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Effect of Papaya Leaf Extract Gel *(Carica papaya)* on Incision Wound Healing in *Rattus norvegicus*

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Abstract: *Carica papaya* is one kind of herbal plant that can help the wound healing process. Scientifically, the leaves of papaya are proven to have anti-inflammatory effects. Flavonoid, alkaloid, tannin, and saponin compounds in papaya leaves have antimicrobial and antioxidant properties to accelerate the re-epithelization and cell migration needed for wound healing. This research aims to determine the effect of papaya leaf extract gel *(Carica papaya)* on the healing of incision wounds in *Rattus norvegicus* based on changes in wound morphology (signs of redness, edema, pus, granulation, moisture, and wound length). This research used female *Rattus norvegicus* aged 12-16 weeks weighing 180-200 grams, divided into five groups (NaCl 0,9%, povidone-iodine, papaya leaf extract gel with concentrations of 10%, 20%, and 30%). Incision wounds on the back of the rat with a length of 2 cm and depth of 1 cm. The normality test used the Shapiro-Wilk test, and the homogeneity test used the Levene test. The research data were not normally distributed nor homogeneous, so they were analyzed using the Kruskal Wallis and Mann-Whitney tests. The results showed that the extract of papaya leaves with concentrations of 10%, 20%, and 30% had significant differences in positive and negative control groups in the wound healing process with the differences in redness (p=0.038), granulation tissue (p=0.039), moistures (0,48), and wound length (p=0,049). It can be concluded that papaya leaf extract gel *(Carica papaya)* is effective in accelerating the healing process of incision wounds in *Rattus norwegicus* at concentrations of 10%, 20%, and 30%, so for further research, it is hoped that a histopathological examination can be carried out so that changes that occur in collagen, neutrophile cells, monocytes, and lymphocytes are seen.
Keywords: Incision wounds; papaya leaf extract gel; wound healing

INTRODUCTION

A wound is a damage or loss of body tissue that occurs due to the presence of a factor that interferes with the body's protection system. The shape of the wound varies depending on the cause, some are open, and some are closed. One example of an open wound is an incision wound with a linear tear on the skin and underlying tissue. Wound treatment is needed to improve healing, prevent skin damage, and reduce the risk of infection (Winarjo et al., 2021).

Wound healing is a complex change process in restoring anatomical continuity and function (Oktaviani et al., 2019). One of the wound treatments can be done by using herbal ingredients, namely papaya leaves *(Carica papaya)* (Dewi & Wicaksono, 2020). Starting from stems, roots, flowers, and leaves, all parts of the papaya plant can be used for wound healing or as medicine, but the leaves are most commonly

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used for herbal medicine (Suminarti & Juliana, 2020). People use papaya leaves as a pain reliever, balance sugar blood levels, stimulate hair growth, prevent acne, and relieve inflammation and swelling.

Topical herbal ingredients can provide more optimal results to accelerate wound healing. This is due to the topical use of a drug compound that accumulated more on the wound's surface (Suratmini et al., 2021). The use of thick extracts directly on the skin is less practical and less optimal; it is necessary to make preparations that can stick to the skin surface for a long time and are occlusive so that they effectively heal wounds, namely semi-solid preparations in the form of gels. The appearance of the gel is like a solid substance that is soft and chewy, but at a certain temperature range, it can behave like a fluid (Watung et al., 2020). Previous research stated that the gel preparation of Carica papaya ethanol extract had a test of burn healing activity on white rats. The extract of papaya leaves prepared with a concentration of 5% was not effective in healing the wound ($p = 0.09$). The concentration of 10% and 15% were effective in healing the wound ($p = 0.02$ and $p = 0.014$) (Khor et al., 2021). Other research has also stated that scabs appear on the third day, in the early stages of the proliferation process. Papaya leaf extract gel with a concentration of 10%, 15%, and 20% has activity as wound healing until the fifth day shows the percentage of wound recovery reaching 14%, 20,6%, and 27% (Winarjo et al., 2021).

