COMPARISON OF THE EFFECTIVENESS GEL AND HYDROGEL OF RENGGAK LEAF ON PERINEAL WOUND HEALING IN RATS

Perbandingan Efektivitas Gel Dan Hydrogel Daun Renggak Terhadap Penyembuhan Luka Perineum Pada Tikus

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ABSTRAK

Luka perineum dapat disebabkan oleh persalinan secara spontan oleh alat atau tindakan (episiotomi) dan terjadi selama kelahiran berlangsung. Luka perineum terjadi pada hampir semua persalinan pervaginam yang dialami oleh ibu primipara dan tidak jarang juga terjadi pada multipara. Data Kementerian Kesehatan tahun 2021 menunjukkan bahwa 83% ibu melahirkan pervaginam mengalami ruptur perineum, dengan 63% disebabkan oleh episiotomi dan 38% disebabkan oleh robekan spontan. Luka perineum yang tidak tertangani dengan tepat dan cepat dapat menyebabkan keterbatasan aktivitas fisik serta gangguan laktasi. Penanganan non-farmakologi menggunakan ekstrak daun renggak menjadi solusi alternatif untuk penyembuhan luka perineum. Tujuan penelitian ini untuk mengetahui perbandingan gel dan hydrogel daun renggak (amomum dealbatum roxb) terhadap penyembuhan luka perineum pada tikus dibandingkan kelompok kontrol perawatan bersih kering. Jenis penelitian ini yaitu True Experiment dengan Post-test with Control Group menggunakan simple random sampling dengan jumlah sampel 24 ekor tikus betina (Rattus Norvegicus) yang dibagi menjadi 3 kelompok yaitu kelompok gel, hydrogel dan kelompok perawatan bersih kering. Instrumen yang digunakan yaitu lembar observasi skor skala REEDA. Analisis dalam penelitian ini menggunakan uji friedman dan Kruskal wallis. Hasil penelitian menunjukkan bahwa gel dan hydrogel daun renggak lebih cepat dalam proses penyembuhan luka perineum sejak hari pertama dibandingkan kelompok kontrol perawatan bersih kering. Hasil analisis kelompok intervensi dan kontrol terdapat penurunan skala REEDA yang bermakna dari hari ke 1 sampai hari ke 7, hal ini ditunjukkan dengan p-value sebesar 0,00 (p-value <0,05). Dapat disimpulkan bahwa pemberian gel dan hydrogel daun renggak efektif sebagai alternatif penyembuhan luka perineum.

***Kata Kunci**: gel daun renggak, hydrogel daun renggak, luka perineum*

ABSTRACT

Perineal injuries can be caused by spontaneous delivery by tools or actions (episiotomy) and occur during birth. Perineal wounds occur almost primiparous and not infrequently also occur in multiparous. Data from the Ministry of Health for 2021 shows that 83% of mothers who gave birth vaginally experienced perineal tears, 63% caused by episiotomy and 38% caused by spontaneous tears. Perineal wounds that are not treated quickly cause limitations in physical activity, and lactation disorders. Non-pharmacological treatment using renggak leaf extract is an alternative solution for healing perineal wounds. This research aimed to determine the comparison of gel and hydrogel of renggak leaves on perineal wound healing in rats compared to dry clean wound control group. This study used True Experiment with Post-test Control Group using simple random sampling with a sample of 24 female rats which were divided into 3 groups, namely gel, hydrogel and dry clean treatment. The instrument used REEDA scale score observation sheet. The analysis used the Friedman and Kruskal wallis tests. Results show that gel and hydrogel renggak leaves faster in the healing process

of perineal wounds from the first day compared to the dry clean wound control group. The results of the analysis of the intervention and control groups showed a significant decrease in the REEDA scale from day 1 to day 7, this was indicated by a p-value of 0.00 (p-value <0.05). Based on the research the application of gel and hydrogel of renggak leaves is effective as an alternative to perineal wound healing.

Keywords: perineal wound, renggak leaves gel, renggak leaves hydrogel

INTRODUCTION

Perineal wounds, namely lacerations during birth tears in the perineum, can be caused by spontaneous delivery by tools or procedures (*episiotomy*). Almost all vaginal deliveries by primiparous mothers cause perineal wounds, and multiparous mothers also often experience them [1]. Wounds in the perineum are divided into four levels, namely grade I, grade II, grade III, and grade IV rupture [2]. Perineal injuries can result from a variety of causes, including the perineal rupture, an extended second stage of labor, shoulder dystocia, instrumental delivery, and irregular fetal heart rate patterns. [3].

