

## Evaluation of Coffee Mistletoe Leaf Ethanol Extract on Burn Healing Activity on White Male Rat

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### ABSTRACT

Burns are injuries that can be caused by heat (fire, hot liquids/fats, hot vapors), radiation, electricity, or chemicals. Coffee mistletoe leaves (*Loranthus ferruginous* Roxb) are one type of plant that contains secondary metabolite compounds, such as flavonoids, tannins, saponins, alkaloids, and phenolics, which play a role in the burn healing effects. This research was conducted using an experimental research method with a Completely Randomized Design (CRD) and a post-test only control group design approach. A total of 25 rats were divided into five treatment groups for the study. The groups included a positive control group treated with Bioplacenton gel, a negative control group treated with yellow vaseline, and three experimental groups treated with different concentrations of ethanol extract of coffee mistletoe leaves. The concentrations used were 5% (P1), 10% (P2), and 15% (P3). The burn healing activity and hydroxyproline content were observed as outcome measures. The data were presented as mean  $\pm$  SD and analyzed using one-way ANOVA. Subsequently, Duncan's multiple rank test was performed to determine any significant differences. A significance level of  $p < 0.05$  was considered to define statistically significant results. The results of the study showed that ethanol extract of coffee mistletoe leaves has an effect as a burn treatment, with the best concentration found at 15% concentration, which had a healing percentage of 62.5%, although its effectiveness did not exceed that of the positive control group (72.48%). The hydroxyproline content of the coffee mistletoe leaf extract group demonstrated significant difference when compared to control negative groups, especially P1 group ( $53.62 \pm 6.52$   $\mu\text{g/mL}$ ), and statistically not different with positive control ( $64.34 \pm 6.02$   $\mu\text{g/mL}$ ). For the P2 and P3 groups, the hydroxyproline content were increased but did not reach significant value. Wound-healing activity owing to its richness in various effective chemical compounds present in the extract such as phenolics, saponin, flavonoid and alkaloid. Further investigation is necessary to identify and understand these additional components and their mechanisms of action in the healing process.

**Keywords:** *Loranthus ferrugineus* Roxb., coffee mistletoe leaf ethanol extract, burn healing activity, Hydroxyproline content, Healing percentage

## ABSTRAK

Luka bakar merupakan jenis luka yang dapat disebabkan oleh panas (api, cairan/lemak panas, uap panas), radiasi, listrik, atau bahan kimia. Daun benalu kopi (*Loranthus ferrugineus* Roxb.) merupakan salah satu jenis tumbuhan yang mengandung senyawa metabolit sekunder post-test-only, seperti flavonoid, tannin, saponin, alkaloid, dan fenolik, yang berperan dalam efek penyembuhan luka bakar. Penelitian ini dilakukan dengan menggunakan metode penelitian eksperimental dengan pendekatan desain Rancangan Acak Lengkap (RAL) dan *post-test only control group design*. Sebanyak 25 ekor tikus dibagi menjadi lima kelompok perlakuan, yang terdiri dari kelompok kontrol positif (gel Bioplacenton), kelompok kontrol negatif (vaseline flavum), serta tiga kelompok perlakuan yang diobati dengan ekstrak etanol daun benalu, yaitu 5% (P1), 10% (P2), dan 15% (P3). Aktivitas penyembuhan luka bakar dan kandungan hidroksiprolin diamati sebagai parameter hasil. Data disajikan sebagai rata-rata  $\pm$  SD dan dianalisis menggunakan uji ANOVA satu arah. Selanjutnya, dilakukan uji peringkat berganda Duncan untuk menentukan perbedaan yang signifikan. Tingkat signifikansi  $p < 0,05$  digunakan untuk menentukan hasil yang signifikan secara statistik. Hasil penelitian menunjukkan bahwa ekstrak etanol daun benalu kopi memiliki efek sebagai pengobatan luka bakar, dengan konsentrasi terbaik ditemukan pada konsentrasi 15%, yang memiliki persentase penyembuhan sebesar 62,5%, meskipun efektivitasnya tidak melebihi kelompok kontrol positif (72,48%). Kandungan hidroksiprolin pada kelompok ekstrak daun benalu kopi menunjukkan perbedaan yang signifikan dibandingkan dengan kelompok kontrol negatif, terutama pada kelompok P1 ( $53,62 \pm 6,52 \mu\text{g/mL}$ ), dan secara statistik tidak berbeda dengan kontrol positif ( $64,34 \pm 6,02 \mu\text{g/mL}$ ). Pada kelompok P2 dan P3, kandungan hidroksiprolin mengalami peningkatan namun tidak mencapai nilai yang signifikan. Aktivitas penyembuhan luka ini disebabkan oleh kandungan senyawa kimia yang efektif dalam ekstrak, seperti fenolik, saponin, flavonoid, dan alkaloid. Penelitian lebih lanjut diperlukan untuk mengidentifikasi dan memahami komponen tambahan ini serta mekanisme aksinya dalam proses penyembuhan.

