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Ethanol Extract of Jackfruit Leaves (*Artocarpus heterophyllus* Lmk.) Promotes Burn Wound Healing in Sprague Dawley Male Rats

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Abstract

Burn wounds have the potential to become infection, dehydration, and serious complications if not treated properly. Jackfruit leaves (Artocarpus heterophyllus Lmk.*) contain secondary metabolites such as flavonoids, tannins, saponins, and steroids which has big potential to accelerate of burn wound's healing. The purpose of this study is to learn more about the effect of jackfruit leaves ethanol extract application on the burn wound healing. The experimental animals were 25 Sprague Dawley rats separated into five groups: negative control group, positive control group, and test groups G1 (94 mg/Kg BW), G2 (188 mg/Kg BW), and G3 (376 mg/Kg BW). The wound area, wound recovery (%), and wound healing time were all measured. To determine the difference on a given day of observation, wound area data were evaluated using a one-way ANOVA test. The ethanol extract of jackfruit leaves (Artocarpus heterophyllus Lmk.) was found to have an effect on burn healing. On the 14th day, the percent recovery values for burns in the positive control, negative control, G1, G2, and G3 groups were 89.9%, 76.5%, 88.8%, 87.2%, and 100%, respectively. Treatment group 3 had the quickest burn healing time and the highest percentage of recovery.*

I. Introduction

Burns are a common occurrence in the community. According to basic health research data from 2018, the prevalence of burn injuries is 1.3%. The largest occurrence is found in adults between the ages of 35 and 44 (Balitbangkes, 2019). Burns are a regular occurrence in everyday life, particularly in the home, and the most common are second degree burns. Burns are caused by contact with heat sources such as fire, hot water, chemicals, electricity, and radiation. Burns to the skin, mucous membranes, respiratory tract, and digestive tract are all possible. Pain, swelling, redness, and blisters can occur as a result of increased vascular permeability (Hasyim *et al.*, 2012).

Burns are classified according to depth, with first degree burns causing minor damage to the superficial epidermal layer, hyperemic dry skin, and spontaneous healing occurring within 5-10 days (DeLaune and Ladner, 2010). There is damage to all layers of the epidermis as well as a layer of the dermis in second degree burns. Where the wound's base is red or pale. Third-degree burns (Full Thickness burns) include damage that extends throughout the dermis and deeper layers, there are no bullae, the skin appendages are injured, and the burned skin is white and pale (Chavan *et al.*, 2022).

Burn healing is divided into three stages, there are inflammation, proliferation, and maturation, which occur in second-degree and third-degree burns. The inflammatory phase, also known as the lag phase, can persist up to 3-4 days. Starting on day 4 to 14, there is a creation of granulation tissue, which is the heart of the proliferative phase. On day 21, the maturation or remodelling phase begins, with wound re-modelling as a result of an increase in collagen tissue, breakdown of excess collagen, and regression of wound vascularity (DeLaune and Ladner, 2010).

As society continues to seek remedies that are more accessible and come from nature, many studies have been done to identify the pharmacological activity of plants. Jackfruit leaves (*Artocarpus heterophyllus* Lmk.) are a traditional medication that has been used empirically by most people to cure wounds (Kementrian Kesehatan RI, 2018). Saponins, flavonoids, tannins, and steroids are found in jackfruit leaves (Murlistyarini and Intan Yuniasih, 2023). Saponins are also known to induce the production of new epithelial cells and to aid in the epithelialization process, reducing the size of burns (Widyantoro and Sugihartini, 2015). Flavonoids and steroids have anti-inflammatory and antioxidant properties. Flavonoids act as tyrosinase inhibitors in

skin pigmentation because the hydroxyl groups in the B ring of flavonoids can block the tyrosinase enzyme in skin cells. Flavonoids have anti-inflammatory properties because they inhibit the synthesis of pro-inflammatory chemicals such as NO and PGE-2 (Florentina and Supriyanti, 2009).

According to the findings of Kurniawan and Layal's (2017) study, breadfruit leaf extract gel (*Artocarpus altilis*) can accelerate burn healing in mice. Breadfruit leaf extract gel can help to minimize burn diameter. Giving breadfruit leaf extract gel at a 25% concentration can help burns heal faster, with an 80% recovery rate. Breadfruit is a plant in the same family as jackfruit (artocarpus). As a result, it is hypothesized that jackfruit leaves, which have never been examined for their burn healing activity, will perform similarly to breadfruit leaves.

