HASIL CEK_Nanogel activity of java bark extract (lannea coromandelica (houtt.) merr.) as wound healing in diabetic rats

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Nanogel activity of java bark extract (*lannea coromandelica* (houtt.) merr.) as wound healing in diabetic rats

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Abstract. Java bark (*Lannea coromandelica* (Houtt.) Merr.) is used traditionally to heal wounds. In this research, nanogel made from Javanese wood bark extract (EKBKJ) was tested to see its ability to heal wounds in diabetic mice. EKBKJ nanogels were made in three different concentrations: 1%, 4%, and 7%, and tested to see their physical properties such as particle size, pH, dispersing ability, and adhesiveness. The EKBKJ nanogel activity test was carried out on six groups of mice for 14 days by monitoring the level of wound healing and visual appearance of the wound. The results showed that the three types of EKBKJ nanogel met nanogel quality standards, with 1%, 4%, and 7% nanogel able to heal wounds better than gel base in diabetic mice ($p<0.05$). Furthermore, 1% EKBKJ nanogel showed significantly higher healing rate compared with 4% and 7% EKBKJ nanogel. Thus, it can be concluded that 1% EKBKJ nanogel has a better effect on healing diabetic wounds.

1 Introduction

Diabetes mellitus is a non-communicable disease (NCD) that is characterised by disturbances in the metabolism of the body. Diabetes mellitus is caused by an increase in the level of glucose in the blood that exceeds the normal limits [1]. Based on the global prevalence of diabetes in people aged 20-79 years of 10.5% (536.6 million people) in 2021, it will increase to 12.2% (783.2 million people) by 2045 [2]. In addition, data from the International Diabetes Federation (IDF) in 2021 states that Indonesia ranks 5th in the world with the highest number of diabetics. This indicates that diabetes is a disease caused by uncontrolled blood glucose, which has the potential to cause diabetic wounds [3]. Diabetic wounds that are not treated properly can lead to infection, which causes the wound to become larger and, as it gets worse, can make it harder for the wound to heal and can even lead to amputation [4]. So far, the treatment of diabetic wounds using chemical drugs is still less effective because it has a higher risk of side effects, so this is the basis for the need for other alternative treatments, namely using herbal plants that have a lower risk of side effects [5].

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One of the herbs used empirically for the treatment of internal and external wounds is the stem of Kayu Jawa (*Lannea coromandelica* (Houtt.) Merr.) [6]. A study by Calsum et al. (2018) reported that Java bark extract can be used as a wound healer [7]. The bark of Java contains compounds such as flavonoids, saponins, and tannins, which play an important role in the healing of wounds [8]. Flavonoid compounds play a role by stopping bleeding through the mechanism of vasoconstriction of blood vessels, free radical scavengers, inhibitors of enzymatic hydrolysis and oxidation, and anti-inflammatory. Saponin compounds work by increasing the rate of epithelialization, while tannin compounds act as astringents in wounds [7].

Many researchers, including the development of nanotechnology, have conducted research related to the efficacy of herbal medicines. According to some research, the mechanism of action of nanotechnology can help to optimize the physicochemical properties of herbal medicines, and one of them is in the form of nanogel preparations [9]. Our study in line with one of the agendas of Sustainable Development Goals (SDG's) were to ensure healthy lives and promote well-being for all, at all ages. To promote well-being we propose the nanogel as the alternative of wound healing.

Nanogel is a gel preparation that contains nano-sized active ingredients [10]. The presence of nano-sized active ingredients can facilitate the absorption of drugs into the body [11]. Furthermore, gel preparations have excellent stability, are non-sticky, have a cooling effect on the skin and are aesthetically preferred. Nanogel preparations can also accelerate the wound healing process. They can therefore be used as wound dressings to protect wounds from contamination [12, 13].