**Kata Kunci:** *Loranthus ferrugineus* Roxb., ekstrak etanol daun benalu kopi, aktivitas penyembuhan luka bakar, kandungan hidroksiprolin, persentase penyembuhan

## INTRODUCTION

Burn injuries are a highly impactful form of trauma or inflammation that can occur unpredictably and affect individuals regardless of age, location, or circumstances. These injuries can arise from various sources, including friction, cold, heat, radiation, chemical exposure, or electrical incidents. However, the majority of burn injuries are caused by heat from hot liquids, solids, or fires (Jeschke et al., 2020). The skin affected by burns will experience damage to the epidermis, dermis, and subcutaneous tissue, depending on the causative factors and the duration of skin contact with the causative agent (Rawlings et al., 2022).

Indonesian society has been using coffee mistletoe as a traditional remedy for healing various diseases such as cancer by boiling dried mistletoe leaves and drinking the resulting infusion (Yulian, Safrijal, Tarbiyah, Uin, & Aceh, 2018). On the other hand, coffee mistletoe has also been widely utilized in traditional medicine to lower blood

pressure, treat coughs, cancer, and has anti-allergic effects. It is also known to contain high levels of antioxidant compounds and has gastrointestinal effect, such as including functional dyspepsia, constipation, and postoperative ileus (Ameer, Salman, Quek, & Asmawi, 2015).

Oxidative stress plays a significant role in the conversion of burn wounds. The excessive production of reactive oxygen species (ROS) and free radicals during the initial stages of burn injury contributes to oxidative stress, which can further exacerbate tissue damage. Previous research conducted by (Yulian et al., 2018), showed that antioxidant activity of the coffee mistletoe leaf ethanol extract had a very strong antioxidant activity against radical DPPH 0.05 mM, with  $IC_{50}$  values was obtained  $6.063 \mu\text{g/mL}$  compared to ascorbic acid  $3.127 \mu\text{g/mL}$ . This strong antioxidant activity may potentially halt or arrest the advancement of burn injury, preserving the viability of tissues and preventing the conversion of the zone of stasis into necrotic tissue.

Based on the description above, considering the untapped potential of coffee mistletoe leaves as a source of anti-inflammatory properties and its high antioxidant activity, this study aims to explore coffee mistletoe leaf extract (*Loranthus ferrugineus* Roxb.) as an alternative treatment for burns on the backs of male rats.

## RESEARCH METHOD

### Plant Collection and Identification

Coffee mistletoe leaves (*Loranthus ferrugineus* Roxb.) were obtained from Koto Tengah district, Padang city, West Sumatra. The plant was identified in Herbarium Jatiningor, Plant Taxonomy Laboratory, Department of Biology, Faculty of Mathematic and Natural Science, Universitas Padjadjaran, with voucher specimen number 42/HB/11/22. Sample collection was done by plucking fresh coffee mistletoe leaves, including mature leaves, in the morning with a total amount of 3 kg.

