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EFFECTIVENESS TEST OF WOUND PATCH PREPARATIONS OF GOTU KOLA LEAF EXTRACT (*Centella asiatica* (L.) Urb.) ON INCISION WOUND IN RABBITS

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ABSTRACT

A wound patch is a dosage form that delivers drugs through the skin to produce systemic effects, with the advantage of controlled drug release. *Centella asiatica* (L.) Urb.) is widely used to heal incision wounds on the skin. The most important component was asiaticoside, which plays a major role in accelerating wound healing. This study was conducted to test the effectiveness of transdermal patches from *Centella asiatica* (L.) Urb.) against incision wounds was performed on 5 rabbits divided into different treatment groups, namely group I without treatment, group II wound patch base (negative control), group III plaster (positive control), and groups IV and V, comprising a wound patch of gotu kola leaf extract at concentrations of 16% and 32%, respectively. The data obtained were statistically tested for normality using the Shapiro-Wilk test. The results showed that the wound patch preparation of 16% gotu kola leaf extract showed a significant difference ($p < 0.05$) in wound length reduction compared to the negative and normal controls. The wound healing time observed at concentrations of 16% and 32% provided wound healing effects. The best effect was observed at a concentration of 16%, with an average wound closure time of 12 days. It can be concluded that gotu kola leaf extract in the form of a wound patch preparation was effective in wound healing.

Keywords: Gotu kola leaf extract; incision wound; Wound patch; Effectiveness test

INTRODUCTION

A wound is a state of physical damage due to open or broken skin that causes an imbalance between normal function and anatomy. This type of injury is characterized by damage to body tissue, involving connective tissue, muscle, bone, skin nerves, and torn blood vessels that disrupt homeostasis of the body (Nagori and Solandi, 2011). Generally, wounds occur both intentionally and unintentionally. Intentional wounds are meant to be therapeutic, such as in surgical procedures or venous function. Unintentional or accidental wounds include knife cuts, gunshots, and burns (Fiandri & Sutarto, 2020).

According to 2018 Basic Health Research data, the national incidence of injury or wounds has increased by 9.2%, with the most common causes being bruises, sprains, and incisions. The data also showed that older people were at a higher risk of developing injuries. To accelerate the wound healing process, it is necessary to find a solution that not only helps the healing process, but is also practical, inexpensive, permanent, and reduces scars (Mustika, Kardena, and Pemayun, 2015).

The use of extracts, simplisia, or parts of a plant as medicines has not been maximized because of various difficulties. Therefore, medicines should be prepared and applied directly to whole simplisia or extracts to achieve greater effectiveness and efficiency (Muin, 2021). The use of wound patch plasters for wound closure is popular in the medical world. A simple wound patch containing an antiseptic or antibacterial (absorbent layer) is typically used to treat acute wounds (Moon and Crabtree, 2003).

Gotu kola (*Centella asiatica* (L.) Urb.) is one of the plants that is widely used as traditional medicine in Indonesia, specifically for wound healing (Sutardi, 2017). The main component of the plant is a triterpenoid glycoside, asiaticoside, which plays a major role in the production of collagen 1 and healing wounds on human skin (Anu, Amat and Sasputra, 2019). This process occurs as the activity of the Malpighian cell layer in the skin epidermis increases, topically healing wounds (Moerfiah, Muztabadihardja, 2014).

According to previous studies, topical administration of the ethanol extract of gotu kola leaves affects the healing process of incision wounds in white male rats (Harsa, 2020). In addition, Galomat (Galomat, de Queljoe and Datu, 2021) stated that the administration of an extract ointment at a concentration of 16% accelerated the healing of incision wounds in male white rats. It has also been reported that the preparation of handle leaf ointment is better at accelerating the healing process of incision wounds than tea leaf ointment at the same dose (0.2 mL (Khuluqi, 2017).

There are currently no reports on the effectiveness of gotu kola extract as a wound medicine in the form of a wound patch. Therefore, this study aims to determine the effectiveness of incision wound healing from wound patch preparations containing gotu kola (*Centella asiatica* (L.) Urb.) leaf extract from rabbit test animals.

