

Test of the Effectiveness of Rose Apple Leaf Ethanol Extract (*Syzygium aqueum*) on the Healing of Cut Wounds in White Rabbits (*Oryctolagus cuniculus*)

Uji Efektivitas Ekstrak Etanol Daun Jambu Air (*Syzygium aqueum*) Terhadap Penyembuhan Luka Sayat Pada Kelinci Putih (*Oryctolagus cuniculus*)

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Abstract

Cut wounds, physical damage to the skin often caused by sharp instruments, require alternative treatments. This study aims to evaluate the effectiveness and determine the optimal concentration of water apple leaf (*Syzygium aqueum*) ethanol extract in accelerating the healing of cut wounds. Rose apple leaves are known to be rich in bioactive compounds such as flavonoids, alkaloids, and tannins, which have the potential to be wound healing agents. Extraction was carried out using the remaceration method with 96% ethanol for three days, and the extract was then formulated into concentrations of 5%, 10%, and 20%. Effectiveness tests were carried out on incision wounds on the backs of rabbits. The results showed that the healing time was inversely proportional to the extract concentration. The treatment group with a concentration of 5% healed on the 13th day, the concentration of 10% on the 12th day, while the concentration of 20% showed the highest effectiveness among all extract groups, with healing on the 10th day. Statistical analysis using the One Way ANOVA test ($p=0.000$; $p<0.05$) showed a significant difference between treatment groups. The higher the concentration of rose apple leaf ethanol extract, the faster the healing process of the incision wound, but the effectiveness of the 20% extract was still lower than the positive control (Bionet Cream), which healed the wound faster (10 days vs. 10 days) through a different mechanism, so further research is needed to compare their effectiveness statistically.

Keywords: Rose apple leaf, Effectiveness, Rabbit, Incision, Best concentration.

Abstrak

Luka sayat, kerusakan fisik pada kulit yang sering disebabkan oleh instrumen tajam, memerlukan alternatif penyembuhan. Penelitian ini bertujuan mengevaluasi efektivitas dan menentukan konsentrasi paling optimal dari ekstrak etanol daun jambu air (*Syzygium aqueum*) dalam mempercepat penyembuhan luka sayat. Daun jambu air diketahui kaya akan senyawa bioaktif seperti flavonoid, alkaloid, dan tanin, yang berpotensi sebagai agen penyembuh luka. Ekstraksi dilakukan melalui metode remaserasi dengan etanol 96% selama tiga hari, dan ekstrak kemudian diformulasikan menjadi konsentrasi 5%, 10%, dan 20%. Uji efektivitas dilakukan pada luka sayat di punggung kelinci. Hasil menunjukkan bahwa waktu penyembuhan berbanding terbalik dengan konsentrasi ekstrak. Kelompok perlakuan dengan konsentrasi 5% sembuh pada hari ke-13, konsentrasi 10% pada hari ke-12, sedangkan konsentrasi 20% menunjukkan efektivitas tertinggi di antara semua kelompok ekstrak, dengan penyembuhan pada hari ke-10. Analisis statistik menggunakan uji One Way ANOVA ($p=0,000$; $p<0,05$) menunjukkan adanya perbedaan signifikan antar kelompok perlakuan. Semakin tinggi konsentrasi ekstrak etanol daun jambu air, semakin cepat proses penyembuhan luka sayat yang terjadi, namun efektivitas ekstrak 20% masih lebih rendah dibandingkan kontrol positif (Bionet Cream) yang menyembuhkan luka lebih cepat (10 hari vs 10 hari) melalui mekanisme berbeda, sehingga diperlukan penelitian lanjutan untuk membandingkan efektivitasnya secara statistik.

Kata Kunci: Daun jambu air, Efektivitas, Kelinci, Luka sayat, Konsentrasi terbaik.



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Introduction

A wound is physical damage caused by the opening or destruction of the skin, resulting in an imbalance in the function and anatomy of normal skin. Wounds occur due to damage or loss of body tissue caused by factors that disrupt the body's protective system, such as trauma, extreme temperatures, chemicals, electric shocks, or animal bites. One example of an open wound is an incision/cut wound, where there is a linear tear in the skin and underlying tissue. A cut wound is a wound caused by being cut by a sharp instrument, and the characteristics of a cut wound are that it is open, painful, and longer than it is deep [1]. Slow wound healing not only interferes with quality of life but can also lead to serious complications. Therefore, effective alternative therapies are needed to accelerate the healing process.

