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The Effect of *Cep-Cepan* (*Castanopsis costata*) Leaf Extract Ointment on Post-Incision Wound Healing in Wistar Rats

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Abstract

Wound healing remains a challenge in medical practice, as available topical medications are often expensive, less effective, or associated with side effects. This study aimed to evaluate the effect of *cep-cepan* (*Castanopsis costata*) leaf extract ointment on post-incision wound healing in Wistar rats using a post-test only control group experimental design. *Cep-cepan* leaf extract was obtained through maceration method using 96% ethanol, with 22% yield. This extract was then formulated into ointments with concentrations of 15%, 30%, and 45%, subsequently tested for physical stability, phytochemical content, and wound healing effectiveness. The results showed that *cep-cepan* leaf extract contained alkaloids, flavonoids, saponins, tannins, and steroids/triterpenoids. In vivo tests on rats showed that ointments containing 30% and 45% extract significantly increased skin tensile strength and collagen density compared to the control group. The effectiveness of the 45% extract ointment was almost equivalent to gentamicin ointment as the standard group. This study indicates the potential of *cep-cepan* leaves as an alternative agent in wound care, providing clinical benefits at a more affordable cost and minimal side effects.

Keywords: *Castanopsis costata*; incisional wound; tensile strength; wound healing; herbal ointment.

INTRODUCTION

The skin is the largest organ of the human body by surface area and serves as the primary barrier protecting internal tissues from mechanical trauma, microbial infection, ultraviolet radiation, and extreme temperatures, making it susceptible to injury. (Rodrigues et al., 2019) A wound is defined as a discontinuity of living tissue caused by physical, chemical, thermal, microbial, or immunological injury. (Masson-Meyers et al., 2020) Based on type, wounds can be classified as open wounds, closed wounds, puncture wounds, or burns, while by healing time they are categorized into acute and chronic wounds. (Abeje et al., 2022)

The incidence of wounds increases annually. In the United States, approximately 8.2 million people suffer from wounds with or without infection, costing about 50 billion USD annually, with incision/trauma wounds accounting for 12 billion USD and burns for 7.5 billion USD. (Abeje et al., 2022; Shiffman & Low, 2021) In Africa, wounds contribute to 30–42% of hospital admissions and 9% of annual mortality. (Abeje et al., 2022) Chronic wounds affect 1–2% of the global population; in the United States, 6.5 million people are affected, costing around 25 billion USD annually.(Shedoeva et al., 2019) In Indonesia, the prevalence of wounds is 9.2%, with nearly 10% leaving permanent scars that impair comfort. (Kementerian Kesehatan Republik Indonesia, 2019)

Wound management remains a medical challenge, as only 1–3% of drugs listed in the Western pharmacopoeia are registered for wound treatment. Topical wound therapy is used for antisepsis and to maintain a moist healing environment, but such products are often expensive, less effective, or cause side effects. (Abeje et al., 2022; Kasmadi et al., 2022) This has driven growing interest in the use of herbal medicines and traditional remedies, which have been practiced for centuries. (Swamy & Kumar, 2023; Taheri et al., 2020) Traditional medicine, generally more affordable and with fewer side effects, remains the preferred wound therapy in many developing countries. (Abeje et al., 2022; Arifin & Ibrahim, 2018; Kasmadi et al., 2022)

One such medicinal plant used traditionally in North Sumatra, particularly by the Karo ethnic group, is *cep-cepan* (*Castanopsis costata*). This plant has a wide range of uses, including for digestive disorders, malaria, diabetes, hyperlipidemia, fever, pain, inflammation, and wound healing. (Alkandahri et al., 2019, 2021; Alkandahri, Arfania, et al., 2022; Alkandahri, Kusumiyati, et al., 2022; Nasirah Maulidia Ajhar et al., 2023) Ethanolic extracts of *C. costata* leaves contain alkaloids, flavonoids, glycosides, steroids/terpenoids, saponins, and tannins. (Nasirah Maulidia Ajhar et al., 2023) These secondary metabolites, particularly flavonoids, alkaloids, tannins, terpenoids, and saponins, play important roles in wound healing through vasoconstriction, free radical reduction, hydrolysis inhibition, anti-inflammatory effects, wound size reduction, and antibacterial activity. (Kasmadi et al., 2022; Nasirah Maulidia Ajhar et al., 2023)

