The Effectiveness Test of Tembelekan (*Lantana camara* L.) Leaf Extract Gel for Cuts Healing in Male White Mice

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Abstract

The study of natural products as alternative medicine for accelerating the healing of cuts has become a significant focus of scientific research. One such plant is tembelekan (*Lantana camara* L.), whose leaves can be formulated into a gel to enhance drug release. This research aims to evaluate the effectiveness of tembelekan leaf extract gel in healing cut wounds in male white mice. The extract was obtained through the maceration method using 96% ethanol. An experimental method was used to observe the wound healing process in five groups of male white mice, each containing five individuals. The positive control group received Bioplacenton®, the negative control group was given a gel base, and the treatment groups were administered 10%, 15%, and 20% tembelekan leaf extract gel. The gel was applied to the wounds twice daily, and the healing process was evaluated using the Likert scale. The results from the Kruskal-Wallis test revealed an Asymp.A sig value of 0.030, which is less than 0.050, indicates that the tembelekan leaf extract gel was effective in healing cuts at all concentrations due to its anti-inflammatory and antimicrobial properties. The most rapid healing occurred within 9 days with the 20% concentration of tembelekan leaf extract gel.

Keywords: cuts, effectiveness test, gel, tembelekan, wound healing

1. INTRODUCTION

Cuts are a type of acute wound that typically heal within days through a dynamic process consisting of four stages: coagulation, inflammation, proliferation, and tissue remodeling. This process is influenced by various factors, including the severity of the injury, the tissue's ability to regenerate, the presence of necrotic tissue, and the risk of foreign body infection. Extensive research has been conducted on the wound healing process, leading to the development of various strategies aimed at accelerating the closure of skin lesions (Zhang et al., 2019).

The study of natural products derived from plants as an alternative medicine to promote faster healing of cuts and enhance skin tissue regeneration has gained significant attention in scientific research (Shedoeva et al., 2019). Natural products are regarded as effective, affordable, and easily accessible treatment options. One such plant known for its healing properties is tembelekan (*Lantana camara* L.) leaves, which have been traditionally used in the form of decoctions and powders to treat cuts (Chitapalli & Kemisetti, 2024).

Tembelekan, a plant from Indonesia, belongs to the Verbenaceae family. Traditionally, all parts of the tembelekan plant are utilized to treat various ailments. The leaves, in particular, are known for their antiseptic, anti-tumor, and antimicrobial properties. They are used to treat cuts, rheumatism, ulcers, and act as a vermifuge (Nawaz et al., 2016). The phytochemical composition of tembelekan leaves includes saponins, alkaloids, tannins, anthocyanins, flavones, isoflavones, flavonoids, coumarins, lignans, catechins, iso-catechins, and triterpenoids, with flavonoids being the predominant components (Ved et al., 2018).

Research has demonstrated the effectiveness of tembelekan leaves in healing cuts and bruises in mice over periods of 9 days and 6 days (Gufron et al., 2023). However, the tembelekan leaves tested on mice have not yet been formulated for practical applications, indicating a need for further research. To address this, tembelekan leaf extract has been formulated into a gel dosage form. This method is advantageous as it can accelerate the release of drugs directly to the site of action, independent of the drug's water solubility, compared to creams and ointments (Gowda et al., 2016).

Research conducted by Ningsi et al. (2015) demonstrated that an ethanol extract of tembelekan leaves, when prepared as a gel at a concentration of 4%, promoted wound healing in rabbits (*Oryctolagus cuniculus*). Additionally, a more recent study found that a gel containing a 20% concentration of ethanol extract from tembelekan leaves had the most significant effect on wound healing in rabbits (Arifin et al., 2023). While the previous studies utilized rabbits as test subjects, this current research employs white male mice (*Mus musculus*). Mice were chosen because they are easy to care for, reproduce quickly, are smaller in size, and are manageable. Consequently, this study aims to evaluate the effectiveness of tembelekan leaf extract gel in healing cut wounds in male white mice.

2. METHOD

MATERIALS

The tools used in this research included a beaker, a glass object, an evaporating dish, a stirrer, a mortar and pestle, an analytical balance, a macerator, an evaporator, a blender, an oven, and various weights (50g, 80g, 100g, 500g), along with a surgical blade and a ruler.

