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EFFECTIVENESS OF PAPAYA LEAF EXTRACT SPRAY ON THE HEALING OF PERINEAL WOUNDS WHITE RATS

Efektivitas Spray Ekstrak Daun Pepaya terhadap Kesembuhan Luka Perineum Tikus Putih

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ABSTRAK

Kejadian robekan perineum pada ibu pasca bersalin mendekati angka 90%. Kondisi luka robekan perineum yang kurang baik dapat menjadi tempat awal terjadinya infeksi. Kejadian infeksi terjadi kisaran antara 0,1%-23,6% pada ibu pascapersalinan. Perawatan luka perineum dapat mencegah infeksi dan mempercepat penyembuhan. Daun pepaya mengandung senyawa flavonoid, saponin, tanin yang dapat mempercepat kesembuhan luka. Tujuan dalam penelitian ini untuk membuktikan efektivitas dari spray ekstrak daun pepaya terhadap kesembuhan luka perineum menurut skor skala REEDA. Penelitian dilaksanakan di laboratorium hewan coba Universitas Muhammadiyah Semarang pada tanggal 6-19 November 2024. Jenis penelitian ini merupakan true experiment dengan metode posttest-only control group design menggunakan teknik simple random sampling. Jumlah sampel 36 tikus betina yang diberi luka insisi ±1 cm. Kemudian, dibagi menjadi 2 kelompok yaitu kelompok intervensi yang memperoleh spray ekstrak daun pepaya 10% dan perawatan bersih kering 2x/hari selama tujuh hari. Pada kelompok kontrol diberikan perawatan bersih kering 2x/hari selama tujuh hari. Analisis data menggunakan Friedman Test dan Mann Whitney Test. Alat ukur penelitian ini menggunakan skor skala REEDA. Spray ekstrak daun pepaya efektif dalam mempercepat kesembuhan luka perineum pada hari ketujuh (0,00±0,000) dibandingkan kelompok kontrol (0,50±0,514) dengan nilai p-value 0,001. Pemberian spray ekstrak daun pepaya efektif sebagai alternatif pengobatan tradisional berbasis herbal dalam praktik kebidanan untuk mempercepat kesembuhan luka perineum.

***Kata kunci**: daun pepaya, penyembuhan luka perineum, spray, tikus*

ABSTRACT

The incidence of perineal tears in postpartum mothers is close to 90%. The bad condition of the perineal wound can be the starting point for infection. Infection rates range from 0.1% to 23.6% in postpartum mothers. Perineal wound care can prevent infection and speed healing. Papaya leaves contain flavonoids, saponins, tannins that can accelerate wound healing. The study aimed to prove the effectiveness of papaya leaf extract spray on perineal wound healing based on the REEDA scale score. The research was conducted in the experimental animal laboratory of Muhammadiyah University of Semarang on November 6-19, 2024. This research design used a true experiment with posttest-only control group design method using simple random sampling technique. The number of samples was 36 female rats that were given incision wounds ±1 cm. Then, divided into 2 groups, namely the intervention group that received 10% papaya leaf extract spray and dry cleaning treatment twice a day for seven days. The control group was given dry clean treatment twice a day for seven days. Data analysis using the Friedman Test and Mann-Whitney Test. The measuring instrument of this study used the REEDA scale score. Papaya leaf extract spray was effective in accelerating the healing of perineal wounds on day 7 (0.00±0.000) compared to the control group (0.50±0.514) with p-value of 0.001. The given of papaya leaf extract spray is effective as an alternative

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herbal-based traditional treatment in obstetric practice to accelerate the healing of perineal wounds.

Keywords: mouse, papaya leaf, perineal wound healing, spray

INTRODUCTION

A tear in the perineal tissue that occurs as a result of a spontaneous or deliberate incision (episiotomy) to aid delivery is known as a perineal laceration. Nearly all first births result in a perineal tear, and it sometimes occurs in subsequent births as well. Perineal tears occur in over ninety percent of vaginal births with or without an episiotomy[1].In postpartum women, poor perineal wound condition can be the primary source of infection. This is due to the open tissue, which allows bacteria and germs to enter. Infection rates in postpartum women range from 0.1% to 23.6%[2]. However, there are several studies that describe the incidence of perineal injuries during normal delivery, although data on perineal injuries cannot be presented internationally. The majority of perineal injuries (76.8%) occur after normal delivery, and 1.9% become infected due to poor care[3]. Postpartum infections are among the leading complications causing maternal death worldwide. These infections can be prevented by maintaining genital hygiene and recognizing early signs and symptoms of infection[4].