Although empirically used, the wound-healing efficacy of *C. costata* leaves has not been widely studied scientifically. Therefore, this study aimed to analyze the effects of *C. costata* leaf extract ointment on post-incision wound healing in Wistar rats, including its physical characteristics, formulation stability, phytochemical composition, effects on skin tensile strength, blood vessel formation, and collagen density.

MATERIALS AND METHODS

Study area

This was an experimental study using a post-only control group design. The study was conducted at the laboratory of Universitas Prima Indonesia. This study had received ethical clearance from the Ethics Committee for Health Research, Universitas Prima Indonesia, Medan.

Materials

This study used some material incluuded *cep-cepan* leaves, ethanol solution, magnesium granules, Hydrocholoric Acid (HCL) solution, amyl alcohol, ammonia solution, chloroform solution, Dragendroff reagent, acetic anhyride solution, sulfic acid (H_2SO_4) solution, Lanolin, hard parrafin, cetostearyl alcohol, and white petrolium, Hematoxylin And Eosin staining, Mallory Azan staining, 10% Phosphate Buffered Formalin solution, and 70% alcohol solution.

Extraction of *Cep-cepan* (*Catanopsis costata*) Leaves

The *cep-cepan* leaves were rinsed thoroughly under running water and then dried. A total of 500 mg of the dried leaf simplicia was macerated in 96% ethanol for three days, with stirring for 10 minutes once every 24 hours. The resulting macerate was then filtered and weighed. The liquid extract was concentrated using a rotary evaporator at 50 °C until a yield of 15% was achieved. The concentrated extract was then further processed in a water bath to obtain a viscous extract. (Alkandahri, Arfania, et al., 2022; L. Chiuman et al., 2023; Salim et al., 2017)

Phytochemicals Screening

Phytochemical screening was carried out qualitatively to examine the presence of flavonoids, alkaloids, saponins, tannins, glycosides, and steroids/triterpenoids. For flavonoids, the extract was placed in a test tube containing Mg/Zn granules, HCl 2N was added, incubated for 5–10 minutes, and then amyl alcohol was added to the filtrate; an orange-red color indicated a positive result. For alkaloids, the extract was mixed with 10% ammonia, extracted with chloroform to form two layers, the lower layer was transferred to a new tube and added with 2N HCl, the acidic upper layer was transferred to another tube and added with Dragendorff's reagent; a yellow to brick-red precipitate indicated a positive result. For saponins, the extract was dissolved in distilled water and shaken vigorously; stable foam on the surface indicated the presence of saponins. For tannins, the extract was mixed with 2N HCl and heated in a water bath for 30 minutes; an orange/red color in the upper amyl alcohol layer indicated a positive result. For steroids/triterpenoids, the extract was placed on a spot plate, covered with acetic anhydride for 10–15 minutes, then one drop of concentrated H_2SO_4 was added; green/blue indicated steroids, while red/orange precipitate indicated triterpenoids. (Depari et al., 2021; Gulo et al., 2021; Suhartomi et al., 2020)

Ointment Formulation

The ingredients were heated according to their respective melting points, and ointments were prepared in different concentrations as described in Table 1. (V. Chiuman et al., 2022; S. Nasution et al., 2019)

Table 1. Formulation of cep-cepan leaf extract ointment.