According to WHO, as many as 80% of *postpartum* mothers in the world experience perineal wounds. These figures show that almost all *postpartum* mothers throughout the world experience perineal wounds. If we look at the degree of perineal injury, the highest prevalence is second-degree 73.4%, first-degree 17.7%, third-degree 8.4%, and fourth-degree 0.5%. In 2009, the incidence of perineal lacerations was 2.7 million cases. This number is estimated to increase by 6.3 million in 2050 [4]. In 2021, the incidence of perineal rupture in women giving birth vaginally was 83% in 2020, of which 63% was caused by episiotomy and 38% was due to spontaneous tearing [5].

Wound care according to WHO is that the wound is always clean particularly after passing urine or faeces, washing the perineum once or twice per day, Sanitary pads must also be changed frequently to prevent infection [6]. The impact if perineal wound care is not good can cause infection, where infection during the postpartum period is one of the causes of post partum maternal death [7]. Furthermore perineal wounds that do not receive appropriate and quick action can cause psychological and emotional disorders such as insomnia, fatigue, anxiety, limited physical activity, lactation disorders, depression, postpartum blues, thrombophlebitis, and infection [8]. Many efforts have been developed to prevent the emergence of infection and accelerate the healing of perineal wounds through pharmacological and non-pharmacological treatment. Pharmacological treatments include oral antibiotics such as *amoxicillin* and *ampicillin*, but these treatments can cause bacterial resistance, and the use of antiseptics such as *povidone-iodine* (betadine) used to treat perineal ruptures can result in unexpected side effects such as allergic hypersensitivity reactions and prolonged wound healing and can inhibit fibroblast proliferation [9].

It has been known for several years that some antiseptics and disinfectants are, on the basis of MICs, somewhat less inhibitory to *S. aureus* [10] .According to research, antiseptics kill existing bacteria and can destroy white blood cells and blood cells, which can kill pathogenic bacteria. The antiseptic povidone iodine kills microbes very well. In addition, the body considers the substances in antiseptics to be foreign objects because their structure and components differ from the body's cells. As a result, the antiseptic content can cause wound irritation [11].

Several researchers are developing other, safer methods, moving to the non-pharmacological drug class, namely drugs that contain ingredients sourced from the natural environment. One treatment for healing perineal wounds is complementary therapy. Traditional medicine, which includes complementary therapy, is based on information that was passed down through generations in many communities prior to the development of modern medicine. In the pharmaceutical sector globally, plant-based medications are becoming more and more popular lately since they are more affordable,

simpler to make, and have less adverse effects than traditional synthetic medications, making them more accessible and safe. [12]. The *World Health Organization* (WHO) states that 65% of developed countries and 80% of people in developing countries use herbs. Therefore, WHO encourages the reuse of traditional medicine and recommends "Back to Nature" to accompany modern medicine [13]. Approximately one-third of all conventional medicines are used in the treatment of skin diseases (including wounds) compared to only 1–3% of contemporary medications [14]

The renggak plant (*amomum dealbatum roxb*) is a wild plant and usually found in forests or gardens, especially in damp soil that is rich in humus. This plant can be propagated by planting the rooted tip of the rhizome. This plant grows widely in India, Nepal, Bangladesh, Yunan, Thailand and Indonesia. In Indonesia, the renggak plant is a typical plant of Lombok Island which is known to be rich in secondary metabolite compounds in the form of *flavonoids* which have activity as a fibrinolysis promoter and can reduce wound inflammation [15]. Based on empirical use, people on the island of Lombok use boiled leaves of the renggak plant as bath water for mothers after giving birth [16]. So research is carried out to reveal and obtain scientifically based knowledge to anticipate problems. Several studies have shown that apart from *flavonoids*, renggak leaves also contain secondary metabolites, namely *alkaloids*, *tannins*, and *triterpenoids*, which are also helpful as antioxidants [16]. The essential oils of some Amomum have been widely studied for chemical composition, antibacterial and antioxidant activities, anti-inflammatory activity and also used as an antimicrobial agent [17], [18]