This research aims to determine the effect of papaya leaf extract gel (*Carica papaya*) on the healing of incision wounds in *Rattus novergicus* by observing the application of papaya leaf extract gel concentrations of 10%, 20%, and 30% on incision wounds in the inflammation phase as seen from the morphology of the wound. Previous research on papaya leaves has been carried out but applied to burns and traumatic ulcers. In back incision wounds, it was only carried out by one researcher who combined papaya leaf extract and binahong leaf for wound healing. The author innovated by looking at the effect of papaya leaf extract gel alone, whether without combination with other herbal ingredients, it can still accelerate the healing of back incision wounds, and the author uses a gel formulation because the gel has a good release of extract content, has high stability, and does not irritate the skin. In addition, the author also innovated by using a 30% gel dose to determine whether a dose of 30% is also effective for healing incision wounds.

MATERIALS AND METHODS

Experimental Animal

The Research Ethics Commission approved this research of the University of Brawijaya No. 66/EC/KEPK/03/2022. This research was conducted at the Materia Medica Batu Herbal Laboratory, Malang, Pharmacology Laboratory and Pharmacy Laboratory, Faculty of Medicine, University of Brawijaya, Malang, Indonesia, using female *Rattus norvegicus* aged 12-16 weeks and weighing 180-200 grams. Acclimatization was carried out for seven days, followed by randomization into five sample groups, each consisting of four rats. The first group is a negative control, a group of experimental animals that had been given NaCl 0,9% in an incision wound on their back. The second group is a positive control group of experimental animals that had been given *povidone iodine* in incision wounds on their back. Groups 3-5 are an experimental group of back incision wounds with treatments. The first treatment was giving papaya leaf extract gel with a concentration of 10% on the wound, the second treatment was applying the gel with a concentration of 20%, and the third treatment was applying the gel with a concentration of 30% to the incision wound. Before the wound was made, the rats were disinfected with 70% alcohol, and the hair

around the back was shaved and anesthetized with 0.1 ml of ketamine. Then the incision was made on the back of the rats with a length of 2 cm and a depth of 1 cm. Papaya leaf extract gel was applied evenly until it covered the wound, is carried out once for three days and once a day at the same hour.

Papaya Leaf Extract

Papaya leaf extract is carried out using the maceration method. Maceration is carried out using 96% ethanol solvent for three days. Papaya leaf simplistic powder of 500 grams is put in a glass jar, leveling the powder while adding 700 ml of solvent until submerged and stirred for 15 minutes. Close the jar tightly for 24 hours. Sift the liquid extract using a filter cloth, accommodating the filtrate in an Erlenmeyer. The macerated obtained are then filtered and evaporated using a rotary evaporator, and the extract is concentrated with a water bath to obtain a thick extract (Femilian et al., 2019).

Phytochemical Screening of Papaya Leaf

The alkaloid, flavonoid, tannin, and saponin chemical compound test: (Wijaya et al., 2020).

1. Alkaloid
   The extract of 30 mg was dissolved using 2 ml of HCL 2N and heated for 3 minutes. Three drops of NaCl are added after it has cooled down and then filtered. The filtrate is added with HCl and gradually supplemented by Dragendorf color reagents; if a yellow precipitate is formed, the sample contains an alkaloid.
2. Flavonoid
   A flavonoid test was performed using the Wilstater method. An extract of 0.5 grams was dissolved in ethanol by 3 ml. The sample solution was mixed with 0.5 ml of HCl p.a and Mg powder. Mg powder was added until a discoloration occurred, then distilled water and 1 ml of butanol were added. The formation of a greenish-yellow shows a positive reaction, orange (flavon), pale red (flavonol), crimson (flavonon), or green to blue (glycoside) color.
3. Tannin
   The 20 mg of papaya leaf extract was added with 1% of FeCl3: Gallotanin and Ellagotanin can give a blue-black precipitate, and condensed tannin can provide a greenish-black precipitate. The extract solution was added with 1% gelatin containing NaCl; if a precipitate appeared, the sample contained tannin.
4. Saponin
   An extract of 0.5 grams was placed into a test tube with 10 ml hot water. After cooling down, the tube was shaken for 10 seconds to form the 1-10 cm stable foam for less than 10 minutes. The solution was then added with one drop of HCl 2N. If the foam does not disappear, then the sample contains saponin.