METHODOLOGY

Materials

The samples used were obtained from the Borobudur Natural Herbal Industry-Indonesia with the botanical name *Centella asiatica* product code 3250D, male rabbit strain (New Zealand White) (Biofarma Company) with No REG/No MR: 22060301190/OTC, PVP, propylenglycol (Dipa Husada Persada Company), 96% ethanol (Hikam Abadi Indonesia Company), 70% ethanol (Pupick Med), and 2% lidocaine injection (Pharos Company).

Tools used include mortars and stamper (medizzy), analytical balance (newtech), sterile surgical blade/scalpel (B'raun), spatel, pH-meter, scrub micrometer, oven (Memmert)

Methods

Place and Time of Study

This study was conducted at the Technology Laboratory of STIKES Muhammadiyah Kuningan, Indonesia between November 2021 and January 2022. An animal ethics license or ethical approval for the use of test animals was obtained from the Health Research Ethics Committee of Bakti Tunas Husada University Tasikmalaya (approval number: 049/ec.02/kepk-bth/VI/2022).

Extract Characterization

Extract characterization includes specific characteristics, which were assessed through an Organoleptic Test performed using the 5 senses of smell, taste, color, and shape (Departemen Kesehatan RI, 2000). Meanwhile, non-specific characterization includes.

Determination of Water Content

A total of 10 g of the extract was placed in a porcelain cup and weighed. The extract was then dried in an oven for 5 hours at 105 °C, weighed, and the percentage of water content was calculated (Departemen Kesehatan RI, 2000).

Determination of Ash

A total of 2 g of the sample was weighed and placed in a silicate crucible that was incinerated and torn. Subsequently, the organic compounds and their derivatives were slowly decomposed and evaporated, leaving only mineral and inorganic elements at 600 ± 25 °C. After cooling, the samples were weighed again. The total ash content was calculated based on the weight of the test material and was expressed as % w/w (Kesehatan and Indonesia, 2008).

Determination of Acid Insoluble Ash

The obtained ash was boiled with 25 mL dilute hydrochloric acid for 5 minutes. The portion that did not dissolve in the acid was collected, filtered through ash-free filter paper, and calculated against the weight of the test material, expressed as % w/w (Kesehatan and Indonesia, 2008).

Determination of water-soluble ash

The obtained ash was boiled with 25 ml of water for 5 minutes, and the insoluble fraction was collected, filtered through a glass crucible or ash-free filter paper, washed with hot water, and incinerated for 15 minutes at a temperature of not more than 450 °C. The weight difference corresponds to the amount of water-soluble ash. The water-soluble ash content of the dried material was also calculated (Kesehatan and Indonesia, 2008).

Determination of Ethanol Soluble Extract

Approximately 5 g of the extract was macerated for 24 hours with 100 mL of ethanol (95%) in a stoppered flask. The mixture was shaken every hour for the first 6 hours and then left to stand for 18 hours. The extract was quickly filtered to avoid evaporation of ethanol, and 20 mL of the filtrate was evaporated to dryness in a shallow calibrated flat-bottomed cup. The residue was heated to 105 °C until its weight remained unchanged. The ethanol-soluble extract content was calculated as the percentage of ethanol-soluble compounds (95%) in the initial extract (Departemen Kesehatan RI, 2000).

Phytochemical Analysis

Qualitative phytochemical tests on gotu kola (*Centella asiatica* (L.) Urb.) The leaf extract filtrate was used to determine the presence of metabolite compounds, such as Alkaloids, Saponins, Tannins, Flavonoids, Steroids, and Triterpenoids, according to standard procedures.

Wound Patch Preparation

The wound-patch preparation formulation of gotu kola leaf extract as a wound-healing agent is shown in **Table I**.

Table I. Wound Patch Dosage Formulation of Gotu Kola Leaf Extract

No	Material Name	Formula		
		F0	F1	F2
1	Gotu kola leaf extract	-	16%	32%
2	HPMC	2.5%	2.5%	2.5%
3	PVP	2.5%	2.5%	2.5%
4	Propylenglycol	0.5 %	0.5 %	0.5 %
5	Aquadest	2 m%	2 %	2 %
6	96% Ethanol	Ad 10 %	Ad 10 %	Ad 10 %

Description:
F0: Wound patch base without addition of extract
F1: Wound patch of gotu kola leaf extract at 16% concentration.
F2: Wound patch of gotu kola leaf extract at 32% concentration.