A current phenomenon is that postpartum mothers still experience discomfort from stitches in the birth canal wound and are afraid to clean the perineal area. The first step in preventing perineal wound infection is having a good understanding of how to manage the healing process.[2]. One way to manage wound healing is to use complementary treatments, such as the use of papaya leaves. Proven effective in healing perineal wounds because *it* has various benefits such as anti-inflammatory, antioxidant, antimicrobial, antiviral, and analgesic. If studied further, Papaya leaves contain compounds such as saponins, flavonoids, and tannins, all of which have pharmacological effects on wound healing. Furthermore, papaya leaves are readily available in every region of Indonesia and are relatively inexpensive[5].

The results of the study show that the Papaya leaf extract gel can heal rabbit wounds compared to 5% concentration extract gel, the 15% concentration extract gel, and the gel base. The 10% concentration papaya leaf extract gel formula has a wound healing effect comparable to the positive control (Bioplacenton®)[6]. HoweverSeveral studies have shown that the spray is easy to use, minimizes skin irritation, and eliminates the need for handwashing before and after use. Furthermore, the solvent evaporates easily, allowing the spray to dry quickly and not feel sticky after application, aiding faster drug absorption. The spray is also believed to offer safety and tolerability advantages compared to conventional formulations (creams, gels, and ointments)[7].

Herbal treatment methods based on local wisdom in treating perineal wounds have been proven safe and effective in accelerating the healing process[8],[9]. Therefore, proper care is necessary for healing and to prevent infection. Perineal wounds can heal without long-term complications. However, some risks can occur, such as bleeding, prolonged pain, sexual dysfunction, and embarrassment.[10].Continued adverse events can result in death. As in the city of Semarang in 2022, the majority of mothers who died were in the postpartum period, namely 67%, while no cases of death during childbirth were found[11].

Based on the above description, effective perineal wound care is essential to prevent serious risks by utilizing papaya leaf herbal medicine as a complementary treatment. This research is one of the latest findings being tested before being applied to humans, such as postpartum mothers. Therefore, researchers intend to conduct animal studies to determine the effectiveness of papaya leaf extract spray (Carica papaya) on perineal wound healing in white rats (Rattus norvegicus).

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METHODS

This type of research is*trueexperiment*with designnamely a posttest with a control group. The posttest was conducted on the intervention and control groups through observation of perineal wound healing results using the REEDA scale on day 7. The treatment given to the intervention group was dry cleaning treatment and spraying 10% papaya leaf extract twice daily for seven days, with three sprays. Meanwhile, the control group was given dry cleaning treatment only twice daily for 7 days.

The subjects in this study were 36 white rats (Rattus norvegicus), divided into 18 in the intervention group and 18 in the control group. The sampling technique used was a random sampling method. Simple random sampling namely white mice that have met the inclusion and exclusion criteria. Then, they were randomly selected by laboratory staff. Inclusion criteria included female white mice, 2-3 months old, weighing 150-300 grams, with no anatomical abnormalities, and active and healthy movements. Exclusion criteria included male white mice, mice that appeared weak or died during treatment.

Research was conducted from November 6, 2024, to November 19, 2024, at the Animal Laboratory of the University of Muhammadiyah Semarang (UNIMUS). This research has obtained ethical approval from the Research Ethics Commission of the Poltekkes Kemenkes Semarang with a statement of ethical feasibility Number: 1233 / EA / F.XXIII.38 / 2024 on October 25, 2024. The research process began with the extraction of 1 kg of papaya leaf powder (*Carica papaya*), which has a certified CoA from CV. Gubuk Herbal and the manufacture of the spray were carried out at the Laboratory of CV. Cendekia Nanotech Hutama (CNH) Semarang.

The selected mice were acclimatized for seven days and placed in a room with adequate lighting to prevent humidity, away from crowds, and out of direct sunlight. First anesthetized using ether, then the area to be incised and given an incision medially, as a picture of a perineal wound. Observations of perineal wound healing in rats were conducted daily for seven days using the REEDA scale observation sheet. Data analysis used the Friedman test to examine paired data in each group and the Mann-Whitney test to examine unpaired data between the intervention and control groups. This analysis was performed because the Shapiro-Wilk test showed that the research data were not normally distributed.