II. Research Method

II.1 Materials

Artocarpus heterophyllus Lmk. leaves were taken in Palembang, South Sumatera, Indonesia. The jackfruit plant was identified at the Purwodadi-LIPI Plant Conservation Center in East Java (certificate no.792/IPH.06/HM/VIII/2019). 900 g of dried leaves was ground into powder and soaked in ethanol 96% (1:10). The maceration procedure was held at room temperature in the amber bottle for 72 hours and occasionally shook. The macerate was filtered and then evaporated with a rotary evaporator at 70°C until a thick extract was obtained. The thick extract was weighed, and the extract yield percentage was calculated using Equation 1.

$$\% \text{ Yield} = \frac{\text{obtained thick extract (g)}}{\text{simplicia used in extraction (g)}} \times 100\% \quad (1)$$

II.2 Phytochemical Identification of Extract

II.2.1 Alkaloid Test

One gram of sample was crushed in the mortar, followed by a tiny amount of chloroform and sand, followed by 5 mL of 0.05 N ammonia solutions in chloroform. The mixture was agitated for a few minutes before being filtered into the test tube. After adding H_2SO_4 2N to the filtrate and shaking it regularly, two layers formed. The top solution (water phase) is separated and examined with reagents from Mayer, Wagner, and Dragendorff. The presence of alkaloid group chemicals is indicated by the formation of sediment.

II.2.2 Flavonoid Test

A total of 0.5 g of sample was placed in the test tube, followed by 5 mL of ethanol and heated for 5 minutes. The extract was then filtered, and a few drops of strong HCl were added to the filtrate. Then, roughly 0.2 mg of magnesium powder was added. If it becomes red, it indicates the presence of flavonoid.

II.2.3 Saponin Test

In 10 mL of hot water, 500 mg of sample was added. Then cool and shake vigorously. The presence of saponin group chemicals was indicated by the development of a stable foam 1 cm or higher in height. Furthermore, adding 1 drop of HCl 2 N will not remove the foam.

II.2.4 Tannin Test

A total of 500 mg of sample was added to 50 mL of distilled water, heated for 15 minutes, and chilled. 5 mL of filtrate was dripped with $FeCl_3$ 1%. If the color turned greenish black, it indicates the presence of tannin class chemicals.

II.2.5 Steroid and Triterpenoid Test

A total of 2 g samples were crushed in mortar, a tiny amount of chloroform and sand were added, and 5 mL of 0.05 N ammonia solutions were added into the chloroform. The mixture was agitated for a few minutes before being filtered into the test tube. H_2SO_4 2N was added to the filtrate and agitated often to form two layers. The bottom solution was separated and placed on the drop plate to dry. After drying, anhydrous acetic acid was added and thoroughly mixed. After that, 3 drops of concentrated sulfuric acid were added and the hue that resulted was noted. The presence of steroid molecules is indicated by the presence of blue or green colour. The presence of triterpenoid is indicated by the presence of orange or purple colour.

II.3 Activity Test of Burn Wounds

II.3.1 Animals and Model Preparation

Male, in good health Sprague Dawley rats weighing 150-200 g and aged 8-10 weeks were selected, and they were acclimated in the research facility on the seventh day. All animals were kept in accordance with the animal care operating procedures approved by the study ethics committee at Ahmad Dahlan University (certificate no.022011029). They were given the regular pellet rat food and unlimited water. They were housed at ambient temperature in a polypropylene cage with a 12h light-dark cycle. Subcutaneously, rats were sedated with 0.02 mL of lidocaine solution (2%). Depilatory lotion was used to shave the skin on the dorsum. A deep, second-degree burn wound was made using a hot iron plate (dimension: 3x2x0.1 cm3) at the same temperature (warmed 5 minutes in boiling water) and put on the skin for 10 seconds with equal pressure.

II.3.2 Experimental Groups and Treatments

Second-degree burn model group, standard medicine (lanakeloid®)-treated group (dosage 1g/kg BW), and ethanolic leaves extract of *Artocarpus heterophyllus* Lmk. with doses of 94 mg/kg BW, 188 mg/kg BW, and 376 mg/kg BW were all randomly divided into five groups of five rats each. The profound second-degree burn was applied to all animal groupings. Lanakeloid® cream, which

contains 1% *Centella asiatica* phytosome, was used as the reference medication. The therapies were administered once a day for 14 days. The first application was made immediately following the injury. For 14 days, the negative control group received no therapy. The wound remained open following therapy.