Using renggak leaves to heal perineal wounds can be made more accessible by making it into a *gel* formulation from this material. *Gel* preparations have many advantages, such as not being sticky, comfortable to use, easy to wash, and not leaving a layer of oil on the skin, so that the wound healing process can be faster, have high viscosity and adhesive power, which prevents them from flowing easily over the skin's surface. They also have thixotropic properties, which allow them to spread quickly when smeared and leave no marks. The gel only forms a thin layer when applied, and it can penetrate farther than cream. It is also preferred cosmetically because it melts instantly upon contact with the skin, forming a single layer that is better absorbed than cream [19]. Apart from using renggak leaf *gel*, there is a wound care treatment using the modern dressing method, which is wound care with a topical preparation in the form of *hydrogel* from renggak (Amomum dealbatum Roxb), the *hydrogel* with the main mixture is water, which can be directly applied to the injured skin and can create a moist atmosphere/rehydrate wounds, provide a cooling effect, and help reduce patient pain because of compliance with the skin. *Hydrogel* has advantages compared to other topical medicines because it can absorb more optimally, has the lowest irritating effect, and is effective in healing cuts, burns, and several other diseases. The material used to make *hydrogel* is water, so it reduces fluid loss in the wound area and is more comfortable to use [20]. Hydrogels may promote fibroblast and keratinocyte proliferation at the wound site. They can also suppress both Gram-positive and Gram-negative bacteria, which is useful for treating wounds caused by bacteria resistant to medications. [21].

Renggak leaf *gel* and *hydrogel* have different formulations, so researchers will compare renggak leaf *gel* and *hydrogel* to accelerate perineal wound healing. The experimental animals used in this research were rats (*Rattus Norvegicus*). This rats is an innovation that needs to be tested before it can be used on humans, namely *postpartum* mother. Therefore, the author is interested in comparing gel and hydrogel with formulations of renggak leaves (*Amomum dealbatum roxb*) with dry clean treatment in perineal wounds healing in rats.

METHODS

Materials

The test animals used were 24 rats (*Rattus Norvegicus*) aged 2-3 months with a body weight of 150-300 grams. The main ingredients for making *gel* and *hydrogel* were 10% renggak leaf extract, HPMC, Carbopol 940, Trietonalamine (TEA), and distilled water.

Research Design

This research is an true experiment using post test with control group design. Data collection tools were a demographic questionnaire, Redness, Edema, Ecchymosis, Discharge, and Approximation (REEDA) scale to measure episiotomy wound healing.

Preparation of renggak leaf extract

The preparation of leaf extracts ,gels and hydrogels was carried out in the chemical and biological analysis laboratory of Cendekia Nanotech Hutama (CNH), Semarang. The renggak leaves are cut and then dried in the oven for 12 hours at a temperature of 45℃. Next, the dried leaves are ground to a dry powder, and then the renggak leaf powder is extracted using the maceration method, which is carried out by soaking the powder in 1 liter of 96% ethanol solution for 3x24 hours. The soaking results are then separated from the debris and filtrate using filter paper. The resulting filtrate is evaporated using a rotary tool to obtain a thick extract.

Making Gel preparations

The gel preparation is made from the basic ingredients of HPMC, Triethanolamine, and distilled water, stirred until homogeneous. Then, 10% renggak leaf extract was added.

Making Hydrogel preparations

The *hydrogel* preparation is made from the basic ingredients of Carbopol 940, Triethanolamine, and distilled water, stirred until homogeneous. Then, 10% renggak leaf extract was added.

Animal treatment test

The research took place in March 2023 in the experimental animal laboratory at the faculty's of medicine Diponegoro University. This research has received research permission from the institution and the Semarang Ministry of Health Polytechnic Ethics Commission No.0149/EA/KEPK/2023. A total of 24 female rats were divided equally into three groups: the control group received dry clean treatment, intervention group 1 was treated with 10% renggak leaf *gel* and intervention group 2 was treated with 10% renggak leaf *hydrogel*. Female rats were acclimated for 7 days by being placed in a cage with a finely shaved wooden floor to keep them warm, kept and given the same treatment throughout the study. The rats were anesthetized using ether then shaved in the area to be incised around the perineum, and a mediolateral incision was made. *Gel* and *hydrogel* are administered by smearing them on the wound 2x1 for seven days.