Composition	Ointment base	15% Extract	30% Extract	45% Extract
Cep-cepan leaf extract	-	7.5 g	15 g	22.5 g
Lanolin	2.5 g	2.5 g	2.5 g	2.5 g
Hard parafin	2.5 g	2.5 g	2.5 g	2.5 g
Cetostearyl alcohol	2.5 g	2.5 g	2.5 g	2.5 g
White petrolatum	42.5 g	42.5 g	42.5 g	42.5 g

Physical Stability Test

The physical stability of the *cep-cepan* leaf extract ointment was evaluated using the Freeze–Thaw Cycle method, in which one cycle consisted of freezing at 4 °C for 24 h followed by storage at 40 °C for 24 h. The procedure was repeated for six cycles. After each cycle, organoleptic properties, homogeneity, spreadability, and pH were assessed. Organoleptic evaluation involved visual observation of the ointment's appearance, odor, and color. Homogeneity was determined by spreading the ointment on a glass slide to detect the presence of clumps and assess texture and color uniformity; samples were taken from the top, middle, and bottom portions of the container. Spreadability was tested by placing 0.5 g of ointment between two glass plates, measuring the spread diameter after 1 min, applying a 100 g weight for 1 min, and remeasuring the diameter; an acceptable range was 5–7 cm. The pH was measured using a pH meter immersed in 0.5 g of ointment diluted with 5 ml distilled water, with an acceptable range of 4.5–6.5 to match normal skin pH. (Aslani et al., 2016; Sing et al., 2020)

Treatment

All rats of similar age and body weight were acclimatized for 7–10 days and provided food and water ad libitum. They were fasted for 12–14 h prior to treatment. The dorsal area was prepared for surgery by shaving the hair, followed by general anesthesia using ketamine 10 mg. The animals were placed on the operating table, and the surgical site was disinfected with 70% alcohol. Two longitudinal paravertebral incisions were made through the skin and muscle, approximately 1.5 cm lateral to the midline on both sides of the vertebral column, using a sharp sterile scalpel. Each incision measured 4–6 cm in length. After hemostasis, the wounds were sutured with interrupted stitches at 0.5–1 cm interval. The wounds were left uncovered, cleaned with gauze, and treatment was initiated from the day of surgery for 10 consecutive days according to the groups in Table 2. Sutures were removed on 7th day, and the animals were euthanized for tensile strength testing on 10th day. Last, all wound tissues were collected for histology study on 11th day. (Thakur et al., 2011)

Table 2. Treatment groups.

Group	Treatment
Control	Ointment base only
Standard	Gentamicin sulfate ointment, commonly used for wound care
Cep-cepan leaf extract ointment 15%	Ointment containing 15% cep-cepan leaf extract
Cep-cepan leaf extract ointment 30%	Ointment containing 30% cep-cepan leaf extract
Cep-cepan leaf extract ointment 45%	Ointment containing 45% cep-cepan leaf extract

Tensile Strength Measurement

Following euthanasia, two parallel lines were drawn approximately 3 mm from each side of the wound. Two clamps were applied firmly to these lines; one was fixed to a stand, while the other was connected to a container suspended via a string and pulley system. Weights were added gradually to the container until the wound edges began to separate. The process was stopped immediately, and the final weight was recorded in grams as the tensile strength. The same procedure was performed on the contralateral wound, and the results were averaged (Figure 1). (Thakur et al., 2011)

Figure 1. Tensile strength testing.

Histology Study

Full-thickness cross-sectional tissue samples were collected on day 11 post-surgery and stained with Hematoxylin-Eosin (HE) and Mallory Azan (MA). Capillary density was evaluated from HE-stained sections, while collagen content in granulation tissue was assessed from MA-stained sections. Collagen density was scored semi-quantitatively as follows: (-) or 0 = no collagen fibers observed; (+) or 1 = very thin or sparse collagen fibers with low density; (++) or 2 = moderately distributed and partially fused collagen fibers with medium density; (+++) or 3 = abundant collagen fibers with high density; (++++) or 4 = fully organized collagen fibers with very high density. (V. Chiuman et al., 2022)

Data Analysis

Data analysis was performed using SPSS software. Descriptive statistics were used to analyze all research variables. Comparative analysis was conducted using one-way ANOVA followed by post hoc testing if the data were normally distributed, or using the Kruskal–Wallis test followed by Mann–Whitney post hoc testing if the data were not normally distributed. (Widiana, 2015)