### Preparation of Extract

The extraction of coffee mistletoe leaf was done using the maceration method with 70% ethanol as the solvent. The powdered herbal material was placed in a dark glass bottle with a ratio of 1:10 dried powdered herbal material to the solvent. During the first 6 hours, the powdered herbal material was soaked in the solvent while occasionally stirred, and then left for 18 hours. Furthermore, the macerate was separated through the filtration process. Subsequently, a remaceration process was performed using the same solvent with at least half the amount of the solvent used in the first filtration. All macerates were collected, and then evaporated using a rotary evaporator to obtain a concentrated extract.

### Characteristics of the Extract

The characterization of the extract involves two types of parameters, namely specific parameters and non-specific parameters. Specific parameters include identity tests and organoleptic tests, while non-specific parameters include the examination of extract water content, extract ash content according to Indonesian Herbal Pharmacopeia (Ministry of Health Indonesia, 2017). The screening phytochemical of secondary metabolites such as alkaloids, flavonoids, phenolics, terpenoids, steroids, and saponins were

determined using the phytochemical test developed in previous research (Efendi, 2019; Efendi, Rusdi, & Dinda, 2022).

### Preparation of Coffee Mistletoe Leaf Extract Formulation

The ethanol extract of coffee mistletoe leaves (*Loranthus ferruginues* Roxb.) was made into 5% (P1), 10% (P2), and 15% (P3) for treatment groups by mixed with yellow vaselin. Bioplacenton is used as the positive control (K+), and yellow vaseline is used as the negative control (K-).

### Experimental Animal

25 Male rats weighing between 200-300 g and aged 2-3 months were used in this study. They were subjected to treatment using a completely randomized design (CRD) with a Post-test Only Control Group Design. The rats were divided into five treatment groups (K+, K-, P1, P2, P3), each comprising 5 male white rats. They were maintained in an environmentally controlled room with access to food and water *ad libitum*. The animal procedures were performed strictly to institutional protocols and followed the animal care provisions outlined by The Ethics Committee of The Faculty of Medicine, Universitas Andalas (No. 1055/UN.16.2/KEP-FK/2022).

### The Creation of Burn Wounds.

The back hair of the rats was shaved and disinfected using ethanol. Subsequently, the rat's skin was anesthetized with acepromazine (castran®). A burn was created on the rat's back using a circular plate with a 20 mm diameter, heated over a blue flame for 3 minutes, and applied to the rat's back for 5 seconds. The burn area was then compressed with distilled water for 1 minute. The resulting burn diameter was measured.

### Observation of burn wound healing

The healing process was monitored for 14 days following the application of each treatment twice a day, both in the morning and afternoon. Observations were conducted throughout the 14-day period by measuring the diameter of the burn area using a vernier caliper with a scale of 0.01 mm. The healing of the burn was determined by observing shrinkage and closure of the wound. Percentage reduction in wound area with respect to initial wound area (Talekar, Apte, Paygude, Tondare, & Parab, 2017).

Healing percentage (%)

$$= \frac{\text{diameter initial} - \text{diameter final}}{\text{diameter initial}} \times 100\%$$

### Observation of Hydroxyproline Content

A piece of skin from the healed wound area on day 14 was collected and analyzed for hydroxyproline content, which is basic constituent of collagen (Dwivedi, Dwivedi, Malviya, & Singh, 2017). The skin tissue is dried at 60°C for 12 hours, then hydrolyzed with HCl 6N at 110°C for 24 hours. The tissue is neutralized to pH 7 using standard solution and NaOH, followed by the addition of 1 mL CuSO<sub>4</sub>, NaOH, and H<sub>2</sub>O<sub>2</sub>. The mixture is heated at 80°C for 5 minutes, cooled, and treated with 4mL H<sub>2</sub>SO<sub>4</sub> 3M and 2 mL 2,4-dimethylaminobenzaldehyde. After heating at 70°C for 16 minutes, the solution is cooled, and the absorbance is measured at 560 nm using a UV-Vis spectrophotometer. The amount of hydroxyproline in the sample is calculated using a standard curve. The standard curve was generated using pure hydroxyproline solutions at concentrations of 9, 18, 27, 36, 45, and 54 µg/mL. The procedure followed for these standard solutions was similar to the one described earlier. The concentrations of hydroxyproline in the samples are then determined

by comparing their absorbance values to the standard curve. The results are expressed as µg/mL of hydroxyproline (Jorge et al., 2008).

