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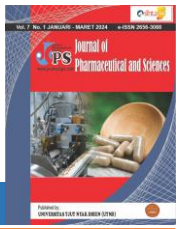

Topical effects of cinnamon leaf extract (*Cinnamomum burmannii*) gel as an incision wound healer in male white rabbits (*Oryctolagus cuniculus*)

Efek topikal gel ekstrak daun kayu manis (*Cinnamomum burmannii*) sebagai penyembuh luka insisi pada kelinci putih jantan (*Oryctolagus cuniculus*)

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Abstract
Cinnamon leaves (*Cinnamomum burmannii*) are plants that have many pharmacological effects. One of them is as a wound healer. The gel formulation becomes a convenient therapeutic solution for use. This study aimed to determine the impact of gel preparations on the healing of incision wounds in male white rabbits. The research method uses experimental methods. The test animal was injured on its back using a tool with a diameter of 2.5cm. There are five treatment groups used, namely: positive control (Bioplasenton), negative control (gel base), Formula 1 (extract 2.5%), Formula 2 (extract 5%), and Formula 3 (extract 7.5%). The results of wound healing observations were analysed using one-way ANOVA with a confidence level of 95%. The results showed that the best formula for wound healing is formula 2. Then, formula three and formula 1 had a significance value between groups of 0.05.

Keywords: *Topical, Gel, Cinnamon Leaves, Wound Healing*

Abstrak
Daun kayu manis (*Cinnamomum burmannii*) merupakan tanaman yang memiliki banyak efek farmakologis. Salah satunya adalah sebagai penyembuh luka. Formulasi gel menjadi solusi pemberian terapi yang nyaman untuk digunakan. Tujuan penelitian ini adalah untuk mengetahui efek sediaan gel terhadap penyembuhan luka insisi pada kelinci putih jantan. Metode penelitian menggunakan metode eksperimental. Hewan uji di lukai punggungnya menggunakan alat dengan diameter 2,5cm. Kelompok perlakuan yang digunakan ada 5 kelompok yaitu: Kontrol positif (Bioplasenton), kontrol negatif (basis gel), Formula 1 (ekstrak 2,5%), Formula 2 (ekstrak 5%), dan Formula 3 (ekstrak 7,5%). Hasil pengamatan penyembuhan luka di analisis menggunakan ANOVA satu arah dengan tingkat kepercayaan 95%. Hasil penelitian menunjukkan bahwa formula terbaik dalam penyembuhan luka adalah formula 2. Kemudian diikuti formula 3 dan formula 1 dengan nilai signifikansi antar kelompok 0,05.

Kata Kunci: *Topikal, Gel, Daun Kayu Manis, Penyembuhan Luka*

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Introduction

The increasing need for safe, effective, selective, and economical treatment is one of the reasons herbal medicine is still the choice of therapy for health problems. Herbal medicine in Indonesia has long been a therapeutic option known as jamu. This condition can be seen from the habits of people who cultivate herbal plants both on a large scale and on a household scale, known as Family Medicinal Plants [1,2].

Wound is a condition of damage to body tissues that sharp objects can cause. Important things that concern the wound healing process are infectious and inflammatory conditions. Infectious conditions will trigger the emergence of microorganisms that can interfere with the wound-healing process. Minor incision wounds can be treated independently at home. However, if the wound occurs widely, it needs serious treatment. The prevalence of wounds in Indonesia is recorded at 70.9%, and they are abrasions and 23.3% lacerations [3–5].

Cinnamon leaves are plants that have been tested for pharmacological effects. The incision wound healing effect of cinnamon leaf extract was carried out by Sani et al. (2021), who obtained data that cinnamon leaf extract with a concentration of 10% had an incision wound healing effect for 14 days of treatment [6]. This effect arises from the work of secondary metabolite compounds in the extract. It is also supported by the content of essential oils such as transinamaldehid, eugenol, and coumarin, which have anti-inflammatory, antioxidant, and antibacterial properties [7–9]. Modifying extracts into topical dosage forms is one effort to improve aesthetics in drug administration and help the process of penetration of the extract. The gel is a topical dosage form with high penetration power on the skin. The advantages of this dosage form are moisturising, soothing to the skin, easy to use, high water content, attractive shape, and good drug release [10–12]. Based on the above problems, researchers felt the need to test the effect of cinnamon leaf extract gel preparations in healing incision wounds on the rabbit's back skin.