One plant used as a medicinal plant is rose apple leaves (*Syzygium aqueum*), which have wound healing properties. Rose apple leaves are commonly used by the community as an antibacterial, antiseptic, cholesterol treatment, face mask, skin smoothing agent, and to treat cuts [2]. Previous research has shown that rose apple leaves contain flavonoids, alkaloids, tannins, saponins, and phenolics [3].

Flavonoids have antimicrobial and astringent properties in wound contraction, which accelerate the wound healing process [4]. Alkaloids function to fight microbial infections by disrupting the components of peptidoglycan in bacterial cells, preventing the cell wall from forming completely and causing cell death [5]. Tannins in rose apples have antiseptic properties that prevent bacterial growth [6]. In addition, they are also useful as antioxidants that work by inhibiting lipid peroxides and stimulating angiogenesis, which is part of the wound healing process [7]. Saponins have bacteriostatic properties that work by damaging the cell membrane structure and can stimulate collagen growth in the wound healing process [6].

Based on the above description, the researcher was interested in conducting a study entitled Testing the Effectiveness of Ethanol Extract of Rose Apple Leaves (*Syzygium aqueum*) on the Healing of Cut Wounds in White Rabbits (*Oryctolagus cuniculus*) with concentrations of 5%, 10%, and 20%. The purpose of this study is to determine the effectiveness and identify the optimal concentration of *Syzygium aqueum* leaf ethanol extract on the healing of incision wounds in white rabbits (*Oryctolagus cuniculus*) at concentrations of 5%, 10%, and 20%.

Experimental Section

Materials and Apparatus

The equipment used in this study included rabbit cages with food and water (Flow Small®), sterile surgical blades (Gea®), razor blades (Gea®), analytical scales (Kenko®), water baths (Memmert®), mortars and pestles (Kenko®), rotary evaporators (Biobase®), metal spatulas (Gea®), glassware (Pyrex®), flannel cloth, aluminum foil, and ointment pots.

The materials used in this study were rose apple leaf simplisia (*Syzygium aqueum*), hyaluronic acid (Bionect Cream®), 96% ethanol, ethyl chloride, 70% alcohol, 0.5% CMC-Na, distilled water, and white rabbits (*Oryctolagus cuniculus*). Bionect Cream® contains 0.2% hyaluronic acid as the active ingredient, and white rabbits (*Oryctolagus cuniculus*). Bionect Cream is used as a positive control because its hyaluronic acid content has been scientifically proven to accelerate wound healing by stimulating fibroblast proliferation, collagen synthesis, and epithelial regeneration during the inflammatory and proliferative phases [8].

Determination

Determination was carried out to identify the type and ensure the accuracy of the sources used [9]. Determination was carried out at the Pharmaceutical Biology Laboratory of Ahmad Dahlan University.

Production of Powder and Ethanol Extract from Rose Apple Leaves

Rose apple leaves are sorted between good rose apple leaves (*Syzygium aqueum*) and poor ones. Wet sorting is carried out. The rose apple leaves are then dried in a drying cabinet at a temperature of 30-40 °C for 3 hours (this can be repeated if they are not yet dry). After drying, dry sorting is carried out, the dry weight is weighed, then ground into powder and sieved with a 30 mesh sieve [10]. Extraction of rose apple leaves was carried out using the remaceration method for 3 days, using 300g of powdered simplisia and 1000ml of 96% ethanol placed in a dark glass container and then tightly closed. The mixture was left for 24 hours while stirring occasionally, then filtered using flannel cloth. The remaceration process was repeated twice with the same solvent, then all the extracts were combined and evaporated using a vacuum rotary evaporator at a temperature of 50 oC and 100rpm, followed by a water bath. The thick extract obtained was stored in a salep pot.

Phytochemical Screening

Flavonoid testing 0.05 mg of sample was reacted with 2 mL of hot water, boiled for 5 minutes, then filtered. The filtrate was added with 0.05 mg of Mg powder and 1 mL of concentrated HCl, shaken until homogeneous. A positive flavonoid result is indicated by an orange, yellow, or red color [11]. Alkaloid testing 0.05 mg of sample is reacted with 5 drops of Dragendroff's reagent. A positive alkaloid result is indicated by a red to orange precipitate [12].

