% extract

Thickness Test

Examination of the thickness of the transdermal patches aimed to determine the similarity of the thickness of each transdermal patch in each formula. The thicker the patch, the greater the effect of the patch's diffusion power on penetrating the active substance in the transdermal patch. One of the factors that influences diffusion is membrane thickness; the thicker the membrane, the slower the diffusion speed (Zakaria et al., 2021).

The thickness of the patch preparation will affect the release of the active substance from the preparation, and the active substance will take longer to release when passing through a thick polymer compared with a thin patch preparation. In addition, the thickness of the patch preparation can affect the comfort of use, and thin patches are more comfortable to use than thick patches (Novia, 2021). The resulting patch thickness was directly proportional to the patch weight. Therefore, an increase in patch weight will cause patch thickness to increase (Fuziyanti et al., 2022). The thickness test results of the three formulas cannot be seen in Table V, below:

Table V. Result of Thickness Test

	Thickness of Patch (mm)		
	F1	**F2**	**F3**
Mean±SD	3,5±0,06	3,8±0,3	2,6±0,5
Requirements for patch thickness <1 mm (Novia, 2021)			

Note:
F 1: Transdermal patch formula containing 5% extract
F 2: Transdermal patch formula containing 10% extract
F 3: Transdermal patch formula containing 15% extract

Folded Durability Test

Fold durability testing was performed to determine the folding durability of the patch. An increase in the folding durability of a patch indicates that the patch has good film consistency, so that it does not tear easily during use and storage. The fold test results for each formula after being folded more than 300 times show that the patch is still in good condition. Thus, it can be said that the base used was good, and the patch met the standards. The results of the fold durability tests are shown in Table VI.

Table VI. Result of the Fold Durability Test

Formula	Folding durability
F1	>300
F2	>300
F3	>300
Requirements for folding durability ≥ 300 folds (Hermanto et al., 2019)	

Note:
F 1: Transdermal patch formula containing 5% extract
F 2: Transdermal patch formula containing 10% extract
F 3: Transdermal patch formula containing 15% extract

pH Test

A pH test was performed to determine the safety of patch preparation. The pH should not be too acidic because it can irritate the skin and should not be too alkaline because it can cause scaly skin. The results of the pH test showed that the pH value ranged from 4.2 to 4.7; therefore, it still meets the safe pH for topical use because the pH range for topical use is between 4–8 (Wardani & Saryanti, 2021). The pH value of the patch preparation was not significantly different from the pH value of the Patah Tulang extract, namely 4.7. The pH test results of the three formulas can be seen in Table VII below:

Table VII. The pH Test Results

	Formula		
	F1	F2	F3
Mean±SD	4,2±0,29	4,5±0,06	4,7±0,31
The pH that meets the requirements is 4–8 (Wardani & Saryanti, 2021)			

Note:
F 1: Transdermal patch formula containing 5% extract
F 2: Transdermal patch formula containing 10% extract
F 3: Transdermal patch formula containing 15% extract

Moisture Test

This test was carried out to improve the stability of the patch, while also preventing brittleness and preventing the patch from drying out so that it is protected from contamination. The higher the hydrophilicity of the polymer or plasticizer used, the higher the percentage of moisture absorption. This research used a hygroscopic PVP polymer, which can affect water absorption (Arifin & Iqbal, 2019). This hygroscopic property can bind water vapor in the environment during patch preparation and storage. This causes the moisture absorption values of the patches on F1 and F3 to be high. F2 has an absorption capacity value that meets the requirement of ≤10%. Factors that influence the drying process include temperature, humidity, and time. The greater the temperature difference, the faster is the heat transfer process will take place, resulting in a faster evaporation process. The lower the humidity of the air in the drying room, the faster the drying process will dry, and vice versa. The higher the room temperature used when drying the patch preparation, the higher the relative humidity of the air, and the lower the temperature, the lower the humidity (Fuziyanti et al., 2022). Therefore, the resulting patch can be declared relatively stable to protect it from microbial contamination (Zakaria et al., 2021). The results of the moisture test for the three formulas are listed in Table VIII.

Table VIII. The Results of the Moisture Test

	Formula		
	F1	F2	F3
Mean±SD	24,32%±0,01	7,30%±0,03	20,07%±0,02

Moisture requirements ≤ 10% (Zakaria et al., 2021)

Note:
F 1: Transdermal patch formula containing 5% extract
F 2: Transderm al patch formula containing 10% extract
F 3: Transdermal patch formula containing 15% extract

CONCLUSION

Euphorbia tirucalli extracts at concentrations of 5%, 10%, and 15% were prepared. The F2 transdermal patch preparation containing 10% *Euphorbia tirucalli* extract had the best characteristics, with a smooth, flexible texture, crease resistance >300 folds, moisture value of 7.30%, and pH 4.5.

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