



## Potential Red Leaves Extract on Improving The Effectiveness of Antibiotic in Postpartum (Study Experiment of Perineum Wound Healing Process)

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### Abstract

**Background:** Puerperal infection is caused by the entry of bacteria through uterine or perineal wounds. These bacteria can trigger proinflammatory cytokines. Excessive proinflammatory response results in tissue damage, septic shock to death. Among the non-pharmacological methods are extracts of red betel leaves which have phytochemical screening of flavonoids and tannins as antibacterial and antiseptic. **Purposes:** Knowing the potential of simplicia extract of red betel leaf on increasing the effectiveness of antibiotic in postpartum (study experiment of the process of healing of perineal wounds). **Method:** Quasi-experimental post-test only with control group design. Subjects were postpartum mothers with episiotomy perineal wounds that were sewn at Ummu Hani Purbalingga Mothers and Child Hospital using purposive sampling with a total of 38 respondents. The treatment group was given amoxicillin and red betel leaf simplicia extract, the control group was given amoxicillin and perineum wound care standard service. Provision of intervention carried out for 7 days, the measurement instrument for perineal wound healing is the REEDA score. Data analysis using independent t-test. **Result:** An independent test between the two groups found a mean difference in perineal wound healing p-value 0.0001. On intervention group the mean of perineal wound healing in day 5 and control group day 7. **Conclusion:** There is potential for simplicia red betel leaf extract to increase the effectiveness of antibiotic in postpartum.

**Keywords:** Red betel leaf extract; Postpartum infections; Perineal injury.

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## Introduction

The puerperium is a period that is still vulnerable to the life of postpartum (Berat et al., 2016). The number of maternal deaths is caused by complications during pregnancy, childbirth and the puerperium. According to the World Health Organization there are 210 million pregnant women, and 130 million births around the world, of which an estimated 558,000 women die each year due to complications of pregnancy and childbirth.<sup>2</sup> In Indonesia, maternal causes of death include 26.9% bleeding, eclampsia delivery 23%, puerperium infection 11%(RI Ministry of Health, 2018).

Cases of maternal deaths in Central Java Province in 2017 were 475 cases or 88.05 per 100,000 live births. In 2017, 69.5% of maternal deaths in Central Java occurred during the puerperium, 24.33% in pregnancy and 18.06% in labor. The postpartum mortality rate continues to increase from 2016 to 71.87%. Data in Central Java maternal mortality due to the incidence of puerperal infections by 4.04%.(GOVT, 2017) In Purbalingga there were 3 cases during 2019. Besides causing death, puerperal infection

also resulted in morbidity and problems for mothers including infertility and pelvic

inflammatory disease Kemenkes RI, 2014 Perineal injury is the biggest contributor to the causes of morbidity with complications in the form of puerperal infection (4.5%) (Manuaba, 2011). There are 2.7 million cases of perineal injury in maternal women. This figure is estimated to reach 6.3 million in 2020 (Health, 2014).

In cases of perineal wounds with episiotomy experiencing morbidity based on redness of 6.6%, edema 26.2%, ecchymosis 8.2%, discharge 11% and approximation 34.3% (Health, 2014). Scoring for self-evaluation of wound healing is with REEDA tools from Davidson 1974. This tool is to study redness, edema, ecchymosis (purplish patch of blood flow), discharge and approximation (closeness of skin edge). REEDA assesses five components of the healing process and perineal trauma. Each factor is given a score between 0 to 3 which represents the absence of signs until the signs of the worst level. The total scale score ranges from 0 to 15, with higher scores indicating worse wound healing.

Heal wounds can be marked with a REEDA score = 0 (Sujiyanti, 2010).

The infection itself occurs due to the entry of bacteria through uterine or birth canal injuries.(Pakasi & Kartikawati, 2013) The bacteria that cause puerperal infections release some toxins, namely Peptidoglycan (PepG) and lipoteichoic acid (LTA) which make the inflammatory response begin, then respond by macrophages by releasing proinflammatory cytokines such as Tumor Necrosis Factor-Alpha (TNF- $\alpha$ ), Interleukin 6, and then responding by macrophages by removing proinflammatory cytokines such as Tumor Necrosis Factor-Alpha (TNF- $\alpha$ ), Interleukin 6, and 1-Beta (IL-1 $\beta$ ) (Barrientos S, Stojadinovic O, 2015).