Tannin testing A total of 0.05 mg of sample is mixed with 5% FeCl₃ and homogenized. A positive result for tannin is indicated by a greenish-black or bluish-black color [12]. Saponin Test: 0.05 mg is mixed with 2 drops of HCl and shaken until homogeneous. A positive saponin result is indicated by the formation of stable foam for 7 minutes [12]. Phenolic Testing 0.05 mg of the sample is reacted with 0.75 mL of Follin-Ciocalteru reagent, left to stand for 8 minutes, then 0.75 mL of 7.5% Na₂CO₃ is added. A positive phenolic result is indicated by the formation of a blue color [12].

Preparation of Test Animals and Creation of Incision Wounds

The test animals used were three rabbits (*Oryctolagus cuniculus*) aged 2-3 months and weighing 1.5-2 kg. The test animals were acclimatized in the laboratory for 7 days with daily weight monitoring [10]. Before wound creation, the rabbits' back fur was shaved and cleaned with 70% alcohol cotton. The rabbits' backs were anesthetized using ethyl chloride, then 5 incisions ±2 cm long and ±0.1 cm deep were made in the back area parallel to the spine (*os. Vertebra*) using a scalpel.

The number of test animals in this study was limited to only three rabbits, each of which had five incisions made on their backs. This design was chosen to minimize the use of animals in accordance with the 3R principle (Replacement, Reduction, and Refinement). However, this design falls into the category of repeated measures because several incisions were made on the same individuals, so that the incisions were not completely independent. The statistical analysis using One Way ANOVA in this study only provides a general overview of the differences between treatments and does not fully reflect independent comparisons.

Data analysis

The measurement of incision length was analyzed based on the average percentage of wound healing using SPSS, with a One Way Anova test followed by a Post-Hoc Tukey HSD test [13].

Results and Discussion

Research Ethics

In the initial stage, research ethics were established, which are provisions stating that this research is feasible. In this study, research ethics were issued by the Harapan Bangsa University Ethics Commission No. B.LPPM- UHB/1048/11/2024. Next, the plant to be used in this study was identified, namely rose apple leaves (*Syzygium aqueum*). This step aimed to verify that the material used was indeed rose apple leaves, so that there would be no errors when collecting the material [9].

Results of Powder and Ethanol Extract Production from Rose Apple Leaves

The production of rose apple leaf simplisia begins with the selection of good leaves that are dark green and fresh because they have higher active compound content [14]. A total of 2 kg of leaves were wet sorted to separate impurities and foreign matter, then washed with running water and drained immediately to reduce the water on the leaf surface [15]. After draining, the rose leaves are thinly sliced to speed up drying. Drying is carried out in a drying cabinet at a temperature of $\leq 60^{\circ}\text{C}$ to reduce moisture content, prevent damage, and stop enzymatic activity and microorganism growth. Temperatures above 60°C can damage secondary metabolites such as flavonoids [16].

Dried rose apple leaves were dry-sorted to ensure they were free of foreign matter, then ground with a blender to expand the surface area of the particles and facilitate the extraction of active compounds [17]. A total of 600 grams of simplisia powder was obtained. The extract was prepared using the remaceration method, which involves soaking the simplisia in a solvent that is replaced every day to extract the remaining active compounds [18]. This method is simple and effective, but it is time-consuming and requires a lot of solvent [19]. A total of 300 g of rose apple leaf powder was soaked in 96% ethanol for 24 hours at room temperature. 96% ethanol was chosen because it is selective, non-toxic, and capable of extracting non-polar to polar compounds and producing a more concentrated extract [20]. Stirring was performed occasionally to prevent solvent saturation [21].

After filtration, the process was repeated twice with the same solvent for a total of 3 days. The maserate obtained was evaporated with a vacuum rotary evaporator at a temperature of 40°C , then continued with a water bath until a thick extract was formed. Evaporation using a water bath until a thick extract is formed. This evaporation keeps the active compounds stable and prevents damage due to excessive heat [22]. Yield reflects the amount of bioactive content extracted; the higher the yield, the more substances are successfully extracted [23]. The ethanol extract yield of rose apple leaves was 14.71%, which meets the minimum standard for thick extracts of 10% and is in line with previous research of 15.36% [7]. Extraction results are influenced by variety, growing location, temperature, solvent type, extraction method, and particle size of the crude drug [24].