RESULTS

Table 1. Phytochemical Screening

Compound	Results	Average Level
Flavonoid	(+)	134.921 mg QE/100 g
Tannin	(+)	1830.677 mg GAE/100 g
Saponin	(+)	1859.244 mg DE/100 g

Table 1 shows the results of phytochemical tests on papaya leaf extract conducted in the laboratory for flavonoid, tannin, and saponin compounds. In this study, flavonoids were found to contain 134.921 mgQE/100g, tannins 1830.677 mgQE/100g, and saponins 1859.244 mgQE/100g.

Table 2. Spray Test of 10% Papaya Leaf Extract

Spray Test	Results
Organoleptic	Liquid form, distinctive papaya leaf smell, blackish green color, and non-sticky texture
pH	pH 5.12
Viscosity	0.937 cPs
Spread Power	Before 2x2 cm and after 3x3.3 cm
Adhesive Power	10.83 seconds
Spray Pattern	Spread well

Table 2 shows the results of the organoleptic test of 10% papaya leaf extract spray,

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which has a liquid form, a distinctive papaya leaf odor, a blackish green color, and a non-sticky texture. The pH test results of 10% papaya leaf extract spray are pH 5.12. The viscosity test results of 10% papaya leaf extract spray are 0.937 cPs. The results of the spread ability test of the papaya leaf extract spray were previously 2x2 cm and afterward spread to 3x3.3 cm, which indicates an increase in spread ability. The results of the adhesion test of 10% papaya leaf extract spray for 10.83 seconds. The results of the spray pattern test of the 10% papaya leaf extract spray are well spread.

Based on Table 3, the p-value of the paired data test (Friedman test) between the intervention and control groups is 0.000 (p<0.05), which means there is a significant difference in the REEDA score in perineal wound healing for seven days. Meanwhile, the unpaired data test (Mann-Whitney test) shows a p-value on the seventh day of 0.001 (p<0.05), which means there is a significant difference in the process of accelerating perineal wound healing. This is also supported by the comparison between the REEDA scores in Table 4, namely on day 7 compared to day 1, which shows a significant difference in perineal wound healing.

Table 3. Paired and Unpaired Data Test Results for REEDA Scores

Measuring instrument	Observation Time	Group Intervention	Group Control	*p-value*[b]
		Mean±SD	*Mean±SD*	
REEDA Score	First day	10.61±0.850	10.56±0.784	0.899
	The second day	7.78±0.732	8.61±0.608	0.002
	The third day	4.67±0.686	6.78±0.732	0.000
	The fourth day	2.11±0.832	5.28±0.958	0.000
	The fifth day	0.22±0.647	3.83±0.707	0.000
	The sixth day	0.00±0.000	1.94±0.639	0.000
	The seventh day	0.00±0.000	0.50±0.514	0.001
p-value[a]		0,000	0,000	

[a]Friedman test and Mann Whitney test

Table 4. Paired Data Test Between Times of REEDA Scores

Measuring instrument	Time Comparison	Intervention Group	Control Group
		*p**	*p**
REEDA Score	Day 1 >< Day 2	0.000	0.000
	Day 2 >< Day 3	0.000	0.000
	Day 3 >< Day 4	0.000	0.000
	Day 4 >< Day 5	0.000	0.000
	Day 5 >< Day 6	1.567	0.000
	Day 6 >< Day 7	1.000	0.000
	Day 7 >< Day 1	0.000	0.000

*Wilcoxon Post Hoc Test

Table 5. Effectiveness of Papaya Leaf Extract Spray on Healing Perineal Wounds

Measuring instrument	Group	N	*Mean±SD*	*p**	Effectiveness **	*Effect Size***
REEDA Score Day 7	Intervention	18	0.00±0.000	0.001	100%	1.376
	Control	18	0.50±0.514		95.33%	

*Mann Whitney Test **N-Gain Score ***Cohen's d

Table 5 shows that papaya leaf extract spray was effective in accelerating perineal wound healing with a p-value of 0.001 (<0.05). Furthermore, the intervention group (100%) had a higher perineal wound healing percentage of 4.67% compared to the control group (95.33%).Furthermore, the effect size value was 1.376, indicating that the administration of papaya leaf extract spray and dry cleaning treatment had a very strong effect on perineal wound healing based on the REEDA score.