II.3.3 Measurement of Mean Wound Area (% Recovery)

Every two days after treatment, the average wound area of all group rats was measured with a caliper. Using Eq. 2, the change in wound surface area (WSAday-x) on a given day was expressed as a percentage of the wound area on the first day of wound induction (WSAday-0).

$$\text{Recovery } (\%) = \frac{(WSA_{day\text{-}0} - WSA_{day\text{-}x})}{WSA_{day\text{-}0}} \times 100\% \quad (2)$$

II.3.4 Measurement of Burn-Wound Healing Time (Day)

Burn wound healing time is determined by the formula below

$$\text{Recovery each day } (\%) = \frac{\text{recovery on day } 14^{th}\ (\%)}{14\ (\text{day})} \times 100 \quad (3)$$

$$\text{Burn wound healing time (day)} = \frac{100\%}{\text{recovery each day } (\%)} \quad (4)$$

II.4 Statistical analysis

The data is presented as mean ± SD. Multiple group comparisons were carried out using one-way ANOVA with SPSS ver.26 software, followed by the Duncan test to find intergroup differences. $P < 0.05$ was regarded as statistically significant.

III. Results and Discussion

III.1 Extraction

Maceration method for 2x24 hours and 2 times re-maceration. Re-maceration tries to extract chemical components that were not extracted during the previous maceration cycle. The maceration results were concentrated using a rotary evaporator at a temperature of 70°C because the boiling point of ethanol is 78.73°C. The rotary evaporator works on the premise of evaporating solvent below its boiling point, preventing excessive temperatures from harming the chemical compounds contained within. The evaporation process is aided by the use of a vacuum pump, which causes the ethanol solvent to evaporate more quickly even when it has not yet reached its boiling point. The yield percentage of 27.64% was obtained from 900 grams of jackfruit leaf simplicia. The higher the yield percentage, the higher the concentration of bioactive chemicals recovered (Dewatisari, Rumiyanti and Rakhmawati, 2018).

A phytochemical test was performed to detect the qualitative content of chemicals in jackfruit leaf extract. The compounds tested included alkaloids, tannins, saponins, flavonoids, steroids and terpenoids. Phytochemical experiments on jackfruit leaf extract produced the results presented in table 1. The presence of flavonoids was detected by the appearance of a red-orange colour shift with the addition of Mg-HCl. The addition of Mg and HCl metals reduces the benzo-pyron nucleus present in the structure of flavonoids such as flavonols and flavonones, resulting in red or orange flavilium salts. Positive saponins were identified by a steady foam of approximately 10 minutes height of 1-10 cm. Saponins contain both hydrophilic and hydrophobic molecules. Saponins generate foam when shaken because the hydrophilic group attaches to water and the hydrophobic group binds to air. The addition of HCl 2 N seeks to improve the polarity of the hydrophilic groups, making the bonds more stable and the foam more stable (Susanty, 2014). The presence of steroid compounds was detected through the production of green color after the addition of Liebermann-Burchad reagent (acetic anhydride solution and concentrated sulfuric acid solution). When the solution is dropped on the drip plate, the addition of sulfuric acid produces a green colour. The colour is caused by the oxidation process in the steroid chemical group, which results in the creation of conjugated double bonds. The presence of tannins was identified as positive by a shift in color to blackish green. The presence of a covalent bond between Fe^{3+} ions and the oxygen atom of the OH group of tannin compounds causes the production of a black-green color, which releases H atoms and produces complex compounds (Tanaya, Retnowati and Suratmo, 2015).

Table 1. Phytochemical Screening of Jackfruit Leaf Extract

Phytochemicals	Result
Alkaloids	-
Flavonoids	+
Saponins	+
Triterpenoids	-
Steroids	+
Tannins	+

III.2 The Effect of Jackfruit Leaf Extract on Burn Wound

The burn wound healing test in this study was based on the effect of jackfruit leaf ethanol extract on burn wound area, burn healing percentage (% recovery), and burn healing time (Akhoondinasab, Akhoondinasab and Saberi, 2013). Tables (2) and (3) provide the findings of the average area of burns and the percentage of burn healing (% Recovery), and Figure 1 shows a graph of the percentage of burn healing.

Table 2. The effect of Jackfruit leaf extract on burns wound area

Group	Burn wound area (cm^2) (mean ± SD)							
	Observation day							
	0	2nd	4th	6th	8th	10th	12th	14th
Positive control	5.33±0.40	4.78±0.37	4.11±0.14	3.86±0.25	2.67±0.67	1.79±0.51	0.92±0.52	0.55±0.31
Negative control	5.34±0.22	4.83±0.27	4.47±0.35	4.16±0.25	3.78±0.14	3.37±0.25	2.51±0.54	1.25±0.34
G1(94mg/kg BW)	4.33±0.29	3.86±0.34	3.48±0.35	3.06±0,48	2.49±0.43	1.92±0.35	1.26±0.32	0.49±0.29
G2(188mg/kg BW)	4.01±0.67	3.57±0.64	3.16±0.67	2.72±0,53	2.19±0.44	1.71±0.38	1.07±0.29	0.54±0.26
G3(376mg/kg BW)	4.87±0.29	4.24±0.26	3.33±0.17	2.53±0.14	1.63±0.18	0.89±0.24	0.24±0.22	0