Phytochemical Screening

The study involved analyzing metabolite compounds from rose apple leaves through phytochemical screening, which included testing for flavonoids, alkaloids, tannins, saponins, and phenolics, as shown in Table 1.

Table 1. Results of Phytochemical Screening of Rose Apple Leaf Extract

Compound Groups	Reagent	Test results	Description
Flavonoids	Mg metal and 1 mL concentrated HCl	(+)	Orange color formed
Alkaloids	5 drops of Dragendorff's reagent	(+)	Orange-colored sediment formed
Tannins	FeCl_3	(+)	Blue-black color formed
Saponins	10 mL hot water + HCl	(+)	Foam present after solution is shaken
Fenolics	Follin-Ciocalteu reagent + 7.5% $\text{Na}_2\text{CO}_3\text{CO}$	(+)	Blue color formed

The phytochemical screening results showed that the ethanol extract of rose apple leaves (*Syzygium aqueum*) contained flavonoids, alkaloids, tannins, saponins, and phenolics, in line with previous studies [3]. The flavonoid content was confirmed by the appearance of an orange color due to the formation of a complex between magnesium ions and flavonoid compounds during the reaction process [25]. The alkaloid content was indicated by the formation of an orange precipitate. This color appeared due to a complex reaction between alkaloids and metal ions from the Dragendorff reagent. HCl is used in reagents to prevent the hydrolysis of Bi^{3+} ions and help form stable complexes [26]. Bi^{3+} ions from bismuth nitrate are stabilized by HCl reacting with KI to form a BiI_3 precipitate, which dissolves in excess KI to form an orange-colored $\text{K}[\text{BiI}_4]$ complex. In the Dragendorff test, nitrogen in the alkaloid binds with Bi^{3+} in the $[\text{BiI}_4]^-$ complex, producing an orange color as an indicator of the presence of alkaloids [27].

Test results show that ethanol extract of rose apple leaves (*Syzygium aqueum*) positively contains tannins, indicated by a blue-black color due to the complex between Fe^{3+} ions and tannin phenolic groups

[28]. The extract also positively contains saponins, indicated by stable foam for 7 minutes. The foam is formed due to the amphipathic nature of saponins, and its stability is enhanced by the addition of 2N HCl, which strengthens the bonds of the hydrophilic groups and the micelle structure [7]. Additionally, test results showed that the ethanol extract of rose apple leaves (*Syzygium aqueum*) positively contained phenolics, indicated by a deep blue color. This color appears due to the reaction between the phenolic hydroxyl group and the follin-ciocalteu reagent. The addition of 7.5% Na₂CO₃ creates an alkaline environment that activates the phenolic group into phenolate ions, accelerating the reaction and stabilizing the blue color[29].

The Healing Effects of Ethanol Extract of Rose Apple Leaves on Incision Wounds in Rabbits

Before macroscopic observation, topical treatment was administered according to the experimental group. Each incision wound was applied with 0.1 g of the preparation, either in the form of 5%, 10%, and 20% ethanol extract of rose apple leaves (*Syzygium aqueum*); Bionect Cream as a positive control; or 0.5% CMC-Na gel as a negative control. The treatment was administered twice daily (morning and evening) for 14 consecutive days. During the treatment period, the rabbits were placed in separate cages with controlled temperature and humidity, and the wounds were observed daily to record changes in color, scab formation, and the rate of wound closure.

Macroscopic observations were conducted over a period of 14 days, monitoring physical changes in the treatment area daily from day 1 to day 14 in each treatment group. When skin tissue is injured, the healing and cell regeneration process occurs automatically as a physiological response of the body. The wound healing process occurs in three main phases, namely: the inflammatory phase, the proliferation phase, and the maturation or remodeling phase. The inflammatory phase occurs immediately after injury and peaks on the third day. The proliferation phase lasts from the fourth to the seventh day, characterized by an increasing number of fibroblasts throughout this phase. Fibroblasts are the primary factor dominating wound healing and serve as the framework or basic structure for collagen production. The maturation phase is the wound healing phase that occurs over a long period (3-6 months or even years) [30].