Experimental Section

Materials and Apparatus

Materials

Cinnamon Leaf, ethanol 70%, HCl, $H2SO_4$, NaOH, $CUSO_4$, Mg Powder, $FeCl_3$, H_2O_2 6%, mayer reagent, dragendorff reagent, aquadest, ether, karbopol, glycerin, triethanol amine, propylenglycol, methylparaben, propylparaben, alluminium foil, cotton bud, Veet®, and Bioplacenton®.

Apparatus

Glass bottles, stirring rods, analytical balances, evaporation dishes, glassware, veterinary surgical tools, animal scales, rotary evaporators, test animal cages, shavers, barns, pestles, UV-Vis spectrophotometry, and metal plates 2.5 cm in diameter.

Preparation Cinnamon Leaf Extract

Extraction is carried out using the maceration method. Seven hundred fifty grams of cinnamon leaf powder were macerated using 70% ethanol solvent for 2 x 24 hours while occasionally stirring. Then, the Maserati results were separated and macerated two times using the same process as the first maceration. The collected fibre was concentrated using a rotary evaporator at 60^0C.

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Cinnamon Leaf Extract Gel Formulation

The gel formulation of cinnamon leaf extract uses an active substance concentration of 2.5%, 5%, and 10%. This is because a large amount of extract affects the stability of the gel that uses gelling agent carbopol. In addition, previously tested at a concentration of 10% sdh showed maximum healing effect as a healer of incision wounds [6].

Table 1. Cinnamon leaf gel formula design

Materials	Concentration (%)				Description
	F0	F1	FII	FIII	
Cinnamon Leaf Extract	0	2,5	5	10	Active substance
Carbopol	1,5	1,5	1,5	1,5	Gel base
Glycerin	5	5	5	5	*Humectant*
Propylene glycol	10	10	10	10	Increased penetration
TEA	1	1	1	1	Pendapar
Methylparaben	0,18	0,18	0,18	0,18	Preservative
Aquadest add	0,02	0,02	0,02	0,02	Solvent
Nanoparticle Extract	Ad 100	Ad 100	Ad 100	Ad 100	Active substance

Cinnamon leaf extract gel is formulated by making two mixtures in different containers. Mixture 1 is made by developing a 1.5-gram carbopol gelling agent that equates to as much as 15 ml in a mortar accompanied by grinding; then, this mixture is allowed to stand for 1x24 hours to produce a clear gel mass. Then, mixture one is added 0.18 grams methylparaben, 0.02 grams propylparaben and triethanolamine little by little until homogeneous. Then, in another mortar, a mixture of 2 was made by mixing various variants of thick ethanol extract concentrations of cinnamon leaves (2.5 grams, 5 grams, and 10 grams) with 5 ml glycerin and crushed until homogeneous. After that, a mixture of 2 and propilenglikol 10 ml is mixed in a mortar containing the mixture one little by little until it forms a homogeneous gel, and the remaining aquades are added until homogeneous.

The evaluation of the gel preparation includes organoleptic, homogeneity, pH, dispersion, adhesion and viscosity of the preparation for 28 days with examination at weeks 0, 1, 2, 3, and 4 storage at room temperature. First, organoleptic tests are carried out through visual observation, observing colours, odours, and dosage forms. Secondly, the homogeneity test is carried out by applying the preparation on a transparent glass and observing the homogeneity of the preparation. Third, pH was monitored using a calibrated pH meter, dipping the reference and glass electrodes into the ointment. Fourth, the dispersion test is carried out by weighing 0.5 grams of gel preparation and placing it in a glass glass glass with another glass. After a minute, add a load of 150 grams and leave for 1 minute. The result is determined by measuring the diameter formed. Fifth, a stickiness test of 0.25 grams of preparation is placed between two glasses on the adhesion test equipment, then a load of 1 kg and let stand for 5 minutes.