Therefore, the aim of this research is to determine the activity of the nanogel of the bark extract of java (*Lannea coromandelica* (Houtt.) Merr.) as a wound healing agent in diabetic rats. The results of this research are expected to provide the basis for the development of diabetic wound dressings from effective natural ingredients.

2 Material and Methods

2.1 Tools and materials

The tools used were a set of glassware (Iwaki®), a vernier caliper (Vernier Caliper®), a set of surgical tools (Arugamed®), a blender (Miyako®), a glucometer (Accu-Chek®), a pH meter (Lutron Digital®), a magnetic stirrer (Thermo Scientific®), a biopsy punch (Ribbel®), a rotary evaporator (IKA®), and an analytical scale (Kern-Germany®).

The materials used were Java bark obtained from Nangahale Village, Talibura, Sikka, East Nusa Tenggara Indonesia, 1% acetic acid (Merck®), 0.9% NaCl solution (Otsu-NS®), Na-CMC (Sigma-Aldrich®), Na-tripolyphosphate (Sigma-Aldrich®), chitosan (Sigma-Aldrich®), propylenglycol USP (DOW®), alloxan monohydrate (Sigma-Aldrich®), 70% ethanol (Onemed®), aqudest (Onemed®), ketamine (Pfizer®), and bioplacenton (Kalbe®).

2.2 Determination of the plant and pollination

The bark of the Javanese was identified at the Laboratory of Pharmacognosy, Ahmad Dahlan University. The Javanese bark was then dried and pulverised using a blender to obtain dry Simplisia powder [7].

2.3 Extracting and screening phytochemicals from Java Bark extracts

In total, 500g of Javanese bark powder was extracted with 70% ethanol for 3x24h. The maceration results were concentrated using a rotary evaporator to obtain a thick extract and weighed to calculate the yield [5].

2.3.1 Flavonoid test

An extract of 2 mL was heated for 5 minutes. Then 0.1 g of Mg metal and 3 drops of concentrated HCl are added. If both solutions form an orange to red colour, the test is positive for flavonoids.

2.3.2 Alkaloid test

5 mL of the extract was mixed with 5 mL of 1% HCl, homogenised and filtered. 1 mL of the filtrate is added to each test tube, followed by Wagner's reagent and Dragendorff's reagent. The presence of brown precipitates in Wagner's reagent and reddish brown precipitates in Dragendorff's reagent indicates the presence of alkaloids.

2.3.3 Saponin test

Extract to 1 mL and add 1 mL of distilled water. Then shake. Positive results contain saponin compounds if foam is formed.

2.3.4 Tannin test

Place the figure as close as possible after the point where it is first referenced in the text. If there is a large number of figures and tables, it might be necessary to place some before their text citation.

2.4 Preparing Java Bark Extract nanoparticles

The preparation of nanoparticles of Java bark extract was in accordance with the formulation in Supplementary Table 1.

The Java bark extract-chitosan nanoparticles were prepared by mixing Java bark extract with chitosan and Na-tripolyphosphate in ratio of 0.6:1:1. 2% chitosan was incorporated into the extract dropwise by stirring with a magnetic stirrer at 500 rpm for 90 min. Then 0.07% Na-tripolyphosphate solution was added dropwise and stirred at 500 rpm for 90 minutes until a nanoparticle solution was formed. The resulting nanoparticles were then subjected to a PSA (particle size analyser) test to see the particle size distribution [5].

2.5 Formulation of Java bark extract nanogel preparation

A total of 0.02 g of nipagin was dissolved in distilled water heated to 80 0C. Na-CMC, propylenglycol and glycerine were added to the solution until a gel was formed (Supplementary Table 2). The nanoparticle solution was then added to the gel and stirred until homogeneous. The mixture was then placed in a container and stored overnight in a cool location. The finished Java bark extract nanogel preparation was evaluated by organoleptic testing, pH testing, adhesion testing and spreadability testing [15].