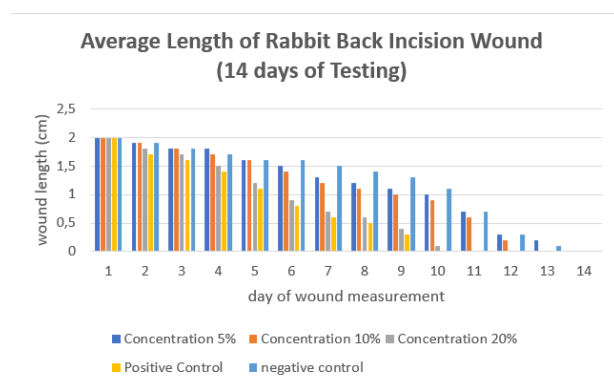


Figure 1. Graph of average incision length (14 days of observation)

Figure 1 shows a graph of the length of the incision wound, where on the first day after the incision, the wound experiences a vascular reaction in the form of brief bleeding that stops due to the constriction and retraction of blood vessels. The next day, bruising appears, indicating the inflammatory phase characterized by redness, swelling, warmth, and pain. The inflammatory phase occurs simultaneously with hemostasis and marks the beginning of the healing phase (lag phase), which lasts until day 5 [31]. In the positive control and test groups (5%, 10%, and 20%), the wound entered the proliferation phase, characterized by drying, exfoliation, and the formation of granulation tissue and epithelialization. Scabs began to form on average on the 6th day [12]. In contrast, in the negative control, the wound had not dried, was still red, and moist, indicating that the healing process was slow because it was not supported by active substances. The test group with water hyssop leaf ethanol extract and the positive control showed faster wound healing due to the effects of Bionect cream and the flavonoids, tannins, saponins, and alkaloids in the extract. These compounds help stimulate new tissue formation[3].

Tannins also play a role in damaging bacterial cell membranes, thereby accelerating the healing process [32]. On day 9, the positive control and the rose apple leaf ethanol extract test group showed thick scabs that began to peel off and turn pink, indicating new skin formation and cell growth. On the 10th day, the wounds

in the positive control and 20% concentration group were completely healed with new white skin, while the 5%, 10%, and negative control groups were still in the healing stage at the edges of the wound [31].

Table 2. Average percentage of incision wound healing

Hari ke-	Ekstrak 5%			Ekstrak 10%			Ekstrak 20%			Kontrol Positif			Kontrol negatif		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	5	15	5	0	10	0	0	0	25	5	5	5	0	5	0
3	5	15	5	0	10	0	5	5	30	10	10	15	0	5	0
4	10	20	10	10	15	10	15	20	45	20	25	50	5	10	5
5	15	25	20	25	20	15	30	35	55	35	45	55	5	15	10
6	20	30	35	35	30	25	45	55	60	60	55	65	10	20	15
7	25	35	40	40	40	35	60	65	65	70	65	75	15	25	25
8	30	40	45	45	45	40	65	70	75	80	70	80	20	30	30
9	35	45	50	55	50	45	80	75	80	85	80	85	25	35	40
10	45	50	60	60	55	50	85	90	90	100	90	100	45	45	50
11	60	60	75	75	65	75	100	100	100	100	100	100	65	55	65
12	80	70	85	80	70	100	100	100	100	100	100	100	75	70	80
13	90	85	90	100	100	100	100	100	100	100	100	100	85	80	85
14	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100