The materials used in this research comprised *Lantana camara* L. leaves (collected from Tanjung Raya Village, Pesisir Barat Regency, Lampung), 96% ethanol, 70% ethanol, magnesium, concentrated HCl, $FeCl_3$, male white mice (Mus musculus), methylparaben, sodium carboxymethyl cellulose, glycerin, distilled water, and Bioplacenton®.

PREPARATION OF SIMPLICIA

One kilogram of tembelekan leaves was cleaned to remove any attached dirt and then washed with clean, running water. After washing, the tembelekan leaves were dried in the sun, ensuring they were not exposed to direct sunlight. Once they were completely dry, the leaves were blended into a fine powder, resulting in tembelekan dry leaves powder.

EXTRACTION

Five hundred grams of dried tembelekan leaves powder were soaked in 3.5 liters of 96% ethanol. The mixture was covered and left to stand for five days, with occasional stirring. After five days, the soaked mixture was filtered, resulting in filtrate 1 and residue 1. The residue was then treated with 1.5 liters of 96% ethanol solution, covered, and left to stand for another two days. After this period, the sample was filtered again, producing filtrate 2 and residue 2. Filtrates 1 and 2 were combined, and the resulting mixture was evaporated using a rotary evaporator to obtain a concentrated extract of tembelekan leaves (Arifin et al., 2023).

PHYTOCHEMICAL SCREENING

For the flavonoid test, the thick extract was dissolved in 5 ml of 96% ethanol. Then 2 ml of the extract solution was added with 0.1 gram of magnesium powder and 10 drops of concentrated HCl, shaken gently. The formation of red-orange to purple-red colors indicates the presence of flavonoids. The formation of an orange-yellow color indicates the presence of flavones, alcohol and aurone (Muslimin, 2021).

For the tannin test, the sample was boiled with 20 ml of water, then filtered, and several drops of 1% $FeCl_3$ were added. The formation of a greenish brown or blackish-blue color indicates the presence of tannins (Muslimin, 2021).

FORMULATION OF TEMBELEKAN LEAF EXTRACT GEL

The gel formula used in this formulation was adopted from Meilani's (2022) research on the gel formulation of tembelekan leaf extract, as shown in Table 1. The extract was formulated in three concentrations, namely 10% (X1), 15% (X2) and 20% (X3). The negative control (K(-)) used was gel base, and the positive control (K(+)) used was Bioplacenton®.

Table 1. Formula for Tembelekan Leaf Extract Gel Formulation

Ingredients	Compositions (%)				Functions
	X_1	X_2	X_3	K(-)	
Tembelekan Leaf Extract	10	15	20	-	Active substance
Sodium Carboxymethyl Cellulose	3	3	3	3	Gel formation
Glycerin	15	15	15	15	Humectan
Methyl Paraben	0.02	0.02	0.02	0.02	Preservative
Distilled Water	ad 100	ad 100	ad 100	ad 100	Solvent

*X1: Tembelekan leaf extract gel with a concentration of 10%, X2: Tembelekan leaf extract gel with a concentration of 15%, X3: Tembelekan leaf extract gel with a concentration of 15%, K(-): Basis gel as negative control

The procedure for preparing the gel formulation is as follows: Distilled water was heated until it reached a boil, then transferred into a mortar. Sodium carboxymethyl cellulose was added and crushed until a gel was formed. Next, glycerin, methyl paraben, and tembelekan leaf extract were added to the mortar. The mixture was then thoroughly crushed until it became homogeneous. The resulting gel was poured into a container for storage.

EVALUATION OF GEL

The evaluation of the gel involved several tests, including organoleptic, pH, homogeneity, spreadability, adhesion, syneresis, and cycling tests (Astriani, 2023).

Organoleptic Test

This test was conducted by observing the gel's appearance, color, and odor.

pH Test

The pH value was measured using universal pH paper, which was dipped into 0.5 grams of gel that had been diluted with 5 ml of distilled water. The desired pH range is between 4.5 and 6.5, as this corresponds to the skin's natural pH (Astriani, 2023).

Homogeneity Test

Homogeneity was assessed by applying the gel onto glass or another transparent material. The key parameter for this test is the absence of lumps; the preparation should exhibit a uniform composition without any visible coarse particles (Muslimin, 2021).