2.5.1 Organoleptical test

Organoleptical observations were made in the form of visual observations of the odor, color, and consistency of the nanoparticle gel of Java bark extract [16].

2.5.2 Scatterability test

The spreadability test was carried out by weighing 1 g of nanogel and placing it in the center of the glass of the spreadability test device. Then covered with another glass for 1 minute and each has known weight. The gel that spread then measured the average diameter of the 4 sides. Then the nanoparticle gel was given a weight of 150g, and allowed to stand for 1 minute and measured its diameter. The spreadability of the gel was calculated using the formula 1.

$$S = \frac{m \; x \; l}{t} \qquad (1)$$

Description:
S = spreadability (g.cm/sec)
m = weight of the load (150 g load + cover glass) = diameter after 1 minute (cm)
t = time (seconds) [16].

2.5.3 pH test

A total of 0.5 g of nanogel was diluted with 5 mL of distilled water and then measured the pH using a pH meter.

2.5.4 Adhesion test

A total of 0.5 g of nanogel was placed on a glass, then covered using another glass with a predetermined area. The nanogel was pressed using a 1 kg weight for 5 minutes and then released. The glass is installed on the test device until both glasses are released and the time is recorded [17].

2.6 The test animal

This study used male Wistar rats weighing between 200-250 g obtained from LPPT UGM. Rats were maintained in the Pharmacology Laboratory with room temperature 23-25ºC, humidity 60-70% with light intensity 12 hours light and 12 hours dark.

2.7 The test animal treatment

The treatment of test animals in this research has been approved by the Ahmad Dahlan University Research Ethics Committee (KEP) with No. 012206063. A total of 30 rats were adapted for 7 days and then the rats were randomly divided into 6 groups. Rats from all groups (except Normal) were injected with alloxan monohydrate at a dose of 120 mg/kgW subcutaneously. After 3 days, blood sugar levels were measured (Table 1). Wound treatment is done if blood sugar levels > 200 mg/dL [5].

Table 1. Treatment group of test animals

Group	Treatment
Normal	Non-diabetic rats and treated with gel bases (normal) Bases Diabetic rats and treated with gel bases (negative control)
Bases	Diabetic rats and treated with bioplacenton (positive control)
Bioplacenton	Diabetic rats and treated with 1% Java bark extract nanogel
Nanogel 1%	Diabetic rats and treated with 4% Java bark extract nanogel
Nanogel 4%	Diabetic rats and treated with 7% Java bark extract nanogel
Nanogel 7%	Non-diabetic rats and treated with gel bases (normal) Bases Diabetic rats and treated with gel bases (negative control)

Mice were anesthetized before and during wound excision by intramuscular injection of ketamine (20 mg/KgW) and shaved. Then the skin was smeared with 70%b/v alcohol and then wounded with a biopsy punch with a length of 10 ± mm and a depth of 2 ± mm in the dorsal area parallel to the vertebral os. Wounds in rats were given preparations as much as 100 mg according to each group topically. Administration of the preparation was carried out twice a day at 09.00 and 16.00 WIB. Observations were made for 14 days by measuring the diameter of the wound and macroscopic observations of the wound [18]. On days 1, 3, 5, 7, and 14 after wound excision, rats in each group were measured for wound diameter. The percentage of wound healing was calculated using formula 2.

$$\text{Wound healing (\%)} = \text{wound diameter (Day 1} - \text{Day (n))/ Wound diameter Day 1} \times 100\% \quad (2)$$

2.8 Data analysis

Data from the measurement of wound healing percentage were statistically analyzed using the Kruskal-Wallis test. Then continued with the Mann-Whitney test using the IBM SPSS software program version 25. Significance was determined if $p<0.05$.

3 Results and Discussion

3.1 Java bark extract yield and phytochemical screening

The extract of Java bark obtained in this research amounted to 240.8 g with a yield of 15.05%. The results of phytochemical screening of Java bark extract showed positive for flavonoids, saponins, and tannins (Table 2). This is in accordance with the research of Fitriyanti et al. (2019) that Java bark contains flavonoids, saponins, and tannins [19].