Papaya Leaf Extract Gel

The first step is to prepare the tools and materials and weigh the ingredients according to the gel formula. It was making papaya leaf extract gel according to the formula in Table 1. The next step is to heat the water to 70^{o}C. The heated water is added by carbopole evenly, and let us stand for 15 minutes at room temperature. The water is then stirred to the gel phase, and Phenoxyethanol, Propylene glycol, EDTA, and Triethanolamine is added and then stirred. The extract of papaya leaf and the rest of the aquadest have been weighed and then stirred until homogeneous and formed a gel (Das et al., 2020).

Table 1. The Formulation of Papaya Leaf Extract Gel

Ingredients	Amount (gram)		
	Gel Formulation 10%	Gel Formulation 20%	Gel Formulation 30%
Papaya Leaf Extract	2	4	6
Carbopole	0.4	0.4	0.4
Phenoxyethanol	0.12	0.12	0.12
Propylene glycol	1.4	1.4	1.4
EDTA	0.02	0.02	0.02
Triethanolamine	0.118	0.118	0.118
Aquades (add)	16	14	12

Statistic Analysis

Observation is conducted descriptively on each treatment group on the scoring method for all rats. The condition of the wound is observed daily by taking into account the morphological parameters of the wound (signs of redness, edema, pus, granulation, moistures, and wound length). Then the data analysis was done using SPSS with a confidence level of 95%, including a normality test, Saphiro-Wilk test, and a homogeneity test using the Levene test. The One-Way ANOVA test was used to analyze normally distributed and homogeneous data, and the Kruskal-Wallis and Mann-Whitney tests were used to determine significant differences between groups.

RESULTS AND DISCUSSION

Table 2. Observations on *Rattus norvegicus* İncision Wound

Parameters	Groups				
	Negative Control	Positive Control	T1	T2	T3
	%	%	%	%	%
Redness Mark					
Without reddish mark	25	5	100	100	100
Reddish mark	75	50	0	0	0
Edema					
Without edema	100	100	100	100	100
With edema	0	0	0	0	0
Pus					
Without pus	100	100	100	100	100
With pus	0	0	0	0	0
Granulation					
Without granulation	50	25	0	0	0
Partial granulation of the wound	50	75	100	100	100
Granulation of the entire wound	0	0	0	0	0
Moisture					
Dry wound	25	25	100	100	75
Moist wound	75	75	0	0	25
Wound Length					
1.8-1.9 cm	25	0	0	0	0
1.6-1.7 cm	50	75	0	0	25
1.4-1.5 cm	25	25	100	100	75

Description : T1 = first treatment (given papaya leaf extract gel with a concentration of 10%), T2 = second treatment (given papaya leaf extract gel with a concentration of 20%), T3 = third treatment (given papaya leaf extract gel with a concentration of 30%), % = percentage of sample count.

Redness Mark (Wound Color)

Table 2 shows that in the negative control group, there were 3 (75%) samples with redness; in the positive control group, there were 2 (50%) samples with no redness; in all treatment groups from groups 1 to 3, there was no redness around the wound. The normality test results show that the data were abnormally distributed (p-value 0.024 < 0.05). The result of the homogeneity test using the Levene test shows a significant result of 0.021 < 0.05; thus, the data were not homogeneous and continued with the Kruskal-Wallis test to find out whether there is any effect on the acceleration of redness time around the incision wound in *Rattus norvegicus* from each the five groups. A significance value of 0.038 < 0.05 is obtained from the Kruskal-Wallis test, meaning that papaya leaf extract gel affects the acceleration of redness time around the incision wound of *Rattus norvegicus*; subsequently, a Mann-Whitney test was carried out to find out the difference in effectiveness in each group.

Edema and Pus

From the third-day observation result regarding edema and pus around the wound, researchers did not find edema and pus macroscopically in all five groups.