Data Analysis

The analysis carried out was the *Shapiro-Wilk* normality test. Paired data tests were carried out using the *Friedman* and *post hoc Wilcoxon* tests. Meanwhile, unpaired data were tested using ANOVA and *Kruskal Wallis* tests with post hoc ANOVA LSD and *post hoc Mann Whitney.*

RESULT

Table 1. Mean and Standard Deviation of Wound Healing in the Gel, Hydrogel and Groups Dry Clean

Variabel	Mean and Standard Deviation of Gel, Hydrogel and Dry Clean		
	Gel	*Hydrogel*	Dry Clean
	Mean ±SD	Mean ±SD	Mean±SD
Day 1	11,63 ±0,52	11,38 ±0,74	11,75±0,46
Day 2	9,38 ±0,74	8,50±1,19	11,38±0,74
Day 3	6,13 ±2,10	6,13±1,35	9,13±0,99
Day 4	4,75 ±1,83	4,38±1,99	6,25±1,48
Day 5	4,25 ±1,98	2,38±1,68	3,88±1,64
Day 6	2,00 ±1,60	0,88±0,99	1,75±0,88
Day 7	0,38 ±0,51	0,13±0,35	0,75±0,46

Based on table 1 above, it can be concluded that the average wound healing from the REEDA score from the first day to the seventh day in the intervention group, namely by administering renggak leaf *gel* and *hydrogel* and in the control group by administering dry clean treatment has decreased, namely by the mean REEDA score in the *gel* group, it was 11,63 on the first day and 0,38 on the seventh day. Average value The REEDA score in the *hydrogel* group was 11,38 on the first day and 0,13 on the seventh day. The mean REEDA score in the control group was 11,75 on the first day and 0,75 on the seventh day.

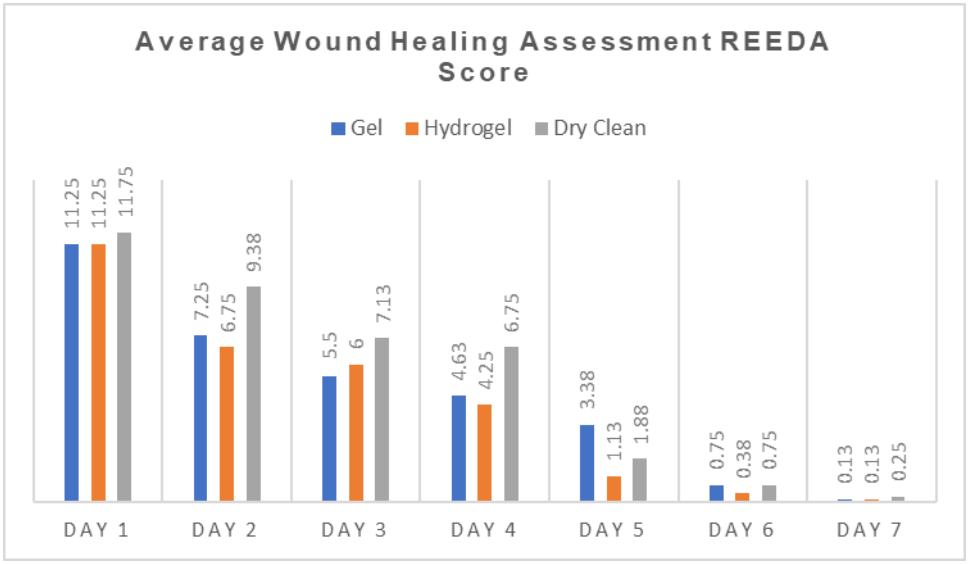

Figure 1. Graph of Average Wound Healing REEDA Score

Based on the graph in Figure 1, it is explained that the average rate of wound healing has decreased daily. The average of the *hydrogel* intervention group fell more quickly than the *gel* and dry clean groups. The lower average REEDA score resulted in better wound regeneration results. Based on graph one shows that wound healing in the *hydrogel* group was better than gel and dry clean treatment.