These bacteria will attack the placental implantation or the presence of perineal injury due to childbirth originating from normal cervical bacteria inhabitants and the birth canal or from the outside. Bacteria in the puerperium infection are gram-positive *Streptococcus Agalactiae*. *Streptococcus Agalactiae* which is a major cause of premature birth, premature rupture of membranes, infections, pneumonia, meningitis and newborn sepsis (Juliantina, F., Citra, DA, Nirwani, B., Nurmasitoh, T., Bowo, 2014). Beside being able to result in infection, the presence of perineal wounds in the mother also gives pain and discomfort during the postpartum period the mother goes

through (Eghdampour F, Jahdie F, Kheyrikhah M, 2013).

One of the pharmacological drugs of antibiotics used as an effort to heal wounds and prevent infection of the puerperium is amoxicillin, which is too often used and not in accordance with the provisions can cause the emergence of resistance in bacteria. This is because synthetic antibiotics are no longer effective, even giving side effects while the side effects of herbal medicines are less compared to conventional medicines (pharmacological drugs) (Friambodo B, Purnomo Y, 2017). Therefore the addition of the use of herbal or non-pharmacological drugs can increase the effectiveness of the drug by achieving the target of recovery in the inflammatory process more quickly because of the synergistic effect obtained from the pharmacological drug amoxicillin (Nurdjanah R, Besar B, Postharvest P, 2019).

Indonesia is one of the centers of biodiversity. Various plants contain chemicals that have the potential as medicinal ingredients (Nurdjanah R, Besar B, Postharvest P, 2019). Herbal medicine is one of good treatment because it is believed to be an easily obtainable drug, making it simple, inexpensive and harmless because it is made from natural ingredients and also supported by the Ministry of Health's regulation of herbal medicine in 2010 (Nurdjanah R, Besar B, Postharvest P, 2019).

Red betel leaf (*Piper crocatum* Ruiz & Pav.) Can be used as a non-pharmacological therapy in overcoming inflammation and preventing infection. This is due to phytochemical screening, namely essential oils, alkaloid, saponin, tannin and flavonoids. The content of flavonoids and tannins as phenols and polyphenols has the highest activity as an antimicrobial that is able to fight gram-positive bacteria, namely *Streptococcus Agalactiae* and *Candida Albicans* by disrupting the integrity of bacterial cell membranes by changing the properties of bacterial cell proteins so that bacterial cell wall permeability increases and bacteria become lysis (Inggit PA, 2011). Flavonoids also function as antifungal, antioxidant, anti inflammatory and natural antibiotics (Alfarabi M, Bintang M, Suryani, 2010). The presence of cavinol compounds which is a phenol group also contributes to the role as a power to kill bacteria and five times stronger than ordinary phenol groups (Anggraini V, 2017).

To get the best chemical content from an ingredient, it must go through an extraction process that aims to remove certain components from the main ingredient with the help of a solvent. Polar and semi-polar compounds are found maximally in ethanol solvents *hydrogen* 70%, namely flavonoid compounds and tannins (Nurdjanah R, Besar B, Postharvest P, 2019). The product form of the sympetic extract in this study was

packaged in a shell capsule from beef gelatin and using 10% sagu starch maltodextrin coating because the water content in starch was low compared to vegetable starch so that the stability of the material was better and not easily damaged when stored. The encapsulation process was chosen with the aim of the respondents getting easier, regular and efficient in consuming (Adisti, 2016). Making extracts was carried out according to the SOP at the Soegijapranata Catholic University of Semarang Food Engineering Laboratory. The dosage of simplicia extract of red betel leaf in this study was by confession of the absolute dose of rat 50 mg/ kg (Anggraini V, 2017).

BB rat dose 200 gr:

$$20/1000 \times 50 \text{ mg} = 1/5 \times 50 \text{ mg} = 10 \text{ mg}.$$

Human dose BB 70 kg:

$$10 \text{ mg} \times 56 = 560 \text{ mg}$$

Dosage for BB Women 50 kg:

$$50/70 \times 560 \text{ mg} = 400 \text{ mg} / \text{day}.$$

D.R. Laurence and A.L. Bacharach, Pharmacometrics.

An acute toxicity test showed practically non-toxic red betel leaf extract (LD50 > 5000mg) based on OICD (Alfarabi M, Bintang M, Suryani, 2010). Then the recommended doctor's dose is 400mg/capsule according to the needs of humans in taking 2x/day.