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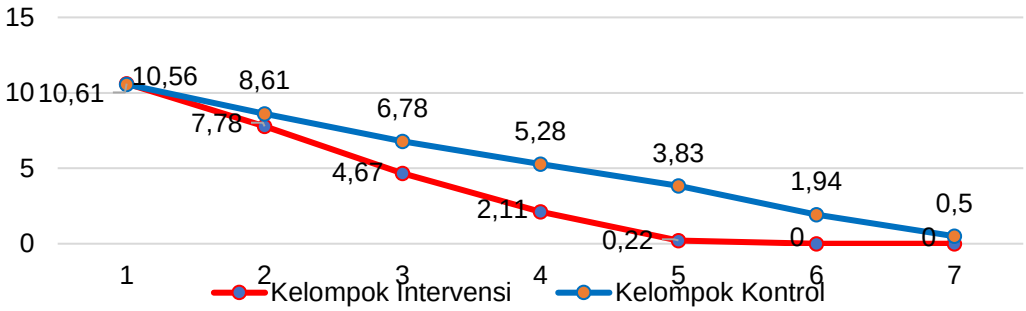

Figure 1. Average Decrease in REEDA Score in Perineal Wound Healing

The graph in Figure 1 also shows a significant decrease in the mean REEDA score in the intervention group compared to the control group. This demonstrates that the spray of Papaya leaf extract was more effective in accelerating perineal wound healing on day 6 (0.00±0.000) compared to the control group on day 7 (0.50±0.514).

DISCUSSION

The intervention group experienced a lower average decrease in REEDA scores compared to the control group. This indicates that wound healing in the intervention group was better than in the control group. Based on the results of the Mann-Whitney test, the average REEDA score between the intervention and control groups had a significant difference with a p-value of 0.001, which means that administering 10% papaya leaf extract spray and dry cleaning treatment twice a day for seven days was effective in healing perineal wounds in rats.

Based on the results of the calculation of the effectiveness formula, it can be said that the administration of papaya leaf extract spray and dry cleaning treatment has more potential in healing rat perineal wounds by 100%, while in the control group, only using dry cleaning treatment by 95.33% on the 7th day. Thus, it can be seen that the intervention group has a higher wound healing percentage of 4.67% compared to the control group. Then, the magnitude of the effect size value is 1.376, which means that the administration of papaya leaf extract spray and dry cleaning treatment has a very strong influence on perineal wound healing based on the REEDA score.

Based on the description above, it is known that administering 10% papaya leaf extract spray twice daily is effective in accelerating the healing of perineal wounds in mice. This is supported by the average REEDA score on day 6 in the intervention group, which is 0, meaning the wound has healed, compared to the control group with an average REEDA score of 1.94, which is still in the wound healing process. The wound healing process in this study entered the inflammatory and proliferative phases. The inflammatory phase occurs on days 0 to 5, where there is a cellular and vascular response that occurs due to tissue damage. Meanwhile, the proliferation phase occurs on days 3 to 14. During this phase, granulation tissue works to cover the wound surface, and keratocytes migrate to help close the wound with new epithelial tissue[12].

The results of this study are directly proportional to the use of 10% Carica Papaya Leaf Extract (EDPC) ointment, which has the potential to accelerate the healing of perineal wounds in mice.[5]. Other potential is also proven by research showing that crushed papaya leaves have the effect of accelerating the healing of superficial second-degree burns in mice.[13]. In addition, other research results also revealed that administering papaya leaf extract gel with a concentration of 20% can increase collagen density faster in female mice on the 10th day compared to administering Povidone Iodine with a score of 2 (thick collagen) based on histopathological tests[14].

Based on quantitative phytochemical analysis, papaya leaves contain flavonoid compounds of 134.921 mg QE/100 g, saponins of 1859.244 mg DE/100 g, and tannins

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of 1830.677 mg GAE/100 g. Therefore, spraying 10% papaya leaf extract can accelerate the healing of perineal wounds in rats. This is directly proportional to previous research that papaya leaves contain flavonoids, saponins, and tannins, which have the potential as anti-inflammatories and antiseptics that play a role in wound healing[5].

The flavonoid content in papaya leaves plays an important role in wound healing activity. Crude and fractionated extracts of papaya leaves exhibited significant antioxidant activity, the strongest free radical scavenging effect, and accelerated cell migration within 24 hours of wounds. This significantly influences wound closure, increasing fibroblast cell count and scar tissue formation. Furthermore, its flavonoid content also has antibacterial properties[15]. Flavonoid compounds react with proteins to kill bacteria that can inhibit wound healing or prevent infection[16].