### Data Analysis

The data were presented as mean ± standard deviation and analyzed using one-way ANOVA followed by Duncan's multiple rank test. Significance different were defined as p<0.05).

## RESULTS AND DISCUSSION

### Identification and Characteristic Extract

The aim of this study was to evaluate the effect of coffee mistletoe leaf ethanol extract on burn healing activity. The research was initiated by conducting the plant determination process at the Herbarium of Universitas Padjajaran, with reference number 42/HB/11/2022. The determination process confirmed that the plant sample used in this study is the coffee mistletoe leaf, belonging to the family Loranthaceae and the species *Loranthus ferrugineus* Roxb. The extract preparation methods adhered to the guidelines as stated in the Indonesia Herbal Pharmacopeia (Ministry of Health Indonesia, 2017). The results of specific and non-specific parameters were presented in Table 1.

**Table 1.** Results of specific and non-specific parameter tests for coffee mistletoe leaves

Parameter	Results	
<b>Specific</b>	<i>Organoleptic</i>	
	Form	Thick liquid
	Smell	Characteristic smell
	Color	Dark brown
	Taste	Bitter astringent
<i>Identity</i>	Extract name	<i>Loranthus ferrugineus</i> Extractum
	Species of the plant	<i>Loranthus ferrugineus</i> Roxb.
	Plant part used	Coffee Mistletoe Leaves
	Indonesian name of the plant	Daun Benalu Kopi
	Family	Loranthaceae
<b>Non-specific</b>	Ash Content	6%
	Water Content	14,3%

In phytochemical screening, reagents for testing each observed compound are added, and then the resulting changes are observed. Phytochemical analysis of the coffee mistletoe leaf ethanol extract also revealed the presence of

several constituents, including alkaloids, flavonoids, saponins, steroids, and phenolics. The results of phytochemical screening tests can be seen in **Table 2**.

**Table 2.** Results of the Phytochemical Screening Test

Secondary Metabolite Compounds	Results
Alkaloids	+
Flavonoids	+
Saponins	+
Triterpenoids/steroids	-/+
Phenolics	+

Note: (+) = Positive for containing secondary metabolites; (-) = Negative for containing secondary metabolites

### Burn Healing Activity

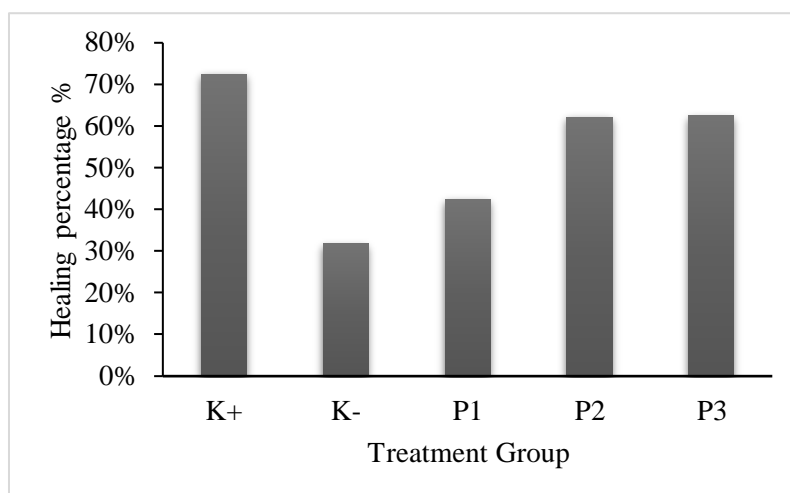
**Table 3.** The Effect of Coffee Mistletoe Leaf Ethanol Extract on Area Under Curve (AUC) and Healing Percentage

Treatment Group	AUC Diameter $\pm$ SD	Healing Percentage (%)
K+	28,55 $\pm$ 0,5	72,48%
K-	31,87 $\pm$ 0,61	31,79%
P1	28,93 $\pm$ 0,56	42,45%
P2	28,82 $\pm$ 1,05	62,16%
P3	28,63 $\pm$ 0,7	62,5%