A Petri dish was prepared as a patch-preparation container, and the bottom was covered with aluminum foil. PVP was placed in a mortar, and HPMC was added and finely ground to homogeneity. Next, 2 mL distilled water was added until a homogeneous gel was formed. The gel was placed in a glass beaker and 96% ethanol was added and stirred until it dissolved completely. Gotu kola leaf extract was added together with propyleneglycol 0.5 mL, and the mixture was stirred until homogeneous. Subsequently, 96% ethanol up to 10 mL was added and poured into a previously prepared petri dish. The solution was allowed to stand for ± 1 hour until no bubbles were formed, after which it was dried at room temperature (20-25ºC) for 48 hours. After the patch was dried, it was removed from the Petri dish by peeling it off. It was also cut into 3 × 1 cm² pieces and stored in a 5 × 2 cm² Hypafix plaster.

Evaluation of Wound Patch Preparations

Organoleptic examination included observation of the shape, color, and odor of the plaster produced. This test was conducted using 5 senses: sight, smell, shape, and color (Depkes RI, 2020).

Weight Uniformity

The average weight of the patches was calculated by taking three randomly selected patches from each formula, and weighing each patch individually. Standard deviation was calculated using these measurements (Depkes RI, 2020).

pH

The pH test was performed by adding 10 mL CO_2-free distilled water to the patch and allowing it to stand for 1 hour. was performed using universal pH indicator paper in contact with the patch surface (Fitriani, 2019).

Patch Thickness

The thickness of the plaster patch obtained was measured using a scrub micrometer. The thickness was measured in micrometers using 3 patches of each formula, and the average thickness was calculated and expressed in micrometers (µm) (Inayah *et al.*, 2018).

Patch Crease Resistance

A patch-crease resistance test was conducted to determine the folding resistance of the patches. Patch can be folded repeatedly in the same place until it is damaged. Therefore, the number of patches that could be folded in the same location without cracking or damage was determined. A patch was considered to meet the criteria when it was resistant to folding more than 300 times (Lakhani, Bahl and Bafna, 2015). When a patch has high folding resistance, the binding force between the polymers is good, which implies good flexibility.

Wound Patch Effectiveness Test in Rabbits (*New Zealand White*)

5 male rabbits (*New Zealand White*) aged 2-3 months with body weights of 2 - 2.5 kg were divided into 5 treatment groups. The day before wounding, the backs of the rabbits were cleaned of fur until they were smooth with a mark of 3 treatment areas and a distance of 2 cm between them. The shaved area was cleaned with 70% alcohol and the animals rested for 24 hours. The following day, each marked area was anesthetized using lidocaine 2% at a concentration of 20 mg/mL injected subcutaneously into the upper skin of the back (Nugrahani, Andayani and Sukmanadi, 2019). The anesthetic effect commenced after 5 minutes and to ensure efficacy, a needle puncture was made on the back. When the rabbits were silent during the puncture experiment, the anesthetic drug was administered. The incision was performed using a bisturi knife with a length of 2 cm to a depth of ± 0.2 cm. After incisions were made in the treatment and control groups, wound care was performed on all samples. The wound was cleaned first using sterile distilled water and then closed by attaching a transdermal patch preparation of *Centella asiatica* (L.) Urb. leaf extract, measuring 5 × 2 cm in the 16% and 32% concentration groups, respectively. The normal group was not treated, the positive control group was treated with Hansaplast, and the negative control group was treated with a transdermal patch base without the main

substance. Treatment began every day from days 1 to 14, according to the normal wound healing process. The healing effect was measured based on the wound healing profile of the incision wound, including closure time and decrease in length. In addition, observation of wound healing by calculating the average diameter of wound healing was carried out every day.

Data Analysis

Data analysis was performed using parametric tests, and the normality test was performed using the Shapiro-Wilk test. The data homogeneity test was conducted and continued with the One-Way ANOVA method using the SPSS version 26 application to determine the possibility of differences in data variances. The test was considered significant when the p-value was <0.05.