RESULTS AND DISCUSSION

The ethanolic extract of *Castanopsis costata* (*cep-cepan*) obtained through maceration yielded a *yield* value of 22%. Phytochemical screening revealed the presence of alkaloids, saponins, flavonoids, tannins, and steroids/triterpenoids, consistent with previous findings. (Alkandahri et al., 2016, 2019; Alkandahri, Arfania, et al., 2022)

The extract was then formulated into ointments with concentrations of 15%, 30%, and 45%, all of which demonstrated good physical stability over six freeze–thaw cycles. Organoleptic evaluation showed a gradation in color from pale green to dark green with increasing extract concentration, a distinct *cep-cepan* aroma, semisolid consistency, and homogeneous texture. The pH ranged from 6.30 to 6.38, indicating a slightly acidic formulation. Spreadability measurements showed increased values with higher extract concentrations and additional load, ranging from 3.3 cm (no load) to 5.2 cm (150 g load). (Nawangsari & Sunarti, 2021)

The *cep-cepan* leaf extract ointment, which had undergone physical characteristic evaluation, was then applied as a treatment to all incision wounds in each treatment group for 10 days. After 10 days of treatment, the wound healing strength of the incision wounds was measured using the skin break test method in the form of tensile strength, expressed in grams. The tensile strength data were first analyzed for distribution using the Shapiro–Wilk test, and it was concluded that all data had a normal distribution, as indicated by a P-value > 0.05. Therefore, the tensile strength data were analyzed using one-way ANOVA, as described in Table 3.

Table 3. Comparison of tensile strength in all treatment groups.

Treatment Group	Tensile Strength (gram)	P-value
Control	438.00 ± 22.80a	
Standard	616.00 ± 102.13c	
Cep-cepan leaf extract ointment 15%	424.00 ± 30.50a	< 0.05
Cep-cepan leaf extract ointment 30%	480.00 ± 25.50ab	
Cep-cepan leaf extract ointment 45%	578.00 ± 69.79bc	

Table 3 showed that there were significant differences in tensile strength values among all treatment groups, as indicated by the P-value < 0.05. Differences in the concentration of cep-cepan leaf extract ointment significantly affected the tensile strength values. The ointment at the lowest concentration showed tensile strength values not significantly different from the base ointment. However, increasing the extract concentration to 30% significantly increased tensile strength. The 45% extract ointment showed a significant increase in tensile strength compared with the lowest concentration, and the tensile strength value at this highest concentration was not significantly different from that of gentamicin ointment as the standard. Finally, the distribution of tensile strength values across all treatment groups can be seen in the bar chart below.

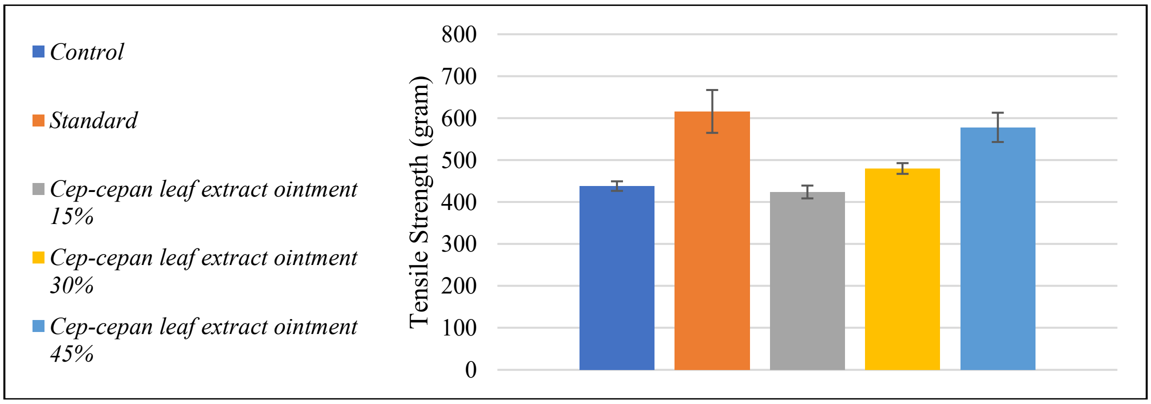

Figure 2. Bar chart of skin tissue tensile strength in incision wound healing across all treatment groups.