## Method

This type of research is a quasy experiment post-test only with control group design. The sampling technique is to use a purposive sampling technique with a study sample of normal postpartum mothers who suffered perineal injury by episiotomy and suturing and fulfilling the inclusion and exclusion criteria in January-March, amounting to 38 mothers in Ummu Hani Purbalingga Mothers and Child Hospital Regency. The interventions in the two groups were the same for 7 days, namely the assessment of the healing process of the perineal wound using the REEDA score assessment sheet which was conducted every morning on day 1 (as a pretest) to day 7 (as a posttest) by the enumerator and then recorded on the observation sheet and also giving simplicia red betel leaf extract capsules together with the mother taking amoxicillin for the treatment group and taking amoxicillin only for the control group. The results of the intervention are recorded on the data sheet. Then do the data analysis using the independent t test. This research has obtained etichal clereance from the bioethics commission of the Faculty of Medicine, Sultan Agung University of Semarang. Then do the data analysis using the independent t test. This research has obtained etichal clereance from the bioethics commission of the Faculty of Medicine, Sultan Agung University of

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## Result and Discussion

### 1. Characteristics of Respondents Based on Age, Parity, Nutrition and HB Levels.

The majority of postpartum mothers in the treatment group were at the age of 21-30 years with 14 respondents (73.7%) with higher education as many as 11 respondents (57.9%) parity was mostly multipara with 14 respondents (73.7%) Maternal nutritional status is indicated by the body mass index of all normal respondents is 19 respondents (100%) and HB levels also indicate respondents in normal condition as many as 19 respondents (100%).

In the control group it is known that the majority of postpartum mothers are aged 21-30 years, namely 17 respondents (58.9%) with higher education as many as 10 respondents (52.6%) parity is mostly multipara, 15 respondents (78.9%) the nutritional status of mothers which is indicated by the body mass index of all normal respondents is 19 respondents (100%) and HB levels also indicate respondents are in normal condition as many as 19 respondents (100%). From all

characteristic data after homogeneity test shows the  $p$  value  $> 0.05$ , then the characteristic data can be said to have the same data variant so it does not affect the research results.

## 2. Analysis of the Perineum Wound Healing Process Control and Treatment Group.

Using the independent  $t$  test test analysis in table 1 shows the  $p$  value redness of 0.0001 edema 0.010 ecchymosis 0.001 discharge 0.001 and approximation 0.0001 ( $<0.05$ ) in both groups. This shows that there is an effect of red betel leaf *simplicia* extract to increase the effectiveness of antibiotic use in postpartum mothers with perineal injury on REEDA score and for test results on perineal wound healing using REEDA score = 0 (day of wound healing) showed  $p$  value 0,0001 ( $< 0.05$ ).

## 3. Average Acceleration of Perineal Wound Healing Between Groups.

In the treatment group the average redness was 3.79 edema 3.79 ecchymosis 2.68 discharge 2.79 and approximation 3.74 while in the control group the average redness was 5.37 edema 5.21 ecchymosis 4.21 discharge 4.42 and approximation 5,47. From these results it can be seen that the average value of each REEDA score in the treatment group is smaller than the control group which can be interpreted as the severity of the wound condition during the study group treatment is smaller than the control group. This is consistent with the results of the test value on perineal wound healing using REEDA score = 0 (wound healing day) showing  $p$  value 0,0001 ( $<0.05$ ).

Table 1. Distribusi Frekuensi Karakteristik Responden

Respondent Characteristics	Perlakuan		Kontrol		p value
	f	%	f	%	
<b>Age</b>					
18-20 years old	4	21,5	2	10,5	0,390
21-30 years old	15	78,9	17	89,5	
31-35 years old	0	0	0	0	
<b>Education levels <math>\Sigma</math> (%)</b>					
Elementary school	0	0	0	0	0,571
Middle (junior/senior high school)	8	42,1	10	52,6	
High (D3/S1)	11	57,9	9	47,4	
<b>Parity <math>\Sigma</math> (%)</b>					
Primipara	5	26,3	4	21,5	0,306
Multipara	14	73,7	15	78,9	
<b>Nutritional</b>					
IMT : Kurus <18,5	0	0	0	0	0,662
Normal 18,5-24,9	19	100	19	100	
Overweight 25-29,9	0	0	0	0	
Obesitas 30-39,9	0	0	0	0	
<b>HB levels</b>					
Normal 11-15 g/dL	19	100	19	100	0,920
Anemia <9 g/dL	0	0	0	0	

\*p value = uji homogenitas menggunakan Uji Levene

Table 2. Potential of Simplisia Red Betel Leaf Extract Against Increase Effectiveness of Antibiotic Use in Postpartum Mothers.