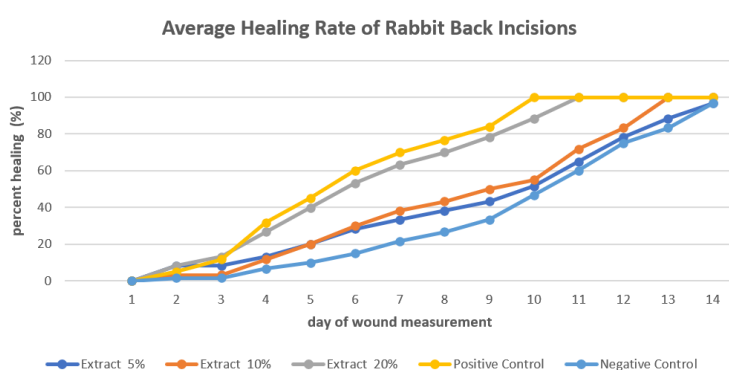


Figure 2. Average percentage of incision wound healing

The test results shown in Figure 2 clearly indicate that the fastest average wound healing was found in the positive control group within 10 days, due to the hyaluronic acid content in Bionect cream. This substance accelerates the formation of new tissue, enhances tissue synthesis during the early inflammatory phase, and supports cell infiltration and the mobilization of pro-inflammatory cytokines such as $\text{TNF-}\alpha$ and interleukin [33]. The fastest healing after the positive control occurred in the 20% ethanol extract of rose apple leaves (10 days), followed by 10% (12 days), and 5% (13 days). The negative control was the slowest, with a healing time of 14 days. The test group healed faster because it contained active compounds such as flavonoids, alkaloids, saponins, and tannins, while the negative control did not contain any active substances [3].

Flavonoids are effective as anti-inflammatories in the healing of incision wounds by inhibiting capillary permeability, arachidonic acid metabolism, and enzyme secretion from neutrophils and endothelial cells. These compounds also inhibit COX and LOX enzyme activity, leukocyte accumulation, neutrophil degranulation, histamine release, and stabilize ROS. In addition, flavonoids maintain permeability and increase capillary strength [34]. Alkaloid compounds are effective in healing incision wounds through several mechanisms. Alkaloids can accelerate the initial phase of open wound closure by stimulating the formation of fibroblasts, which play an important role in granulation tissue formation and new tissue regeneration [35]. Alkaloids are also capable of disrupting the components of peptidoglycan in bacterial cell walls, causing bacterial death and preventing infection in wounds [12].

Tannins effectively heal cuts in rabbits with their astringent properties that stop bleeding and prevent infection [35]. Saponins also play a role in wound healing by increasing macrophage migration to the wound area, which stimulates cytokine production and fibroblast activation for collagen formation. In addition,

saponins stimulate cytokine production and fibroblast activation for collagen formation, as well as stimulate new cell growth in blood vessels and wound tissue, repairing damaged blood vessel walls [36].

Table 3. One-Way ANOVA Test Results

Panjang Luka Sayat	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	689.755	4	172.439	1.822	0.005
Within Groups	6.340	10	398		
Total	676.095	14			

The data obtained from measuring the diameter of the incision wounds were then analyzed statistically. The results of statistical analysis using the One Way Anova test showed that the concentration of rose apple leaf ethanol extract (5%, 10%, and 20%) significantly affected the length of the wound ($p < 0.05$). Next, a *Post-Hoc Tukey HSD* test was conducted to determine the differences between treatment groups. Based on this test, it was confirmed that there were significant differences between treatment groups, indicating that rose apple leaf ethanol extract had an effect on wound healing ($p < 0.05$).

The limitations of this study lie in the small number of test animals and the use of multiple wounds on a single animal, which is a repeated measures design. Because each rabbit received multiple treatments simultaneously, the wounds on the same individual were not statistically independent. Therefore, the One Way ANOVA test used may not have fully accommodated the correlations between wounds in a single animal. Future research should use a larger number of animals (at least 5–6 per group) with one wound per animal, or apply statistical analyses appropriate for repeated measures designs, such as Repeated Measures ANOVA or mixed model analysis, to obtain stronger and more generalizable results.

Another limitation is that phytochemical screening in this study was only conducted qualitatively, which was limited to showing the presence or absence of bioactive compounds such as flavonoids, tannins, alkaloids, and saponins. Without quantitative analysis, such as determining Total Phenolic Content (TPC) or Total Flavonoid Content (TFC), it cannot be ascertained that the differences in wound healing effectiveness between concentrations are actually caused by differences in active compound levels. Further research is recommended to include quantitative phytochemical analysis to more accurately link the levels of bioactive compounds and wound healing activity, thereby providing a stronger mechanistic basis for the extract's effectiveness.

Conclusions

The results of the study show that ethanol extract of rose apple leaves (*Syzygium aqueum*) is effective in healing incision wounds in white rabbits (*Oryctolagus cuniculus*) at concentrations of 5%, 10%, and 20%. A 20% concentration of *Syzygium aqueum* leaf ethanol extract is the optimal concentration for the fastest healing of incision wounds on the backs of rabbits (*Oryctolagus cuniculus*).

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