The saponins contained in papaya leaves stimulate collagen formation, increase wound contraction so that wounds close quickly, and provide strength to wounds so that they do not open easily.[14]. Saponins in the defense system work as a barrier against pathogens.[17]. Furthermore, saponins also act as cleansers, making them effective on open wounds and as antibacterials that disrupt the stability of bacterial cell membranes. They then cause bacterial cell lysis and disrupt membrane permeability, resulting in membrane damage and the release of various important components, such as proteins, nucleic acids, and nucleotides, from the bacterial cell[18].

Similar research also explains that the saponin content in papaya leaves helps modulate fibrocyte cells to synthesize collagen. This is aided by the abundant vitamin C in papaya leaves, which acts as an enzyme cofactor in the hydroxylase process. Vitamin C is necessary for collagen synthesis. Furthermore, saponins also possess numerous biological activities, including antibacterial, antiviral, and anti-inflammatory properties, such as reducing edema and playing a role in wound healing[19].

The tannins in papaya leaves act as astringents, stopping bleeding, accelerating wound healing and inflammation, and promoting regeneration or new tissue formation. Tannins work by narrowing skin pores to prevent exudation and minor bleeding, as well as promoting wound closure.[20]. In addition, the tannin content can also accelerate wound healing through cellular mechanisms such as cleaning free radicals and reactive oxygen, increasing wound closure, and the formation of capillary blood vessels and fibroblast cells[21].

This study used white mice as a preclinical test to determine the effectiveness of the drug in healing perineal wounds. Throughout the study, all the white mice showed no signs of allergies, such as redness or itching on the skin. Previous research also revealed that 10% papaya leaf extract showed no side effects in mice during a 180-day oral administration period, confirming its potential safety for long-term use[22]. Based on the results of preclinical trials, a 10% papaya leaf extract spray can be used as an alternative for healing perineal wounds. Clinical trials in humans can be conducted after the drug has been proven effective and safe in animal models and its suitability has been reviewed by an ethics committee.

The use of 10% papaya leaf extract spray is one of the traditional herbal-based treatments that is useful in obstetric practice, namely, accelerating the healing of perineal wounds in postpartum mothers. According to research, sprays offer advantages in terms of safety and tolerability compared to conventional preparations (creams, gels, and ointments). Furthermore, they are easy to use, minimize skin irritation, and eliminate the need for hand washing after use. Due to their volatile solvent content, spray systems dry quickly and do not adhere to the skin after application, facilitating faster drug absorption through the skin[7].

The results of this study can be applied in health services, especially in obstetrics, as a non-pharmacological treatment made from natural ingredients such as papaya leaves to accelerate the healing of perineal wounds in postpartum mothers. Faster healing of

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perineal wounds can reduce pain and discomfort, allowing mothers to recover more quickly and focus on caring for their babies. This indirectly contributes to the well-being of mothers and babies, especially in supporting exclusive breastfeeding, which is crucial for infant health. Packaging 10% papaya leaf extract in a spray form based on natural ingredients aims to make it easier for postpartum mothers to use and is a more practical and economical solution. Furthermore, the results of this study can also enrich research insights and serve as a reference for future researchers to conduct human research through clinical trials.

This research was not without limitations. The researchers did not conduct stability testing on the papaya leaf extract spray product due to the lengthy timeframe (3 to 12 months) and limited testing costs. They also did not conduct irritation and microbial tests to confirm the safety and quality of the papaya leaf extract spray product. Furthermore, the assessment of perineal wound healing in mice was conducted only macroscopically and not microscopically.

CONCLUSION

Administering 10% papaya leaf extract spray twice daily for 7 days was effective in accelerating the healing of perineal wounds in white rats (p=0.001) compared to clean and dry treatment. The application of 10% papaya leaf extract spray requires further clinical trials if it is to be applied to human health programs, especially postpartum mothers, regarding its formulation, safety, and effectiveness. This study suggests that further researchers look for active compounds in papaya leaves that have the potential to inhibit gram-positive and gram-negative bacteria in perineal wounds, and the need for microscopic examination for a more objective assessment. In addition, it is also recommended that the stability test of the papaya leaf extract spray product be conducted to determine the expiration date.

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