In this study, histological evaluation of the skin was performed by assessing collagen density in the tissue. The results of the histological examination are presented in the following table.

Table 4. Histological evaluation of skin tissue in all treatment groups.

Treatment Group	Collagen Fiber Score [Median (Range)]
Control	2 (1)
Standard	4 (1)
Cep-cepan leaf extract ointment 15%	2 (1)
Cep-cepan leaf extract ointment 30%	3 (1)
Cep-cepan leaf extract ointment 45%	4 (1)

From the table 4, it can be observed that all skin tissues in this study were in the process of keratinization, with no evidence of inflammatory cell infiltration such as polymorphonuclear cells. The main differences observed in the skin tissues were related to collagen and fibroblast density in the dermal layer. Fibroblast density was visualized with hematoxylin and eosin staining, showing the highest density in the gentamicin ointment group (standard) and in the 30% cep-cepan leaf extract ointment group. However, collagen density was highest in the gentamicin ointment group and in the 45% cep-cepan leaf extract ointment group. Representative histological images of the skin are shown in the following figures.

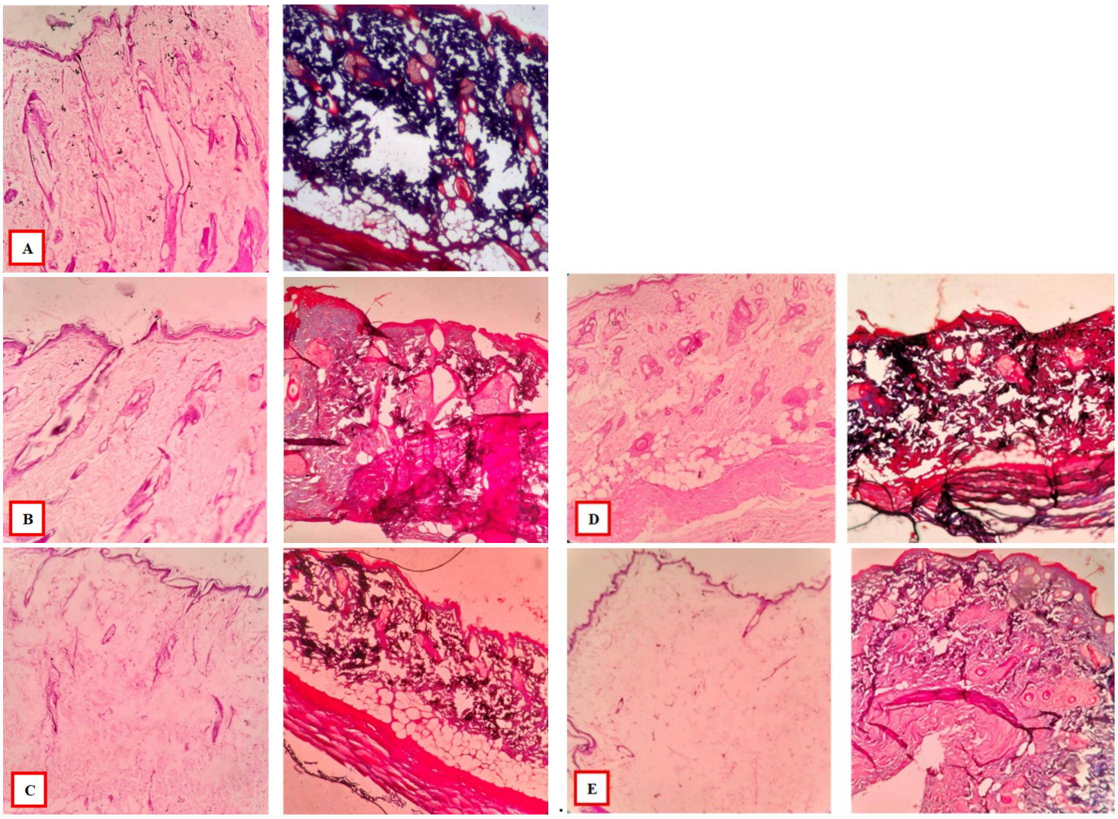

Figure 3. Representative histology of skin tissue from all treatment groups. (A) Ointment Base (Control), (B) Gentamicin Ointment (Standard), (C) Cep-cepan Leaf Extract Ointment 15%, (D) Cep-cepan Leaf Extract Ointment 30%, and (E) Cep-cepan Leaf Extract Ointment 45%. Staining: Hematoxylin–Eosin (left) and Masson's Trichrome (right); Magnification: 100×.

Discussion

This study demonstrated that the ethanolic extract of *Castanopsis costata* leaves, obtained by maceration, had a yield of 22% and contained major phytochemical constituents, including alkaloids, saponins, flavonoids, tannins, and steroids/triterpenoids. These findings are consistent with previous studies reporting similar extraction yields and phytochemical profiles from *C. costata* extracts, although variation may occur depending on the extraction solvent and method. (Alkandahri et al., 2016, 2019; P. R. Nasution et al., 2024; Pandey & Tripathi, 2014)

The phytochemical constituents of *C. costata* are believed to contribute to its wide range of pharmacological activities. Flavonoids, in particular, have been shown to possess analgesic, anti-inflammatory, and antioxidant effects by inhibiting cyclooxygenase activity, reducing prostaglandin synthesis, and scavenging free radicals. (Alkandahri et al., 2024; Salim et al., 2017) These properties provide a strong rationale for the use of *C. costata* in wound healing.