Granulation

Table 2 shows that in the negative control group, there were 2 (50%) samples with no granulation; in the positive control group, there were 3 (75%) samples with partial wound granulation, and in all treatment groups, 1 to 3 (100%) there was partial granulation of the wound. Abnormal data distribution (p-value 0.001 < 0.05) and inhomogeneous (p-value 0.003 < 0.05). The result of the Kruskal-Wallis test is a p-value of 0.039 < 0.05, meaning that papaya leaf extract gel affects the acceleration time of the appearance of the incision wound granulation on *Rattus norvegicus*.

Moisture

Table 2 shows 3 (75%) samples with moist wounds in positive and negative group control. In all of treatment group 1 and treatment group 2, the wounds were dry; in treatment group 3, there were 3 (75%) samples with dry wounds. The data is abnormally distributed (p-value 0.001 < 0.05) and inhomogeneous (p-value 0.014 < 0.05). The Kruskal-Wallis test result obtained a p-value of 0.048 < 0.05. This means that papaya leaf extract gel affects the moisture of incision wounds on *Rattus norvegicus*. Furthermore, the Mann-Whitney test was carried out to see the difference in the effect of each group.

Wound Length

Table 2 shows that 2 (50%) samples of a negative control group had a wound length of 1.6-1.7 cm. The positive group control found 3 (75%) samples with a wound length of 1.6-1.7cm. All samples from treatment groups 1 and 2 had a wound length of 1.4-1.5 cm, and in treatment group 3, there were 3 (75%) samples with a wound length of 1.4-1.5 cm. The data is homogeneous (p-value 0.097 > 0.05), but the One Way Anova test could not be conducted because the data were abnormally distributed (p-value 0.001 < 0.05), so it was continued with the Kruskal-Wallis test to find out if there was any effect on the wound on *Rattus norvegicus* from each group. From the Kruskal-Wallis test, the researchers obtained a p-value of 0.047 < 0.05, meaning that papaya leaf extract gel affects the length of the incision wound on *Rattus norvegicus*.

Furthermore, a Mann-Whitney test was conducted to determine the differences in effectiveness in each group.

Table 3. Mann-Whitney Test Results on the Parameters of the *Rattus norvegicus* Incision Wound

Group		Redness	Edema	Pus	Granulation	Moisture	Wound Length
		p-value	p-value	p-value	p-value	p-value	p-value
Negative Control	Positive Control	0.495	0	0	0.186	1.000	0.617
	T1	0.040*	0	0	0.040*	0.040*	0.046*
	T2	0.040*	0	0	0.040*	0.040*	0.046*
	T3	0.040*	0	0	0.040*	0.186	0.155
Positive Control	T1	0.127	0	0	0.317	0.040*	0.040*
	T2	0.127	0	0	0.317	0.040*	0.040*
	T3	0.127	0	0	0.317	0.186	0.186
T1	T2	1.000	0	0	1.000	1.000	1.000
	T3	1.000	0	0	1.000	0.317	0.317
T2	T3	1.000	0	0	1.000	0.317	0.317

Description: * significance with p-value <0.05.

Redness Mark (Wound Color)

Table 3 shows no significant difference between the negative control and positive control groups (p-value 0.495 > 0.05). There is a significant difference between the negative control and treatment groups of 1 to 3 (p-value 0.40 < 0.05). There is a significant difference between the positive control and treatment groups 1 to 3 (p-value 0.127 > 0.05). Treatment group 1 do not differ significantly from treatment groups 2 and 3 (p-value 1.000 > 0.05) and treatment group 2 also does not differ significantly from treatment group 3 (p-value 1.000 > 0.05).

Granulation

Table 3 shows that between negative control group and positive control group there is no significant difference (p-value 0.196 > 0.05). Between the negative control groups and the treatment group 1 to 3 there is a significant difference (p-value 0.040 < 0.05). The positive control group and the treatment gorup 1 to 3 are not significantly different (*p-value* 0.317 > 0.05). Treatment group 1 do not differ significantly from treatment group 2 and 3 (p-value 1.000 > 0.05) and treatment group 2 do not differ significantly from treatment group 3 (*p-value* 1.000 > 0.05).