According to Table 2, the average burn wound area decreased from day 2 to day 14. In comparison to treatment groups I (G1) and II (G2), treatment group III (G3) performed the best. This is because the ethanol extract of jackfruit leaves in treatment group III (G3) at a dose of 376 mg/kgBW contains more secondary metabolites such as flavonoids, tannins, saponins, and steroids than treatment groups I (G1) and II (G2).

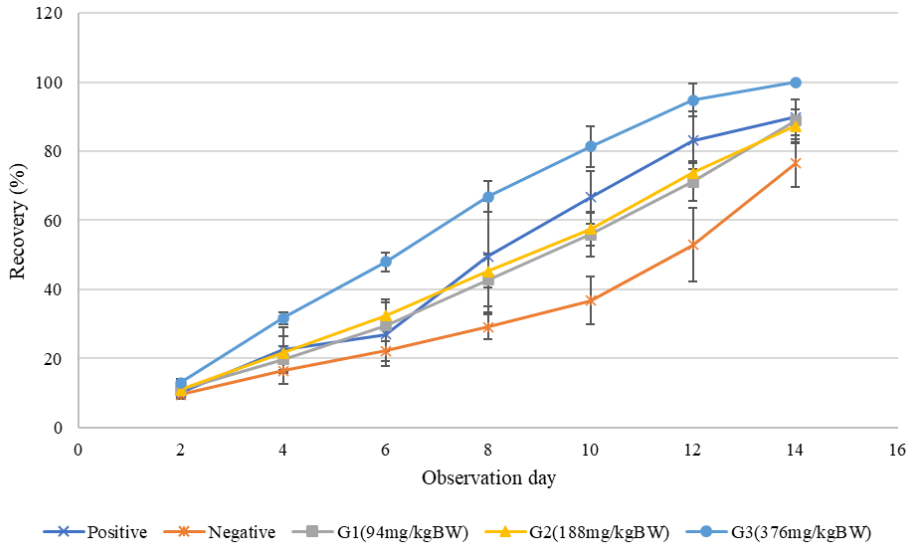


Figure 1. The effect of Jackfruit leaf extract on burns wound recovery (%)

Figure 1 shows that the average percentage of burn healing (% Recovery) in each group increased from day 2 to day 14. When compared to treatment groups I and II, treatment group III was the best. On the 14th day, the burns in treatment group III had been totally covered with a 100% recovery rate. The negative control had the lowest average percentage of burn recovery (% Recovery), which was 76.495 6.892%. This occurred because the negative control group had a longer length of granulation tissue production than the treatment group, hence the scab developed in the negative control group took longer than the other treatments. The occurrence of burn healing activity in negative controls is a normal phenomenon generated by the body's biocellular and biochemical processes (Solihah *et al.*, 2023).

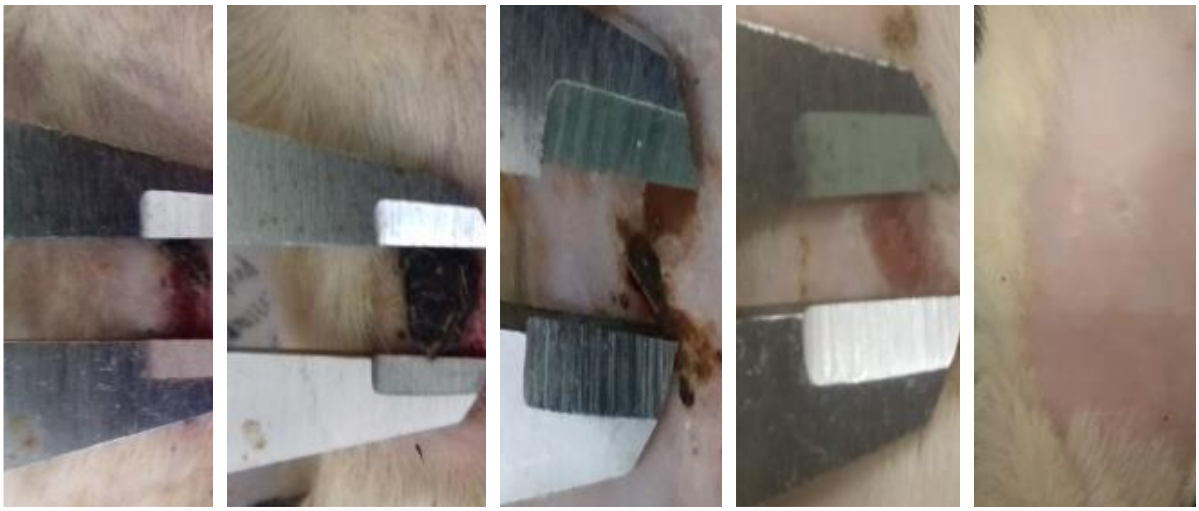
Table 2. The effect of Jackfruit leaf extract on burns wound area