Table 2. Treatment group of test animals

Phytochemical test		Color	Research result
Flavanoids	Ethanol 70% + ammonia vapor	Orange	Positive
	AlCl3	Yellow	Positive
Sapponin	HCl	Bubbly	Positive
Alkaloid	Mayer	No sediment	Negative
	Wegner		Negative
	Dragendrof		Negative
Tannin	Fecl3	Blackish blue	Positive

3.2 Characteristic of nanoparticles of Java bark extract

Synthesis of nanoparticles of Java bark extract coated with chitosan using ionic gelation technique method. The addition of sodium tripolyphosphate (Na-TPP) aims as a cross linker with chitosan. This method is used because it has the advantage of simple and lightweight preparation without heating and without the use of organic solvents. The mechanism of this method is the electrostatic interaction between the amine group on chitosan which is positively charged with the negative charge group on Na-TPP [20].

Nanogel of Java bark extract was characterized using PSA (particle size analyzer) test which was conducted after the nanoparticles of Java bark extract were obtained. The particle size result of 343.5 nm shows that the nanoparticles of Java bark extract have a uniform or homogeneous particle size distribution [16]. This is supported by the polydispersity index value of 0.457. Dipahayu and Kusumo (2021) state that a polydispersity index (PDI) of <0.5 indicates a narrow range of size diversity of dispersed particles and indicates good particle size distribution. Nanoparticles with PDI values > 1 have a very wide size distribution and contain large particles or aggregates that can undergo sedimentation [21].

3.3 Evaluation of Java bark extract nanogel preparation

The results of organoleptical observations of all nanogel preparations have different viscosities. The higher the extract concentration, the thicker the nanogel preparation obtained, and the color of the preparation will be redder with increasing extract concentration. The resulting nanogel has a distinctive odor such as a sweet aroma derived from the aroma of Java bark extract.

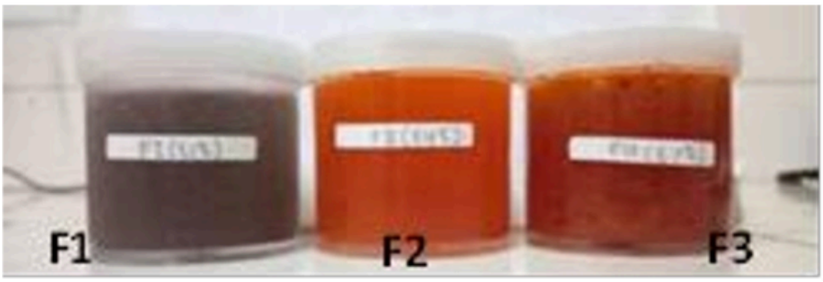

Fig. 1. Results of nanogel 1%, nanogel 4%, and nanogel 7%

Table 3. Evaluation and result of Java bark extract nanogel preparations

Formula	Organoleptic	Test pH	Spreadabillity (cm)	Test Adhesion (second)
F1	Faded, characteristic odor, thick	4.52	5.35	07.77
F2	Orange red, characteristic odor, thick	5.09	5.5	07.34
F3	Red, characteristic odor, thick	4.59	5.0	06.39

The pH test results in all formulas have a pH range that is suitable for topical use, because the formula meets the requirements for good skin pH acceptance, which is in the pH interval 4.5-6.5 [22]. The results of the spreadability test of the three nanogels showed that the nanogels had good spreadability on the skin because they were in the range of 5-7 cm. Nanogels in this range are expected to spread easily when applied, so as to expand the contact surface between nanogels and skin (Table 3) [23].

The adhesion test results of the three Java bark extract nanogel preparations produced also meet the requirements of > 4 seconds, so the nanogels produced are able to adhere well to the skin. Judging from the results of the preparations obtained, formula 1 has better adhesion, so it can be said that the lower the concentration, the higher the adhesion [24].