Moisture

Table 3 shows no significant differences between the negative control and positive control groups (p-value 0.495 > 0.05). Significant differences exist between the negative control group and all three treatment groups (p-value 0.040 < 0.05). The positive control group does not differ significantly from all three treatment groups (p-value 0.127 > 0.05). Treatment group 1 did not differ significantly from treatment group 2 and 3 (p-value 1.000 > 005) also for treatment group 2 did not differ significantly from treatment group 3 (p-value 1.000 > 0.05).

Wound Length

Table 3 shows that there are no significant differences between negative control group and positive control group (p-value 0.617 dan 0.155 > 0.05). The significant

differences are found between negative control group and treatment group 2 and 3 (p-value 0.046 < 0.05). There are also significant differences between positive control group and treatment group 1 and 2 (p-value 0.040 < 0.05), there were no significant difference of positive control group with treatment group control 3 (p-value 0.186 > 0.05). Treatment group 1 was not significantly different from treatment group 2 and 3 (p-value 1.000 dan 0.317 > 0.05) and the treatment group 2 was not significantly from the treatment group 3 (p-value 0.317 > 0.05).

The wound healing process takes place in 3 phases: the inflammatory phase, the proliferation phase, and the maturation or remodeling phase (Yadav et al., 2021). The results of this study indicate that differences in wound healing began to appear on the third day. The negative control group (NaCl solution) and the positive control group (povidone-iodine) showed an optimum incision wound repair effect was the positive group control in the presence of granulation, the wound began to dry, there was no redness, and the length of the wound was 1.6-1.7 cm. This happened because the positive control (povidone-iodine) kills germs, bacteria, fungi, and viruses but does not cause immunity to germs. Povidone iodine has the advantage of regulating the moisture of the wound.

In contrast, the negative control group (NaCl solution) does not contain efficacious substances for wound healing. However, the wound closes independently because the body can protect and restore itself naturally (Femilian et al., 2019). The sooner the wound is closed, the better it reduces the risk of infection and discomfort due to the wound.

Papaya leaf extract gel can be used as an alternative to accelerate the healing process of incision wounds because pharmacologically, papaya leaf extract gel contains flavonoid compounds, alkaloids, saponins, and tannins that are effective for wound healing. In this study, the positive control group showed results that did not differ significantly from the treatment groups of 1 to 3 (papaya leaf extract gel 10%, 20%, and 30%), so there were no significant differences between povidone-iodine and papaya leaf extract gel. In this study, the most optimal effect in accelerating wound healing was at a concentration of 20%, which indicates a decrease in signs of redness, edema, pus, partial granulation of the wound, the wound dries quickly, and closes faster. The effect of papaya leaf extract gel on the healing of *Rattus norvegicus* incision wounds showed significant differences between the study group samples with a p-value of 0.038. This is due to the benefits of the active compounds in papaya leaves, which can accelerate the wound healing process (Sultana et al., 2018).

The acceleration of redness time around the wound in the treatment group was due to the effect of the active compound content derived from the papaya leaf extract gel. In accordance with previous studies, papaya leaf extract provides a significant inflammatory effect. Anti-inflammatory activity of papaya leaf extract due to the presence of flavonoids, alkaloids, saponins, and tannins (Nafiu et al., 2019). Flavonoids limit the release of inflammatory mediators (Wijaya et al., 2020). The anti-inflammatory activity of flavonoids occurs through the development of cyclooxygenation and lipoxigenation, so there is a limitation in the number of inflammatory cells that migrate to the tissues. Furthermore, the inflammatory reaction lasts shorter, and the ability to proliferate is not too late (Winarjo et al., 2021).