The ointment formulations containing 15%, 30%, and 45% of the ethanolic extract exhibited good physical stability, as indicated by consistent organoleptic characteristics, homogeneity, pH within the weakly acidic range (6.30–6.38), and spreadability values of 3.3–5.2 cm. Adequate spreadability is important for topical preparations, as it ensures effective distribution of the active compound over the application site and facilitates diffusion into the skin. (Nawangsari & Sunarti, 2021)

In vivo incision wound models revealed that the 30% and 45% extract ointments significantly enhanced tensile strength compared with the ointment base, while the 45% formulation demonstrated effects comparable to gentamicin ointment. Histological examination further confirmed these findings, with the 45% extract group showing dense and well-organized collagen fibers similar to the gentamicin group. No inflammatory cell infiltration was observed in any treated groups, suggesting that the extract effectively suppressed inflammation while promoting tissue remodeling.

Wound healing involves hemostasis, inflammation, proliferation, and remodeling, with oxidative stress and excessive inflammation known to delay repair. (Mo et al., 2022) The antioxidant and anti-inflammatory activities of *C. costata* extract likely contributed to accelerated wound healing by neutralizing reactive oxygen species (ROS), reducing prolonged inflammation, and supporting collagen synthesis.

Taken together, these findings indicate that ethanolic extract of *C. costata* leaves, particularly at 45% concentration, promotes incision wound healing by enhancing tensile strength and collagen deposition. This effect is consistent with the phytochemical profile of the plant and its previously reported pharmacological properties.

CONCLUSIONS

Based on the results, it can be concluded that ethanolic extract of *Castanopsis costata* leaves contains alkaloids, saponins, flavonoids, tannins, and steroids/triterpenoids. The 30% (480.00 ± 25.50 g) and 45% (578.00 ± 69.79 g) extract ointments significantly increased skin tensile strength in incision wounds ($P < 0.05$). Histological analysis further showed that the highest collagen density was observed in the gentamicin group and the 45% extract ointment group.

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Competing Interests: The authors declare that there are no competing interests.

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