Table 2. Paired data test for REEDA scores

Test paired data REEDA scores			
Variabel	Gel	*Hydrogel*	Dry Clean
	Mean±SD	Mean±SD	Mean±SD
Day 1	11,63±0,52	11,38±0,74	11,75±0,46
Day 2	9,38±0,74	8,50±1,19	11,38±0,74
Day 3	6,13±2,10	6,13±1,35	9,13±0,99
Day 4	4,75±1,83	4,38±1,99	6,25±1,48
Day 5	4,25±1,98	2,38±1,68	3,88±1,64
Day 6	2,00±1,60	0,88±0,99	1,75±0,88
Day 7	0,38±0,51	0,13±0,35	0,75±0,46
*p-value**	0,00	0,00	0,00

**Friedman*

Table 3. Paired data test between times of REEDA scores

Post Hoc test on paired data			
	Gel	*Hydrogel*	Dry Clean
	*p-value**	*p-value**	*p-value**
H1-H2	0,01	0,01	0,08
H2-H3	0,01	0,01	0,01
H3-H4	0,03	0,03	0,01
H4-H5	0,15	0,02	0,01
H5-H6	0,02	0,02	0,02
H6-H7	0,02	0,06	0,05
H1-H7	0,01	0,01	0,01

**Pos Hoc Wilcoxon*

Table 2 shows effectiveness test results of paired data on the *p-value* of the gel intervention group, which is 0,00 (p < 0,05), which means that renggak leaf extract *gel* speeds up the healing process of perineal wounds. The *p-value* of the *hydrogel* intervention group was 0,00 (p<0,05), meaning that the renggak leaf extract *hydrogel* accelerate the perineal wound healing procedure. The *p-value* of the dry clean control group was 0,00 (p<0,05), which means that dry clean treatment accelerates the healing process of perineal wounds. Reflected in the *post hoc* test results in table 3, paired data showed that there were differences on the first day, namely in the gel group 0,01 (p<0.05), *hydrogel* 0,01 (p<0,05) if a comparison was made with the clean care control group dry 0,08 (p> 0,05).

Table 4. Unpaired data test for REEDA scores

Test unpaired data							
Variabel	Gel		*Hydrogel*		Dry Clean		*p-value*
	Mean	±SD	Mean	±SD	Mean	±SD	
Day 1	11,63	0,52	11,38	0,74	11,75	0,46	0,52**
Day 2	9,38	0,74	8,50	1,19	11,38	0,74	0,00**
Day 3	6,13	2,10	6,13	1,35	9,13	0,99	0,00*
Day 4	4,75	1,83	4,38	1,99	6,25	1,48	0,10*
Day 5	4,25	1,98	2,38	1,68	3,88	1,64	0,10*
Day 6	2,00	1,60	0,88	0,99	1,75	0,88	0,08**
Day 7	0,38	0,51	0,13	0,35	0,75	0,46	0,04**

**Anova* ***Kruskal-Wallis*

Table 5. Unpaired data test between groups of REEDA scores

	***Post Hoc* test for unpaired data**		
Variabel	Gel-*Hydrogel*	Gel-Dry Clean	*Hydrogel*-Dry Clean
Day 1	-	-	-
Day 2	0,06	0,00	0,00**
Day 3	1,00	0,00	0,00*
Day 4	-	-	-
Day 5	-	-	-
Day 6	-	-	-
Day 7	0,26	0,14	0,01**

**Pos-Hoc Anova LSD **Pos-Hoc Mann Whitney*

Based on table 4 above, it can be seen that the results of the unpaired data test on the seventh day, the *p-value* for the intervention group and the control group was 0,04 (*p*<0,05) because the results were significant, then continued with the *Post Hoc* LSD test in table 5 showing between *gel-hydrogel* 0,26 (*p*>0,05) means there is no significant difference in the process of accelerating wound healing, *gel*- dryclean 0,14 (*p*>0.05) means there is no significant difference in the process of accelerating wound healing and *hydrogel*-dry clean 0,01 (*p*<0,05) has a significant difference in the process of accelerating woundhealing.

DISCUSSION`

A. Effectiveness of Renggak Leaf *Gel* and *Hydrogel* in Healing Perineal Wounds Based on REEDA Score

Based on the results of research carried out using the *Friedman* statistical test, the results were that the administration of 10% renggak leaf gel and *hydrogel* and the control group, which was carried out routinely 2x1 for seven days was effective in healing perineal wounds by 0,00 (*p-value* <0,05). So, it can be concluded statistically that the healing of perineal wounds in the intervention and control groups is not different. However, in the average value of the REEDA score on the seventh day, there is a greater difference in reduction in the *hydrogel* intervention group 0,13 compared to the dry clean treatment 0,75 this proves that hydrogel has greater value in healing perineal wounds through the REEDA score.