Spreadability Test

For the spreadability test, 0.5 grams of gel was placed in the center of a round glass and covered with another round glass. A weight of 50 grams was placed on top for 1 minute. The diameter of the spread gel was measured by averaging the lengths from several sides. This

procedure was also repeated using a 100-gram weight. The required diameter for satisfactory spreadability is between 5 cm and 7 cm (Muslimin, 2021).

Adhesion Test

In the adhesion test, 0.25 grams of gel were placed between two glass objects and pressed with a 1 kg weight for 5 minutes. Subsequently, another glass object was placed on the testing equipment, and an additional 80 grams were added. The time taken for the gel to release from the glass was recorded. Good adhesion in the gel preparation is indicated by a release time of between 2 and 300 seconds (Muslimin, 2021).

Syneresis Test

Syneresis refers to the release of water from the gel during storage. This was evaluated by storing the gel at 40 °C for 72 hours. Syneresis was quantified by comparing the weight lost during storage to the gel's initial weight (Astriani, 2023).

Cycling Test

The cycling test involved storing the sample in the refrigerator at 4 °C for 24 hours, followed by transferring it to an oven at 40 °C for another 24 hours. This cycle was repeated six times. The gel is considered stable if no significant changes are observed throughout these cycles (Astriani, 2023).

DETERMINING THE NUMBER OF TEST ANIMALS

The number of test animals is determined based on the following Federer formula:

$$(n- 1) (y-1) \geq 15$$

In this study, there were five treatment groups: X1, X2, X3, K(+), and K(-). According to the formula where 'n' represents the number of groups and 'y' represents the number of test animals (Muslimin, 2021), a total of 5 mice were assigned to each group. This resulted in a total of 25 test mice across all five groups.

THE EFFECTIVENESS TEST OF TEMBELEKAN LEAF EXTRACT GEL FOR CUTS HEALING

The experiment began by shaving the fur on the backs of the mice and cleaning the area with 70% alcohol using cotton. A 1 mm deep incision was then made along the back area, parallel to the vertebral bones, using a surgical blade. Any blood that emerged was cleaned up (Muslimin, 2021).

The mice were divided into five groups, with five mice in each group for wound care. The positive control group (K(+)) received Bioplacenton®, the negative control group (K(-)) was treated with a gel base, treatment group I (X1) was given a 10% tembelekan leaf extract

gel, treatment group II (X2) received a 15% tembelekan leaf extract gel, and treatment group III (X3) was administered a 20% tembelekan leaf extract gel. The gel was applied to the wound twice a day until healing was complete. Observations were conducted every evening using Likert scale measurements (Muslimin, 2021).

The degree of healing of the incision wounds was assessed using the Likert scale as follows:

a. Grade 4: Open wound, bleeding, and red.

b. Grade 3: The wound is beginning to close and is not bleeding.

c. Grade 2: Wound closed, slightly dry, and not bleeding.

d. Grade 1: Wound closed and dry.

DATA ANALYSIS

The statistical software used for data analysis was SPSS version 26. A non-parametric test, specifically the Kruskal-Wallis test, was conducted to assess effectiveness, and the Mann-Whitney test was utilized to identify differences between treatment groups (Muslimin, 2021).

3. RESULTS AND DISCUSSION

EXTRACTION

A total of 700 grams of dried tembelekan leaf powder was obtained. This powder was utilized to increase the surface area in contact with the solvent, optimizing the extraction process of the active compounds. The maceration method was chosen due to its simplicity and the minimal equipment required. After maceration, the filtrate was evaporated using a rotary evaporator to remove the ethanol, resulting in 72.77 grams of thick extract.

PHYTOCHEMICAL SCREENING

The phytochemical test aims to identify the active substances present in tembelekan leaves, specifically focusing on flavonoids and tannins. The presence of flavonoids is indicated by a red-orange solution, while the presence of tannins is shown by a blue-black solution in the sample (Agustina et al., 2015). As illustrated in Table 2, both tests yielded positive results, confirming the presence of flavonoids and tannins in the tembelekan leaf extract.