RESULT AND DISCUSSION

Evaluation of the Characteristics of Gotu Kola Leaf Extract

Based on these results, the extract was standardized for both specific and non-specific characterization. The organoleptic test was conducted for initial recognition using 5 senses, including smell, taste, color, and shape (Departemen Kesehatan RI, 2000). The extract had a powdery texture, brownish-green color, distinctive odor, and bitter taste. Furthermore, the non-specific test included the determination of the water content of the extract. The water and total ash content obtained from the gotu kola leaf extract were 1.11% and 0.32%, respectively. These results are consistent with the requirements of the Indonesian Herbal Pharmacopoeia, namely a maximum total ash content of 16.6%. The ash content was tested to provide an overview of the internal and external mineral levels from the initial process to the formation of the extract (Departemen Kesehatan RI, 2000). The acid-insoluble ash content was 0% and the result was good because the value met the maximum limit of 1% (Departemen Kesehatan RI, 2000). High values of acid-insoluble ash indicate the presence of silicates from soil or sand and metallic elements such as silver, lead, and mercury (Any Guntarti, Sholehah Kholif, Irna nurul, 2015). The water-soluble ash content was 100%, indicating the presence of organic mineral salts in the extract. Based on the criteria of the Indonesian National Standard, the water-soluble ash content of the extract must be ≥ 45%. Therefore, the result obtained was considered good because the value met the standards. Soluble extracts in water and ethanol were determined to estimate the number of active compounds that are polar or polar-non-polar (Azis Saifudin, Viesa Rahayu, 2011). The water- and ethanol-soluble contents reached 73.42% and 32.2%, respectively, indicating that the extract is more soluble in water than in ethanol. In other words, the polar compounds in gotu kola leaves are more polar than the non-polar ones.

Moreover, phytochemical screening was performed to identify the compounds in the extract before it was converted into a transdermal patch dosage form. Based on these results, gotu kola leaf extract contains secondary metabolite compounds, such as tannins, flavonoids, saponins, and triterpenoids.

Evaluation of Gotu Kola Leaf Extract Patch Preparation

To prepare the tools and materials and weigh them first, finely ground the PVP in a mortar, add finely crushed HPMC until homogeneous, add 1 ml of crushed distilled water until it is homogeneous and a gel forms, put it in a beaker glass, add a small amount of 95% ethanol, and stir until completely dissolved. Add gotu kola leaf extract, stir until homogeneous, then add propylene glycol, stir until homogeneous. After that, 95% ethanol was added to 10 ml, and then poured into a petri dish whose bottom was lined with aluminum foil and allowed to stand for ± 1 hour until there were no bubbles, and then dried at room temperature. ± 48 hours until drying. After the patch is dry, the patch is removed from the petri dish by peeling it off, then the patch is cut to a size of 3 x 1.5 cm2 (L x W), after that the patch is attached to a hypaphic plaster with a size of 5 x 2 cm2 (L x W)

The organoleptic test results for the transdermal patch preparations are presented in **Table II**.

Table II. **Organoleptic Evaluation**

Formula	Color	Odor	Shape
0	Clear (Colorless)	Typical	Elastic, springy, smooth
1	Light brown	Weakly distinctive (almost odorless)	Elastic, slightly springy, smooth
2	Greenish brown	Weakly distinctive (almost odorless)	Elastic, slightly springy, smooth

The control formula (F0) was clear (colorless) and had a distinctive odor with a chewy texture because it was only made of the base and not mixed with the extract. Formula 1 had a light brown color, a weak distinctive odor of gotu kola leaf, a smooth and elastic texture, and a slightly soft texture. Formula 2 had a slightly greenish-brown color, a weak distinctive odor, and an elastic texture that was slightly soft but rough. This was because the extract was not mixed homogeneously during the production process, culminating in a slightly rough preparation.

Weight Uniformity Test

A weight uniformity test was performed to determine whether the gotu kola leaf extract patch had the same weight, and the results are shown in **Table III**.

Table III. **Evaluation of Weight Uniformity**

	Weight (g)			Description
	F0	F1	F2	
Replication 1	0.08	0.07	0.09	FR
Replication 2	0.08	0.11	0.07	FR
Replication 3	0.09	0.06	0.10	FR
Mean weight	0.083±0.006	0.08±0.026	0.087±0.015	

Description: FR: Fulfill the Requirement, UR: Unfulfill the Requirement

The weight uniformity test results for the transdermal patch preparation showed different mean values and standard deviations for each formula. All the formulas fulfilled the standard deviation requirements, with a good standard deviation of patch being ≤ 0.05 according to previous studies. Factors that might contribute to uneven patch weight include incomplete evaporation of the solvent or uneven pouring of the patch dough into the mold.

pH Test

The 3 formulas had the same pH of 5, which is still within the range suitable for the skin (4.5-6.5), according to (Fitriani, 2019). Therefore, it can be concluded that the 3 gotu kola leaf extract transdermal patch formulas fulfilled the pH requirements.