B. Differences in Perineal Wound Healing Time Based on REEDA Score

Based on analysis of paired data using the *Friedman* test in the intervention group and the control group, it showed significant results, followed by the *Post Hoc Wilcoxon* test to determine the difference in time for healing of perineal wounds. In the *Post Hoc* test on the first day and the second day, the *gel and hydrogel* had a *p-value* <0,05 (0,01), while the dry clean treatment resulted in a *p-value*>0,05 (0,08). It can be stated that the renggak leaf *gel* and *hydrogel* were faster in the process of healing perineal wounds from the first day compared to the dry clean treatment control group.

Next, an unpaired *Kruskal Wallis* test compared the three treatment groups regarding perineal wound healing. The REEDA score assessment on the seventh day of the intervention group and the control group was 0,04 (*p*<0,05) because the results were significant and then continued with the *Post Hoc* test, namely *gel-hydrogel* 0,26 (*p*>0,05) meaning that no significant difference to the process of accelerating wound healing, *gel*-dry clean 0,14 (*p*>0,05) meaning there is no significant difference to the process of accelerating wound healing then *hydrogel*-dry clean 0,01 (*p*<0,05) meaning there is a difference which is significant in accelerating the process of wound healing.

Renggak leaf extract *gel* and *hydrogel* contain the active substances *flavonoids*, *alkaloids*, *tannins*, and *triterpenoids*, which have been proven to be efficacious in healing wounds. The pharmacological activity of *flavonoids* as anti-inflammatory occurs through various mechanisms, including stopping the action of *cyclooxygenase*

(COX) and *lipoxygenase* enzymes, stopping *leukocyte* accumulation, stopping neutrophil degranulation, and stopping *histamine* release [22]. Some *alkaloids* have been reported to increase the antibacterial activity of antibiotics, which can cause disruption of the peptidoglycan component of bacterial cells and cause cell death due to the formation of incomplete cell wall layers [23]. *Tannins* can help wound healing and act as antioxidants and antimicrobials, influencing wound healing and accelerating epithelialization. *Tannins* also act as antiseptics on surface wounds and work as bacteriostatic [22]. *Triterpenoids* have been previously reported to be an effective for the treatment of skin wounds, which is capable of regulating the ROS production in wound environment and promoting wound repair [24].

The wound healing process starts from the inflammation, proliferation, and remodeling phases [25] . According to theory, the wound healing process begins on the first day of the *inflammatory* phase and ends on the seventh day of the *proliferation* phase. This healing stage aims to restore skin integrity and add new tissue to the injured area [26].

The collagen layer and dermis epithelium formation mark the end of the *proliferation* phase. Various growth factors made by platelets and macrophages appear to accelerate this process. Collagen performs a more specific function by forming of new tissue (*connective tissue matrix*), and *fibroblasts* secrete substrate, meaning new *fibroblasts*, macrophages, and blood vessels can enter the wound area. A sign of the *proliferation* phase is the formation of granulation tissue in the wound. Concurrent with constructing new capillaries, fibroblast components, and inflammatory cells are embedded in a loose extracellular tissue consisting of a matrix of collagen, *fibronectin*, and *hyaluronic* acid known as granulation tissue. [27].

Fibroblasts and newly formed vasculature synthesise the extracellular matrix to generate the granulation tissue. Granulation tissue growth is a sign of wound healing and is an essential step in the wound repair process. In addition to filling in tissue deficiencies, healthy granulation tissue acts as a scaffold for the epithelium at the margin of the wound [28].

Before applying Drug discovery and development to humans requires pre-clinical testing and clinical trials. Preclinical tests are carried out with isolated cell cultures (*in vitro*) to test drug binding to receptors, then clinical trials are carried out with intact animals (*in vivo*). In this research, rats (*Rattus Norvegicus*) were used to determine whether the drugs used had toxic effects or were effective and safe. Clinical trials (conducted on humans) are carried out after the drug is proven useful and safe in experimental animals. Tests on humans must first be investigated for feasibility by an ethics committee [29].

CONCLUSION

The results of the study showed that renggak leaf gel and hydrogel were effective in healing perineal wound in rats. The application of renggak leaf hydrogel to perineal wounds shows that hydrogel has greater healing compared to gel and dry clean treatments. This research also suggests the need for further research regarding the content of active substances that have the potential to inhibit gram-positive and negative bacteria in perineal wounds and the need for microscopic examination to make the evaluation more objective.

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