The absence of edema around the wound in the treatment group was due to the effect of tannin content derived from papaya leaf extract gel. However, the mechanism of action of the tannins has not been explained with certainty (Sultana et al., 2018). The analysis results following the research (Siahaan & Chan, 2018) showed that papaya leaf extract has acute and chronic inflammatory activity, as seen from the

reduction in the area of white rats edema in the first 1-3 hours. The presentation of the results of edema comparison in the five sample groups in this study showed that wound care using papaya leaf extract gel had the same effect as the positive control group treated with 10% povidone-iodine. The absence of pus in the treatment group was due to the effect of the content of alkaloids, tannins, and saponins derived from papaya leaf extract gel. Alkaloids can act as antibacterials by interfering with the components of peptidoglycan preparation in the bacterial cell so that the layer of the cell is not formed completely, causing the death of the bacterial cell (Kumar et al., 2022; Wijaya et al., 2020). The analysis results are supported by previous studies that showed papaya leaves could be used as an antiseptic in the form of a gel. The preparation gel with papaya leaf extract levels starting from 10% can reduce microorganisms by up to 57% (Watung et al., 2020).

The growth of granulation tissue in the wound in the treatment group was due to saponins, flavonoids, and tannins. Saponins are steroid compounds or triterpenoid glycosides that can stimulate the Vascular Endothelial Growth Factor (VEGF) and increase the number of macrophages migrating to the wound area, thereby increasing fibroblasts in the wound tissue. Saponins have the potential to help the healing of the wound by forming collagen, which plays a role in the wound healing process (Niveditha et al., 2020; Wadekar et al., 2021). Flavonoids help wound healing by increasing collagen formation, reducing macrophages, and increasing the number of fibroblasts. Flavonoids reduce the onset of cell necrosis by reducing lipid peroxidation. Inhibition of lipid peroxidation can increase collagen fibers' viability and blood circulation, prevent cell damage, and increase DNA synthesis (Kaur et al., 2019; Santi et al., 2022). This follows previous studies that papaya leaf extract affects healing grade II burns in rat skin due to the presence of substances in papaya leaves which can accelerate wound healing, namely flavonoids, alkaloids, tannins, and saponins (Sidat et al., 2020; Wijaya et al., 2020).

After granulation tissue is formed, epithelization begins. The growing epithelial cells will move from the outer side of the injured tissue to the inside of the tissue. In the proliferation phase, there is a process of wound contraction, a centripetal movement from the edge of the wound towards the center of the wound. The wound moves toward the middle with an average distance of 0.6 to 0.75 mm/day so that the length of the wound gets narrower, and over time, the wound will close. Myofibroblast cells commonly found in wound contraction consist of actin and myosin equal to the contraction system in smooth muscle so that myofibroblasts can contract and elongate. Wound contraction that occurs in the late stages of wound healing looks like the changes in the shape of the wound and the reduction of the open wound area and produces a smaller wound area (Watung et al., 2020).

The results of this study have proven the research hypothesis that papaya leaf extract gel has a significant effect on incision wound healing in *Rattus norvegicus* by looking at the changes in wound morphology. Previous studies have been conducted on the effectiveness of papaya leaves on burns using gel concentrations of 5%, 10%, and 15%. The limitation of this study is the time of conducting the study; the variables used are still limited, and there are still many variables related to the wound healing process that has not been discussed in the study, such as histopathological examination to see the changes that occur in collagen, neutrophile cells, monocytes, lymphocytes, epithelial cell growth, fibroblasts, pro-inflammatory cytokine activity, and others. Therefore, further research is recommended to test the effect of papaya leaf extract gel on some of these variables.

CONCLUSION

This study shows that papaya leaf extract gel *(Carica papaya)* concentrations of 10%, 20%, and 30% have the potential to accelerate the healing process of incision wounds, especially at a concentration of 20%, which can help accelerate the growth of granulation, prevent pus, accelerate the drying of wounds, the length of wounds gradually shrink thereby minimizing the risk of infection and reduce the discomfort due to wounds. Papaya leaf extract gel can be an alternative for wound healing, especially for someone allergic to povidone-iodine, because papaya leaf extract gel is toxin-free, has no side effects, is cheap, and is easy to produce.

CONFLICT OF INTEREST

All authors state that there is no conflict or problem with any party in the writing of this journal publication.

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