Test of the Healing Effects of Incision Wounds

This research has passed an ethical review conducted by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, Andalas University, with Number 672/UN.16.2/KEP-FK/2022. Incision wound testing using seven healthy male white rabbits for five treatment groups. The treatment groups are:
Positive control: received Bioplacenton treatment
Formula 0: received gel base treatment
Formula 1: received cinnamon leaf extract gel treatment 2.5%
Formula 2: received cinnamon leaf extract gel treatment 5%
Formula 3: received cinnamon leaf extract gel treatment 10%

Incision wounds were made on the shaved rabbit's back area, and then Veet was given to optimise the removal of back hair and rinse using ethanol. Shaved backs are left for 24 hours before being treated. After 24 hours, the area to be used as the location of the wound is anesthetised using 2% lidocaine. Then, a scalpel makes an incision wound 2.5 cm long and 2 mm deep. All treatments are given two times a day, namely morning and evening, by smearing as much as 0.4 grams of preparation. The data measured is the percentage of wound healing after administration for 14 days through measuring wound length.

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Results and Discussion

Cinnamon leaf extract

The extraction used in this study is the maceration method. This method is the simplest one, with easy, simple, and cost-efficient equipment. It does not require heating, so compounds cannot stand heating [13]. Samples of cinnamon leaf powder of as much as 750 grams with an amount of ethanol as much as 7.5 L obtained an extract weighing 103 grams or 13.73% thick. Ethanol is a universal solvent that is polar and nonpolar to dissolve polar and nonpolar compounds. Besides, ethanol can be used as a solvent to extract dry materials such as cinnamon leaf simplisia powder. The 70% ethanol solvent was chosen because it is more polar than the 96% ethanol solvent and more nonpolar than the 50% ethanol solvent. After all, cinnamon leaf samples contain more phenolic compounds and glycosides that are polar, so it is easier to attract the active substance by using solvents that are also polar.

Identifying secondary metabolites is the initial stage in determining the pharmacological effect of an extract. Based on Table 2, cinnamon leaf extract contains alkaloid metabolite compounds, flavonoids, saponins, tannins, and steroids. This is in line with research conducted by Kasmadi et al. (2022) and Nursofia et al. (2021)[6,14].

Table 2. Phytochemical Screening Results

Phytochemical Test	Results
Alkaloids	+
Flavonoids	+
Saponins	+
Tannins	+
Steroids	+
Terpenoids	-
Phenols	+

Evaluation of gel preparations

Evaluation of the physiological properties of cinnamon leaf gel aims to ensure the stability of the gel preparation that has been made. Here's how the results of making cinnamon leaf ethanol extract gel:

Formula 0 Formula 1 Formula 2 Formula 3

Figure 1. Results of cinnamon leaf extract gel formulation.

The gel evaluation results showed that cinnamon leaf gel preparations did not undergo significant organoleptic changes at room temperature during 4 weeks of observation. pH results are obtained in the range of 4.57 – 5.31; dispersion is 4.12-5.31 cm, and adhesion is in the range of 1.16 – 4.97 seconds. All of these results meet the standards set.

The wound healing effect of incision

The positive control used in this study was Bioplacenton®. Bioplacenton contains two active substance combinations: placenta extract and neomycin sulfate. Placenta extract acts as a biogenic stimulator to accelerate the process of blood coagulation and cell regeneration in wound healing. Meanwhile, neomycin sulfate acts as an antibiotic with a mechanism to kill various types of bacteria[15].

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Observation of wound healing was carried out for 14 days of treatment. On day 14, new wound tissue formed. So, it will look like a formula that can show the best effect in forming new tissue.