Table 2. Phytochemical Screening of Tembelekan Leaf Extract

Phytochemical Test	Result	Summary
Flavonoid	Orange Red Solution	Positive (+)
Tannin	Blackish Blue Solution	Positive (+)

Previous research has indicated that the ethanol extract of tembelekan leaves contains several secondary metabolites, including alkaloids, flavonoids, tannins, and steroids (Edy & Parwanto, 2020). The levels of active tannins and flavonoid compounds in plants are associated with their wound-healing properties (Gufron et al., 2023).

EVALUATION TEST OF GEL PREPARATIONS

The evaluation of the tembelekan leaf extract gel included several tests: an organoleptic test, a pH test, a homogeneity test, a spreadability test, an adhesion test, a syneresis test, and a cycling test. The results are summarized in Table 3. The organoleptic tests revealed that all formulations of the tembelekan leaf extract gel had a gel-like consistency, a slightly watery texture, a characteristic odor of the extract, and a blackish-green color.

Table 3. Evaluation Test Results of Tembelekan Leaf Extract Gel Preparations

Evaluation Test	Results			
	X_1	**X_2**	**X_3**	**K(-)**
Organoleptic Test				
a. Form	Gel	Gel	Gel	Gel
b. Texture	Slight watery	Slight watery	Slight watery	Slight watery
c. Colour	Blackish green	Blackish green	Blackish green	Transparant
d. Odor	Typical extract	Typical extract	Typical extract	Typical base
pH Test	5.81	5.52	5.31	6
Homogeneity Test	Homogenous	Homogenous	Homogenous	Homogenous
Spreadability Test	5 cm	5 cm	5 cm	5.1 cm
Adhesion Test	10.49 s	11.64 s	12.59 s	10.4 s
Syneresis Test	None	None	None	None
Cycling Test	Stable	Stable	Stable	Stable

*X1: Tembelekan leaf extract gel with a concentration of 10%, X2: Tembelekan leaf extract gel with a concentration of 15%, X3: Tembelekan leaf extract gel with a concentration of 20%, K(-): Basis gel as negative control

A pH test was conducted to determine the acidity level of the gel. For a formulation to be safe for skin application, its pH should fall within the range of 4.5 to 6.5; otherwise, it may cause skin irritation (Astriani, 2023). The results indicated that the pH of the tembelekan leaf extract gel met the required range, measuring between 5 and 6.

The homogeneity test involved applying samples from the top, middle, and bottom sections of the gel onto a transparent glass surface. A homogeneous preparation is characterized by a

consistent color and the absence of coarse particles (Muslimin, 2021). The results confirmed that all extract concentrations exhibited a homogeneous gel preparation.

The spreadability test was conducted to ensure that the gel spreads evenly when applied to the skin, which can influence the absorption of the drug. The results of the spreadability test for the tembelekan leaf extract gel showed an average diameter of 5-6 cm. This meets the required range for the diameter in the spreadability test of 5-7 cm (Yusuf et al., 2017).
Additionally, an adhesion test was performed to determine how long the gel adhered to the skin's surface. This is important because the longer the gel stays on the skin, the more effectively the active substances are absorbed. The results for the gel base and the tembelekan leaf extract gel showed adhesion times ranging from 8 to 14 seconds. The requirement for gel adhesion is between 2 and 300 seconds, so the results meet the necessary criteria (Meilani, 2022).

The syneresis test was conducted to assess the syneresis process in the gel. Syneresis occurs when water is expelled from the gel, causing its appearance to diminish and the texture to become slightly denser. Factors such as increased temperature and prolonged storage time can heighten the number of molecules involved, resulting in greater absorption of water by the gelling agent (Syaiful, 2016). For this test, the samples were stored at 40°C for 72 hours, and the results indicated that there was no syneresis observed in the gel base or the tembelekan leaf extract gel, as no water was released.

The cycle test was performed to evaluate the stability of the gel under extreme temperature fluctuations. This involved storing the sample in a refrigerator at 4°C for 24 hours, followed by transferring it to an oven at 40°C for another 24 hours. The process was repeated for a total of six cycles. The gel is considered stable if there are no significant changes in its organoleptic properties, pH, homogeneity, spreadability, and adhesion (Astriani, 2023). The results indicated that both the gel base and all tembelekan leaf extract gels remained stable across all tested parameters.