Values are presented as mean  $\pm$  SD. Different superscripts denote statistical significance ( $p < 0.05$ ). K+ Bioplacenton; K- Yellow Vaseline; P1 5% concentration of coffee mistletoe leaf extract; P2 10% concentration of coffee mistletoe leaf extract; P3 15% concentration of coffee mistletoe leaf extract

Based on the burn healing analysis using One-Way ANOVA, no significant difference ( $p$ -value $>0.05$ ) was found in the average measurement of wound diameter among the treatment groups receiving coffee mistletoe leaf ethanol extract. It can be observed that treatment P3 had the best effect, although its effectiveness did not exceed that of the positive control group.

The results of the analysis indicate that the concentration of coffee mistletoe leaf ethanol extract at 15% is the optimal concentration, followed by concentrations of 10% and 5%. In the process of wound healing, certain compounds play a role, such as flavonoids, alkaloids, saponins, and tannins.



Note: K+ Bioplacenton; K- Yellow Vaseline; P1 5% concentration of coffee mistletoe leaf extract; P2 10% concentration of coffee mistletoe leaf extract; P3 15% concentration of coffee mistletoe leaf extract

**Figure 1.** The Effect of Coffee Mistletoe Leaf Ethanol Extract on Healing Percentage

According to a previous study, flavonoid compounds were isolated from coffee mistletoe, such as quercetin and quercitrin, glycoside 4"-O-acetyl quercitrin in the ethyl acetate fraction. (Ameer et al., 2015) Flavonoids have demonstrated effects on various aspects of the inflammatory process, angiogenesis, re-epithelialization, and oxidative stress. They have been shown to modulate the activities of macrophages, fibroblasts, and endothelial cells by influencing the release and expression of TGF- $\beta$ 1, VEGF, Ang, Tie, Smad 2 and 3, and IL-10. Additionally, flavonoids can suppress the release of inflammatory cytokines, NF $\kappa$ B, ROS, and the M1 phenotype. They exert their effects by positively regulating MMPs 2, 8, 9, and 13 and the Ras/Raf/MEK/ERK, PI3K/Akt, and NO pathways (Carvalho et al., 2021).

The wound-healing activity of plants containing alkaloids is attributed to their capacity to expedite the formation of epithelial cells, thereby accelerating the crucial re-epithelialization process during wound healing. Furthermore, these plant extracts have the potential to stimulate angiogenesis, which is the formation of new blood vessels. Consequently, this enhanced vascularization contributes to an increased blood supply to the newly formed epithelial cells, ultimately leading to a faster rate of wound contraction (Fetse et al., 2014). The accelerated wound-healing potential associated with the total alkaloid extract is likely attributed to the increased deposition of collagen fibers, angiogenesis, and a

decrease in inflammatory cell presence in the granulation tissue of the wound area (Zahra et al., 2011).

Polyphenols exhibit vigorous pro-inflammatory activities, contribute to the recruitment of inflammatory cells, promote cellular proliferation and migration, possess antioxidant properties, and offer antimicrobial effects. These characteristics contribute to their potential to accelerate wound healing and control infections (Guimarães et al., 2021). The richness of the coffee mistletoe leaf ethanol extract in alkaloids, polyphenols, and flavonoids may also synergistically promote angiogenesis. (Hoeben et al., 2004) have previously reported a significant relationship between the phytochemical composition of plant extract and micro-vessels neof ormation in the wound healing process.

### Observation of Hydroxyproline Content

Hydroxyproline, a fundamental component of collagen, is a valuable marker for assessing wound healing. Being one of the predominant amino acids in collagen, its concentration indicates collagen levels in the tissue. A higher concentration of hydroxyproline is associated with a faster rate of wound healing. Therefore, measuring hydroxyproline levels provides insight into the progress and efficacy of the healing process (Dwivedi et al., 2017). Hydroxyproline content was derived from the calibration curve ( $y = 0,0263 + 0,058x$ ,  $R^2 = 0.9962$ ) of hydroxyproline solution (9–54  $\mu$ g/ml) and expressed in  $\mu$ g/mL of

Hydroxyproline. From the calibration curve, the hydroxyproline content of the coffee mistletoe leaf extract ranged from 53.62 - 45.68  $\mu\text{g/mL}$  (Table 4, Figure 2).