3.4 Nanogel activity test of Java bark extract on diabetic wounds in rats

Diabetic wounds of rats are carried out by administering alloxan. Alloxan is one of the diabetogenic agents that can damage **pancreatic beta cells, thereby reducing insulin levels** and increasing blood sugar levels [25]. Figure 2 shows rats that have significantly increased blood sugar levels when compared to before alloxan injection.

Macroscopic observation of the wound on day 14 showed that the normal group of rats given the gel bases showed dry, non-festering, non-red, and non-swollen wounds. This indicates that the wound has begun to close completely (heal). In addition, Figure 4 shows that the normal group had the greatest percentage of wound healing and healed significantly faster than the diabetic rat group. Wound healing in normal conditions is faster due to normal blood sugar levels which make there are no barriers to nutrition, oxygen, and resistance to infectious bacteria in wound healing [26].

The results of the calculation of the percentage of wound healing **on days [29], 5, 7, and 14**, as well as macroscopic observations of the wound are shown in Figure 4. The group of diabetic rats treated with 1% Java bark extract nanogel showed that the wound was dry and not festering, but still slightly red compared [28] the Bioplacenton group. The 1% Java bark extract nanogel has the potential to accelerate diabetic wound healing because the percentage of wound healing in the 1% Java bark extract nanogel group was significantly higher on days 5, 7, and 14 compared to the group of diabetic rats given gel bases, nanogel 1% and nanogel 7%.

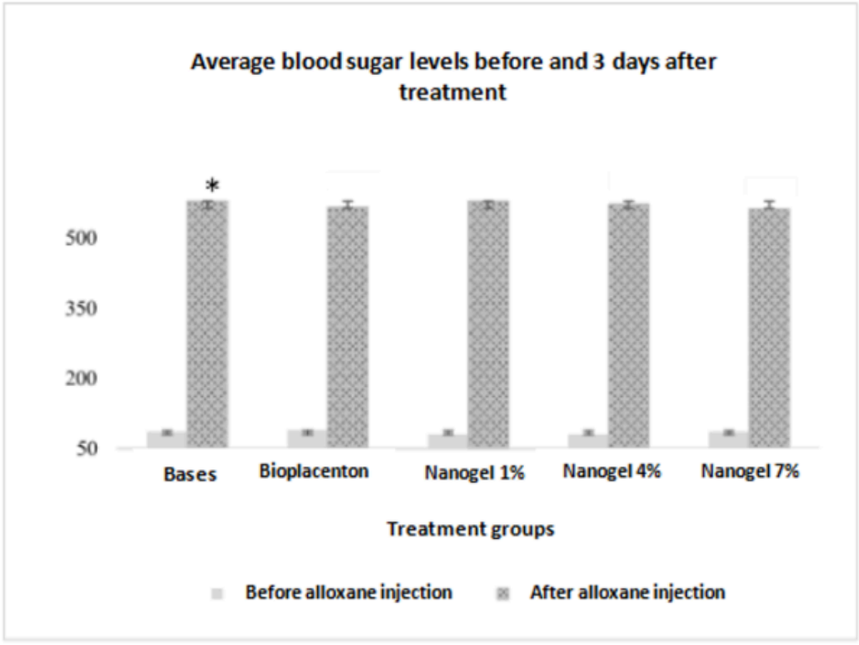

Fig. 2. Comparison of the average blood sugar levels (mg/dL of mice before and 3 days after alloxan injection (* = significantly from before alloxan injection).

Chitosan-based Java bark extract nanogel preparation has the advantage of helping in controlling the release activity of mediators and inflammatory cells, thus creating suitable conditions for wound healing.

The mechanism of chitosan as a nanoparticle carrier agent will be degraded gradually which will then increase angiogenesis, stimulate fibroblast proliferation, and collagen deposition at the wound site which accelerates the wound healing process. The antibacterial properties of chitosan also help in managing infections in chronic wounds such as diabetic wounds [27].