Patch Thickness Test

The thickness of the transdermal patch was measured using a 0.01-micrometer outside with 3 repeats at 3 different points, and then a mean was taken (Jhawat *et al.*, 2013). According to Arifin et al. (2019), a good patch thickness requirement is usually < 1 mm. The results of the gotu kola leaf extract patch thickness test are shown in **Table IV**.

Table IV. Patch Thickness Evaluation

	Thickness Unit (mm)			Description
	F0	**F1**	**F2**	
Replication 1	0.08	0.08	0.10	FR
Replication 2	0.07	0.10	0.09	FR
Replication 3	0.09	0.07	0.10	FR
Mean weight	0.08±0.010	0.083±0.015	0.096±0.006	

Description: FR: Fulfill the Requirement, UR: Unfulfill the Requirement

Based on the results, the mean thicknesses of the patches for F0, F1, and F2 measured at the 3 different points were 0.08 mm, 0.083, and 0.096 mm, respectively. These results are consistent with the requirement for a good patch that must be less than 1 mm (Suryani, Ode Sitti Musnina and Shaliha Anto, 2017). Among the 3 formulas, F0 and F1 were less than F2. Meanwhile, a thin patch is easier to use and more acceptable (Prabhakara *et al.*, 2010).

Patch Crease Resistance Test

A good patch usually has high folding resistance and good flexibility, whereas the requirement for good folding durability is ≥ 300 folds (Fitriyah, 2013). The test results showed that F0 and F1 could withstand 500 folds without breaking and appeared to be in a good condition. F2 experienced some damage to the patch at the 370th fold despite exceeding the minimum requirement of 300 folds. This was presumably due to the high concentration of the gotu kola leaf extract, which reduced the texture. However, F2 is still considered to meet the standard requirements because it has more than 300 folds. It can be concluded that all formulas, namely F0, F1, and F2, meet the standard of patch-folding resistance.

Test Results for Incision Wound Length Parameters

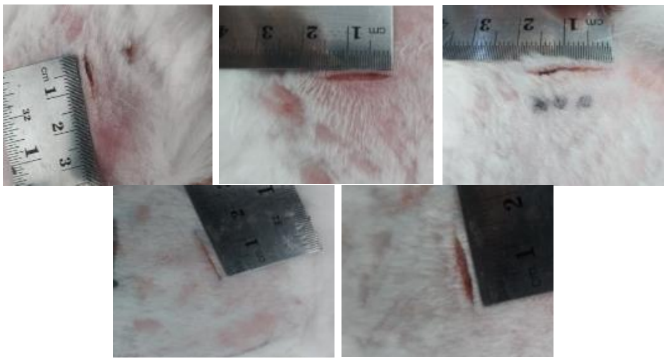
This study was conducted to compare the healing time and decrease in the length of incision in each group after treatment with a wound patch of Gotu kola leaf extract. Observations were made daily for 14 days (Wathoni *et al.*, 2020), and the results of wound healing in each group are shown in **Table V**.

Table V. Observations On The Parameters Of The Incision Wound Healing Time

Group	Replication	Wound closure time 100% (Days)	Mean wound healing time (Days)
Group I (Gotu Kola Leaf Extract Patch 16%)	1	12	12±0.57
	2	13	
	3	12	
Group II (Gotu Kola Leaf Extract Patch 32%)	1	13	13±0.57
	2	13	
	3	14	
Group III (Positive Control)	1	10	10±0.57
	2	10	
	3	11	
Group IV (Negative Control)	1	15	15±0.57
	2	15	
	3	14	
Group V Normal Control	1	16	17±0.57
	2	17	
	3	17	

Finally, the efficacy of the gotu kola leaf extract patch 16% on wound healing ability was evaluated. The gotu kola leaf extract patch with 16% wound closure at 12 days showed a significantly accelerated wound healing ability of the gotu kola leaf extract patch by 16% compared to the negative control and normal control. (**Figure 1**).

gotu kola leaf extract patch 16%, gotu kola leaf extract patch 32%, positive control, negative control, normal control (0 day)



gotu kola leaf extract patch 16%, gotu kola leaf extract patch 32%, positive control, negative control, normal control (7 day)

gotu kola leaf extract patch 16%, gotu kola leaf extract patch 32%, positive control, negative control, normal control (14 day)