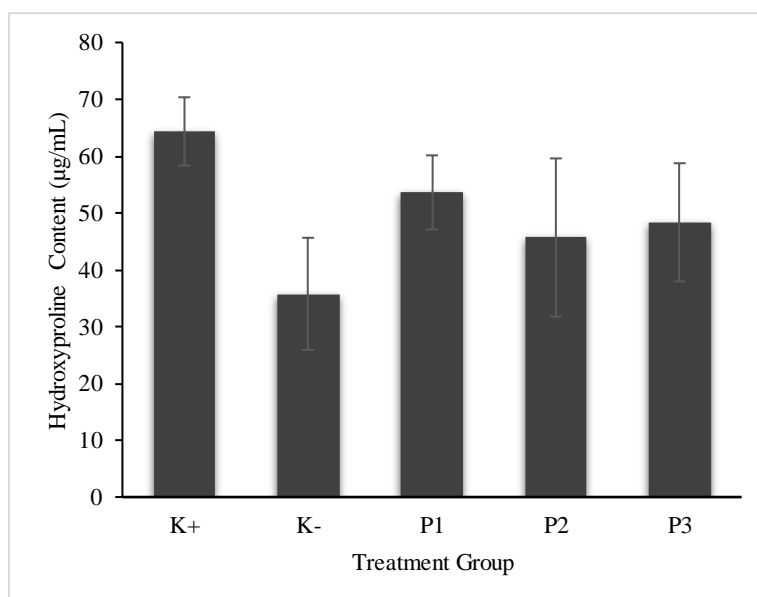
The hydroxyproline content of the coffee mistletoe leaf extract group demonstrated a significant difference when compared to control hostile groups, especially the P1 group ( $53.62 \pm 6.52 \mu\text{g/mL}$ ), and statistically not different from with positive control ( $64.34 \pm 6.02 \mu\text{g/mL}$ ). The

hydroxyproline content increased for the P2 and P3 groups but did not reach a significant value. The results showed conflicting outcomes as the 5% coffee mistletoe leaf extract concentration exhibited higher hydroxyproline content compared to 10% and 15% concentrations. This discrepancy suggests that factors other than collagen content may contribute to the observed healing activity.

**Table 4.** The Effect of Coffee Mistletoe Leaf Ethanol Extract on Hydroxyproline Content

Treatment Group	Hydroxyproline Content ( $\mu\text{g/mL}$ )
K+	$64.34 \pm 6.02^c$
K-	$35.76 \pm 9.87^a$
P1	$53.62 \pm 6.52^{b,c}$
P2	$45.68 \pm 13.92^{a,b}$
P3	$48.35 \pm 10.4^{a,b}$

Values are presented as mean  $\pm$  SD. Different superscripts denote statistical significance ( $p < 0.05$ ). K+ Bioplacenton; K- Yellow Vaseline; P1 5% concentration of coffee mistletoe leaf extract; P2 10% concentration of coffee mistletoe leaf extract; P3 15% concentration of coffee mistletoe leaf extract



Note: K+ Bioplacenton; K- Yellow Vaseline; P1 5% concentration of coffee mistletoe leaf extract; P2 10% concentration of coffee mistletoe leaf extract; P3 15% concentration of coffee mistletoe leaf extract

**Figure 2.** The Effect of Coffee Mistletoe Leaf Ethanol Extract on Hydroxyproline Content

## CONCLUSION

Wound-healing efficacy of the coffee mistletoe leaf ethanol extract observed in this work originates from its richness in various effective chemical compounds present in the extract, such as phenolics, saponins, flavonoids, and alkaloids. Coffee mistletoe leaf extract demonstrates activity in promoting wound healing in male white mice by increasing the healing percentage, reducing wound diameter, and enhancing hydroxyproline collagen levels with a concentration of 15% was the best activity. However, this concentration does not surpass the effectiveness of Bioplacenton. Further investigation is necessary to identify and understand these additional components and their mechanisms of action in the healing process.

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