Table 3. Results of Cinnamon Leaf Extract Gel Evaluation

Formula	Observation	Results				
		Week 0	Week 1	Week 2	Week 3	Week 4
F0	Organoleptic					
	a. Color	Clear	Clear	Clear	Clear	Clear
	b. Smeel	Typical	Typical	Typical	Typical	Typical
	c. Form	Thick	Thick	Thick	Thick	Thick
	Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
	pH	6,50*± 0,076	6,66*± 0,003	6,28* ± 0,003	6,44* ± 0,005	6,51* ± 0,003
	Adhesion	3,84± 0,003	4,12± 0,003	3,93 ± 0,003	3,86 ± 0	4,05 ± 0
	Spreadability	4,57*± 0,034	4,71* ± 0,046	4,97* ± 0,029	4,7* ± 0,065	4,97* ± 0,115
FI	Organoleptic					
	a. Color	Light Brown	Light Brown	Light Brown	Light Brown	Light Brown
	b. Smeel	Aromatic	Aromatic	Aromatic	Aromatic	Aromatic
	c. Form	Thick	Thick	Thick	Thick	Thick
	Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
	pH	6,28* ± 0,003	6,38* ± 0,005	6,11* ± 0,003	6,2* ± 0,005	6,24* ± 0,005
	Adhesion	4,75 ± 0	4,26 ± 0	4,12 ± 0	4,93 ± 0,003	4,91 ± 0,003
	Spreadability	2,35* ± 0,017	2,77* ± 0,005	2,9* ± 0,012	2,96* ± 0,015	2,33* ± 0,069
FII	Organoleptic					
	a. Color	Brown	Brown	Brown	Brown	Brown
	b. Smeel	Aromatic	Aromatic	Aromatic	Aromatic	Aromatic
	c. Form	Thick	Thick	Thick	Thick	Thick
	Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
	pH	5,88* ± 0,003	6,14* ± 0,003	5,72* ± 0,003	5,8* ± 0,005	5,33* ± 0,003
	Adhesion	5,12* ± 0,003	5,03* ± 0,003	5,1* ± 0,003	5,14* ± 0,003	5,11* ± 0
	Spreadability	1,77* ± 0,088	1,94* ± 0,015	1,87* ± 0,048	1,78* ± 0,080	1,83* ± 0,051
FIII	Organoleptic					
	a. Color	Blackish brown	Blackish brown	Blackish brown	Blackish brown	Blackish brown
	b. Smeel	Aromatic	Aromatic	Aromatic	Aromatic	Aromatic
	c. Form	Thick	Thick	Thick	Thick	Thick
	Homogeneity	Homogeneous	Homogeneous	Homogeneous	Homogeneous	Homogeneous
	pH	5,21* ± 0,005	6,03* ± 0,003	5,35* ± 0,003	5,17* ± 0,003	5,1* ± 0,003
	Adhesion	5,26* ± 0	5,28* ± 0,003	5,31* ± 0,003	5,21* ± 0,003	5,27* ± 0,003
	Spreadability	1,21* ± 0,008	1,36* ± 0,003	1,33* ± 0,011	1,14* ± 0,021	1,16* ± 0,027

Note:
1. The sign (*) indicates that the data meets the requirements for evaluating topical preparations.
2. F0: Gel Base, F1: 2.5% extract, F2: 5% extract, and F3: 10% extract

Table 4. AUC Results Diameter and Percentage of Incision Wound Healing

Kelompok Perlakuan	AUC Diameter ± SEM	Persentase Kesembuhan (%)
Kontrol positif	14,367 ± 0,09[a]	100%
Formula 0 (Basis Gel)	21,269 ± 0,03[d]	76%
Formula I (Ekstrak 2,5%)	17,461 ± 0,04[c]	89,80%
Formula II (Ekstrak 5%)	15,197 ± 0,02[b]	97,70%
Formula III (Ekstrak 10%)	17,187 ± 0,03[b]	91%

Note: Superscript with different lowercase letters on the same line shows a noticeable difference ($p<0.05$).

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The results showed that cinnamon leaf ethanol extract gel had an effect as an incision wound healing agent and statistically had significant differences between groups ($p < 0.05$), where the best effect in wound healing is formula II with a concentration of cinnamon leaf extract as much as 5% (97.70%)—then followed by formula III (91%) and formula I (89.80%). This condition occurs because the higher the concentration of the extract, it will affect the amount of active substance that acts on histamine so that it will affect triggering an increase in histamine levels in incision wounds. Under certain conditions, mast cells, given high concentrations, will trigger increased blood vessel permeability, which will cause inflammation [16].

The content of secondary metabolite compounds and essential oils in cinnamon leaves is important in wound healing. Flavonoids play a role in the inflammatory phase, proliferation, and remodelling. Flavonoids have three roles in the wound-healing process. First, antibacterial flavonoids work through the protein denaturation process to stop the metabolic process in bacterial cells. Second, flavonoids also affect the inflammatory process through cyclooxygenase and lipooxygenase inhibition. Third, flavonoids are antioxidants that inhibit and prevent free radicals that can cause tissue damage. Alkaloids are anti-inflammatory and antibacterial that can interfere with the formation of bacterial cell layers. This condition is also supported by the antibacterial effects of saponins and tannins[17,18]. This study's results align with research conducted by Sani et al. (2022).

Conclusions

Cinnamon leaf extract can be made into gel preparations with concentrations of 2.5%, 5%, and 10%. The best formula for healing incision wounds is formula 2, with a concentration of 5%, followed by formula III, with a concentration of 10%, and formula I, with a concentration of 2.5%.

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