THE EFFECTIVENESS TEST OF TEMBELEKAN LEAF EXTRACT GEL FOR CUT HEALING

Based on the observations recorded using the Likert scale, as shown in Table 4, the fastest wound healing occurred in the positive control group (K(+)), followed by the tembelekan leaf extract gel at concentrations of 20% (X3), 15% (X2), and 10% (X1). The negative control group (K(-)) exhibited the slowest healing.

Tabel 4. The Effectiveness Test of Tembelekan Leaf Extract Gel for Cut Healing Results with the Likert Scale

Days to-	Average of Likert Scale				
	X1	X2	X3	K(+)	K(-)
1	4	4	4	4	4
2	4	4	3.8	4	4
3	3.4	3	3	3	3.8
4	3	3	3	3	3.6
5	3	2.8	2.6	2.8	3.2
6	2.8	2.8	2.6	2.6	3
7	2.6	2.6	2.4	2.6	3
8	2.4	2	1.8	2	2.8
9	2	2	1.2	1.6	2.6
10	1.6	1.4	1	1	2
11	1	1	1	1	1.4
12	1	1	1	1	1

*X1: Tembelekan leaf extract gel with a concentration of 10%, X2: Tembelekan leaf extract gel with a concentration of 15%, X3: Tembelekan leaf extract gel with a concentration of 20%, K(+): Bioplacenton® as positive control, K(-): Basis gel as negative control

Initially, all treatment groups of mice were rated at a scale of 4, indicating open, bleeding, and red wounds. By the third day, the wounds in the positive control (K(+)) and the tembelekan leaf extract gel groups at 20% (X3) and 15% (X2) had started to close and were no longer bleeding, resulting in a rating of scale 3. In contrast, the group treated with the tembelekan leaf extract gel at a concentration of 10% (X1) saw an improvement on the fourth day. The negative control group (K(-)) displayed the slowest healing, with wounds still open through the sixth day.

Complete wound closure and drying occurred most rapidly on the tenth day for the positive control group (K(+)) and the tembelekan leaf extract gel at 20% (X3). The groups with the 15% (X2) and 10% (X1) concentrations showed full closure by the eleventh day, while the negative control group (K(-)) had fully closed wounds by the twelfth day.

Table 5. Days of Healing of Mice Cuts After Treatment

Treatment	Mice A (day)	Mice B (day)	Mice C (day)	Mice D (day)	Mice E (day)	Averages (day)
X1	11	10	11	11	10	10.6
X2	10	10	11	10	11	10.4
X3	8	9	9	10	9	9.0
K(+)	10	9	10	10	9	9.6
K(-)	11	12	11	12	11	11.4

*X1: Tembelekan leaf extract gel with a concentration of 10%, X2: Tembelekan leaf extract gel with a concentration of 15%, X3: Tembelekan leaf extract gel with a concentration of 20%, K(+): Bioplacenton® as positive control, K(-): Basis gel as negative control

Healing of cut wounds is characterized by closed and dry wounds, classified as grade 1 on the Likert scale. As shown in Table 5, the average healing duration for cut wounds in mice treated with tembelekan leaf gel extract was as follows: a concentration of 10% took an average of 10.6 days, 15% took 10.4 days, and 20% took just 9.0 days. The positive control group healed in an average of 9.6 days, while the negative control took 11.4 days. The fastest healing occurred in the group treated with the 20% tembelekan extract gel, which was even quicker than the positive control.

This research is consistent with previous studies showing that the ethanol extract of tembelekan leaves, when formulated into a gel at a 20% concentration, has a significant effect on healing burns in rabbits (*Oryctolagus cuniculus*) over 18 days. Bioplacenton® gel, which served as a positive control, demonstrated rapid wound healing due to its 10% placenta extract that promotes new tissue formation. Additionally, it contains 0.5% neomycin sulfate, an antibiotic that helps prevent bacterial infections in wounds, thereby further aiding the healing process. The negative control, which consisted only of the gel base without any active ingredients, exhibited longer healing times.