Group	Burn-wound recovery (%) day 14th	Burn-wound recovery each day (%)	Time burn-wound recovery (day)
Positive control	89.91±5.18	6.42	15.57≈16
Negative control	76.49±6.89	5.46	18.30≈18
G1(94mg/kg BW)	88.78±6.30	6.34	15.77≈16
G2(188mg/kg BW)	87.21±4.86	6.23	16.05≈16
G3(376mg/kg BW)	100	7.14	13.99≈14

Group G3 had the fastest burn healing time. The healing period for positive control burns was the same for groups G1 and G2. The burn recovery period for the negative control is the longest. The difference in burn area on day 14 between group III and the positive group was slightly greater (figure 2) due to the secondary metabolite concentration in jackfruit leaf extract, which has a remarkable ability to accelerate burn wound healing when compared to the positive control. Saponins, flavonoids, tannins, and steroids are found in jackfruit leaves (Table 1).

Saponins, tannins, flavonoids, and steroid chemicals can act as antimicrobials and promote wound healing. Saponins have anti-bacterial properties that disrupt the cytoplasmic membrane and destroy bacterial cells. Saponins are also known to induce the production of new epithelial cells and to aid in the epithelialization process, reducing the size of wound-burns surface area (Florentina and Supriyanti, 2009). Tannins have astringent and anti-bacterial properties. Tannin compounds play a role in healing burns because of their proteolytic activity which effectively sheds necrotic tissue, prevents infection and stimulates the formation of granulation tissue in wounds through the activity of proteolytic enzymes which can remove dead tissue without damaging living cells (Roxas, 2013). Flavonoid compounds have antioxidant action (Anggraini, Mita and Ibrahim, 2015). Flavonoids and steroids as anti-inflammatories work by producing pro-inflammatory mediators that stimulate cells associated with inflammation, such as lymphocytes, monocytes, natural killer cells, neutrophils, macrophages and macrocytic cells (Cushnie and Lamb, 2005).

The antibacterial, anti-inflammatory, and antioxidant properties of the chemicals found in jackfruit leaf extract can speed up the healing process of burns. These chemicals work during the inflammatory phase by suppressing bacterial development, preventing infection and increasing the severity of the lesion. Furthermore, the chemicals in jackfruit leaf extract work in the early proliferative phase by promoting the creation of new tissue in the form of a scab and can potentially stimulate the regeneration of epithelial cells and tissues.



(Positive control) (Negative control) G1 G2 G3

Figure 2. Wound surface area on day 14th

The positive control with *Centella asiatica* extract contained triterpenoid components known as asiaticoside and related compounds (acetic acid and madecassiside). These triterpenoid compounds are beneficial as wound healers, anti-leprosy agents, and can boost macrophage activity. Lanakeloid-E® was employed as a positive control since it contains up to 10 mg of *Centella asiatica* extract (gotu kola) per gram of cream, which has been used to accelerate wound healing (burns, postoperative wounds, and

traumatic wounds). The capacity of gotu kola to treat wounds is related to the presence of asiaticoside, flavonoids, phenolics, essential oils, and saponins, which can stimulate collagen synthesis and cell renewal, hence accelerating burn healing (Sari, Munawaroh and Sofyanita, 2023).

IV. Conclusions

Based on the results of a study on burn healing from the ethanol extract of jackfruit leaves (*Artocarpus heterophyllus* Lmk.) on male white rats of the Sprague Dawley strain, it was concluded that saponins, tannins, flavonoids, and steroids contained in jackfruit leaf extract can accelerate the burns-wound healing. Treatment group 3 with dose 376mg/kg BW had the quickest burn healing time and the highest percentage of recovery. The therapeutic potential of jackfruit leaf extract in healing burns can be enhanced by the development of pharmaceutical formulations that improve phytochemical ingredient absorption and shorten burn healing time.

V. Acknowledgment

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VI. Conflict of Interest

The author declares that there no competing conflicts of interest.

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