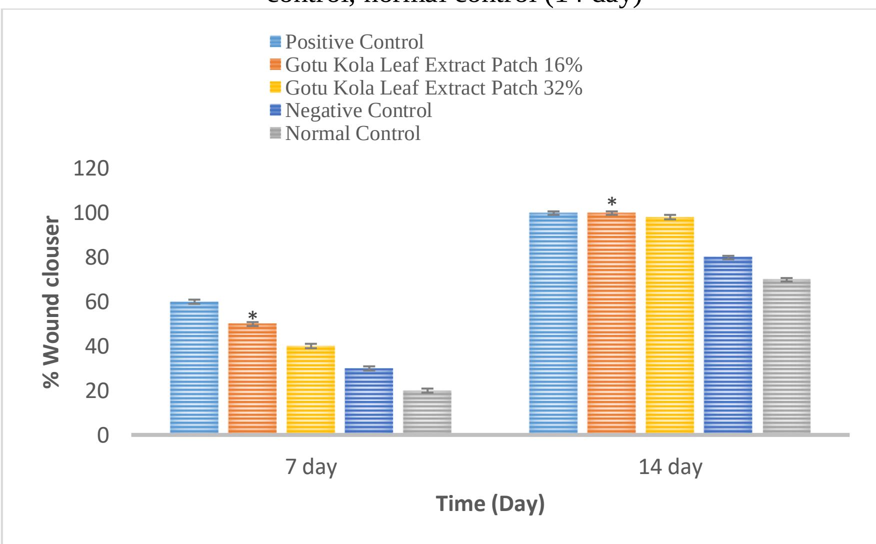


Figure 1. **Wound Closure Study of Gotu Kola Leaf Extract Patch 16% * p < 0.05 Compared to the Negative Control, and Compared Normal Control**

The results of the 5 groups showed that wounds healed at different times, with the fastest healing occurring in the group treated with brand x plaster preparations after an average of 10 days. Plaster brand X has been clinically tested and widely used to heal open wounds. It contains silver, which actively releases antiseptic ions during healing. In the formula group containing gotu kola leaf extract F1, the required incision wound healing time was 12 days, which was faster than that in the F2 group, with an average healing value of 13 days. The healing time was not significantly different from the result obtained in a previous study where the 16% gotu kola leaf extract in patch preparation was more effective in accelerating wound closure than the 32% or higher concentrations.

In natural medicine, a decrease in activity often occurs with an increase in the dose or concentration. This is because the extract components are not singular, but consist of various chemical compounds that interact with each other to produce an effect. However, with increasing doses, the number of chemical compounds increases, causing adverse interactions that decrease this effect (Yunitasari, Alifiar and Priatna, 2016).

The concentration of active ingredients also affects wound healing. For instance, when the active substance adheres to the skin, the membrane structure is altered because of the high molecular concentration, causing a partition coefficient between the carrier and the skin (Ch Muntiaha, Y Yamlean and Widya Astuti Lolo, 2014). Furthermore, an absorption barrier might also occur when the treatment patch is not cleaned daily during the preparation period. At each patch concentration change, the area of the wound was not thoroughly cleaned with aqua, thereby creating an absorption barrier that caused the active substance to be absorbed slowly or incompletely. Another factor that caused the 32% gotu kola leaf extract to take longer than 16% was the behavior of the test animals in the first group. The aggressive behavior of the animals led to scratching and biting of the patch, which negatively affected the wound healing process. For the negative control group (patch base), the mean value was 15 days because the animals were only treated with a wound patch base that acts as an emollient or moisturizer rather than an incision wound healer. Moreover, in the normal control group, the mean healing time was 17 days, which is relatively long.

The results were statistically analyzed using One-Way ANOVA, which revealed a significantly accelerated wound healing ability of the gotu kola leaf extract patch 16% compared to the negative control and normal control. Each group of data had a different mean value or a significant difference ($p < 0.05$).

CONCLUSION

Based on the results, it can be concluded that the transdermal patch preparation of 16% gotu kola leaf extract showed a significant difference ($p < 0.05$) in wound length reduction compared to the negative control and normal control. However, the 16% wound patch preparation resulted in significantly faster healing than the 32% preparation.

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