The 20% tembelekan leaf extract gel formula exhibited a healing time comparable to that of the positive control. This study demonstrates that increasing the concentration of tembelekan leaf ethanol extract can accelerate the wound healing process (Arifin et al., 2023). Wound healing occurs through a dynamic process consisting of four stages: coagulation, inflammation, proliferation, and tissue remodeling. During this process, fibroblasts from the surrounding tissue migrate into the wound area, where they proliferate and release various substances, including collagen. Collagen plays a crucial role at every stage of wound healing, contributing to hemostasis, interacting with platelets, increasing fluid exudation, enhancing the

presence of cellular components, promoting growth factors, and facilitating the fibroblast process. Moreover, collagen accelerates the growth of new tissue in wounds. This entire process is influenced by several factors, including the severity of the injury, the tissue's regenerative capacity, the presence of necrotic tissue, and the risk of foreign body infection (Zhang et al., 2019).

The application of tembelekan leaf extract gel enhances the healing of cut wounds due to its content of secondary metabolites, such as flavonoids, tannins, terpenoids, alkaloids, and saponins. Flavonoid and tannin compounds act as anti-inflammatory and antimicrobial agents. Flavonoids in Tembelekan leaves also contribute to vasoconstriction, which helps stop bleeding in blood vessels. Additionally, tannin compounds aid the healing process by acting as astringents for cut wounds. Saponins promote epithelialization, facilitating collagen formation in the wounds. The presence of alkaloid and terpenoid compounds further accelerates collagen synthesis (Gufron et al., 2023).

DATA ANALYSIS

The results of the data analysis test are presented in Table 6. In this study, normality testing was conducted using the Kolmogorov-Smirnov test, as the sample size exceeded 50. According to the normality test results obtained from SPSS 26, the significance (sig) value for all treatment groups was 0.000, which is less than 0.050. This indicates that the data is not normally distributed. Therefore, non-parametric tests, specifically the Kruskal-Wallis and Mann-Whitney tests, were employed.

Table 6. Data Analysis Test Results

Data Analysis Test	Group Test	Results (Sig. Value)
Kolmogorov-Smirnov	All groups	0.000
Kruskal-Wallis	All groups	0.030
Mann-Whitney	K(+) with X1	0.351
	K(+) with X2	0.676
	K(+) with X3	0.611

The Kruskal-Wallis test was employed to assess the effectiveness of Tembelekan (Lantana camara L.) leaf extract gel in healing cuts in male white mice. The results of the Kruskal-Wallis test yielded an asymptotic significance (Asymp.A sig) value of 0.030, which is less than 0.050, indicating that the Tembelekan leaf extract gel was effective in promoting wound healing.

The Mann-Whitney test was utilized to compare the differences between treatment groups, specifically between the positive control (K(+)) and the Tembelekan leaf extract gel at concentrations of 10% (X1), 15% (X2), and 20% (X3). The results of the Mann-Whitney test comparing K(+) and X1 showed an Asymp.A sig value of 0.351, which is greater than 0.050, indicates no significant difference between K(+) and X1. Similarly, the Mann-Whitney test results comparing K(+) with X2 indicated an Asymp.A sig value of 0.676, also greater than 0.050, means there was no significant difference between K(+) and X2. For the comparison between K(+) and X3, the Asymp.A sig value was 0.611, which is again greater than 0.050, demonstrating no significant difference between K(+) and X3.

It can be concluded that gel preparations made from Tembelekan leaf extract at concentrations of 15% and 20% are equally effective as the positive control in healing cut wounds in male white mice. However, the gel preparation with a concentration of 10% was less effective in healing these wounds compared to the positive control. Among the treatment groups, the most effective was X3, which used a concentration of 20%, as indicated by the average number of days required for wound healing.

These findings are consistent with previous research, which demonstrated that the healing time for cuts in mice treated with Tembelekan leaf extract was 9 days, similar for both control and treatment groups. The study also found that the healing time for bruises in mice given Tembelekan leaves was 6 days, compared to 8 days for the control group. Statistically, a significant difference was noted, with a p-value of <0.050 in the average healing times for cuts and bruises between the two treatment groups (0.000 < 0.050). Thus, Tembelekan leaves are effective in healing cuts and bruises in approximately 9 days and 6 days, respectively (Gufron et al., 2023).

4. CONCLUSION

Based on the research findings, it can be concluded that gel made from tembelekan (*Lantana camara* L.) leaf extract at varying concentrations of 10%, 15%, and 20% has a positive effect on wound healing in male white mice. The most rapid healing of wounds occurred within 9 days when using the gel with a concentration of 20%.

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