The flavonoids, saponins, and tannins in Java bark have antibacterial, anti-inflammatory, and wound healing activities [15]. Flavonoid compounds play a role by stopping bleeding through the mechanism of vasoconstriction of blood vessels, counteracting free radicals, inhibiting enzymatic hydrolysis and oxidation, and anti-inflammatory. Saponin compounds work by increasing the rate of epithelialization, while tannin compounds function as astringents in wounds [7].

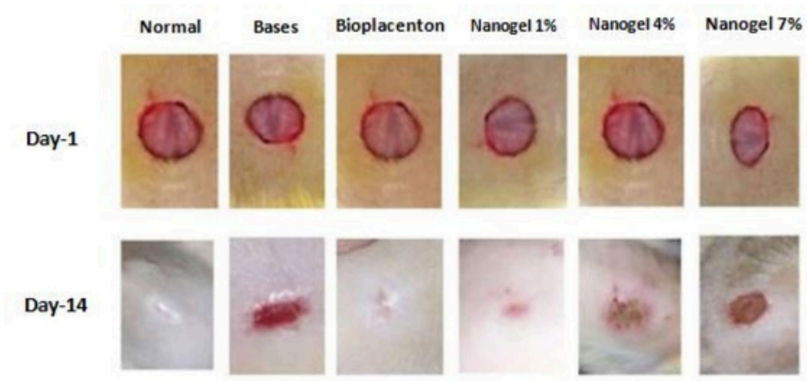

Fig. 3. Macroscopic appearance of wounds on day 1 and day 14 in the normal group (non-diabetes), bases (diabetes), bioplacenton (diabetes), nanogel 1% (diabetes), nanogel 4% (diabetes) and nanogel 7 % (diabetes).

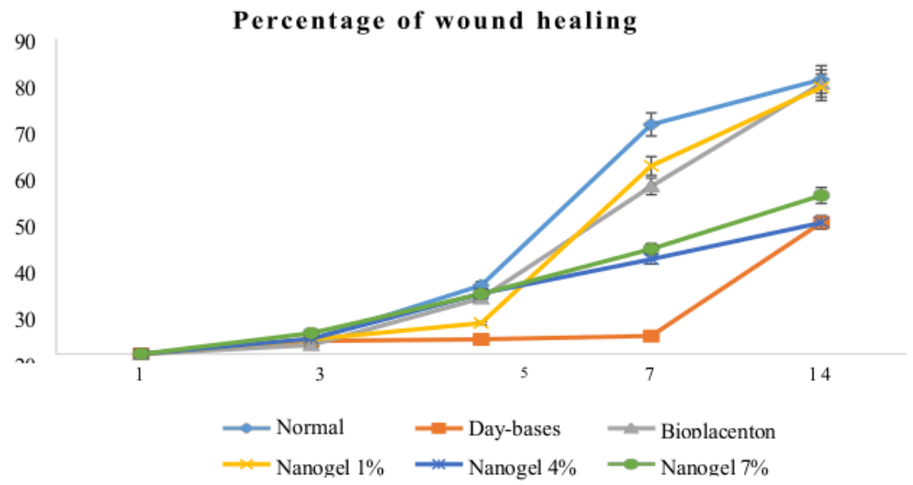

Fig. 4. Graph of the percentage of wound healing on days 1, 3, 5, 7, and 14 in the normal, bases, Bioplacenton, nanogel 1%, nanogel 4% and nanogel 7% groups. Day-Bases

4 Conclusion

Our study highlights that the nanogel of Java bark extract is not only fulfil the requirements as good nanoparticle size but also for a gel preparation with good pH, spreadability and adhesion.

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Data availability statement
Data will be made available on request.

Declaration of competing interest
The authors disclose no conflict.

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