Dependent Variable	Mean $\pm$ SD		p value *
	Treatment	Control	
Redness	3.79 $\pm$ 0.976	5.37 $\pm$ 1,499	0.0001
Edema	3.79 $\pm$ 0.976	5.21 $\pm$ 1.357	0.010
Ecchymosis	2.68 $\pm$ 1.057	4.21 $\pm$ 1,357	0.001
Discharge	2.79 $\pm$ 0.976	4.42 $\pm$ 1,610	0.001
Approximation	3.74 $\pm$ 0.991	5.47 $\pm$ 1.389	0.0001
Perineum Wound Healing Day (REEDA score = 0)	4.58 $\pm$ 0.838	6.58 $\pm$ 0.838	0.0001

\*p value independent test t test

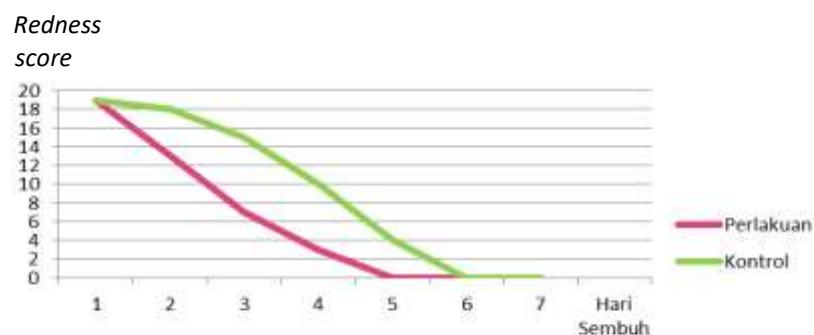


Figure 1. Redness Score Graph

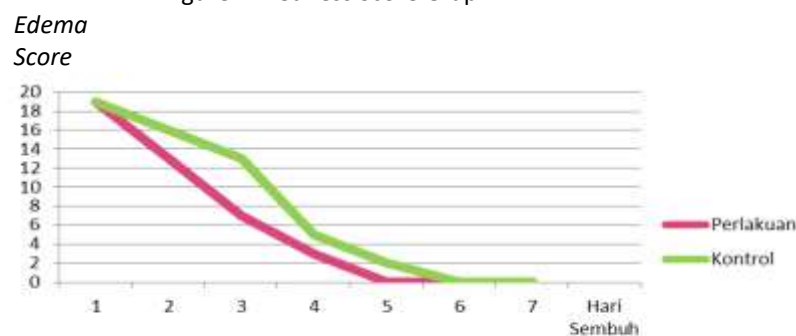


Figure 2 Graph Edema Score

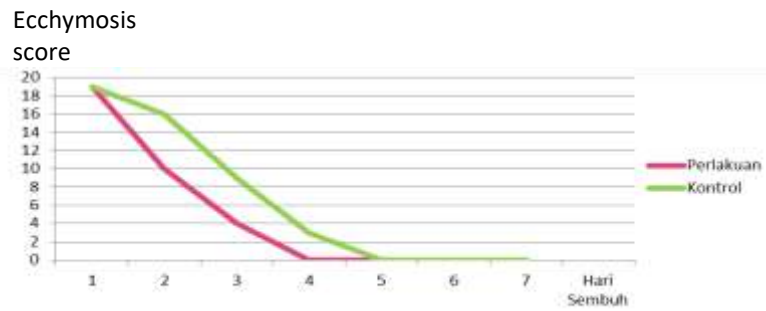


Figure 3 Ecchymosis Score graph

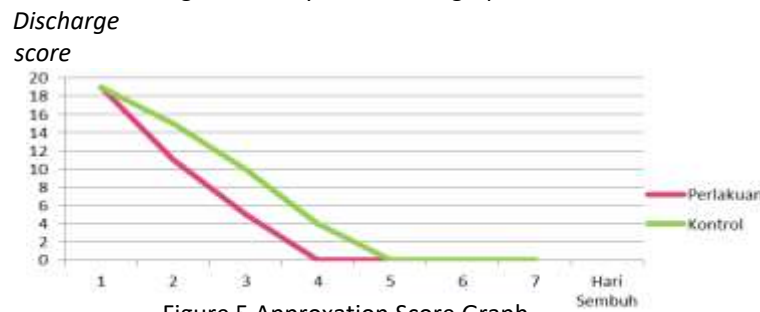


Figure 5 Approxation Score Graph

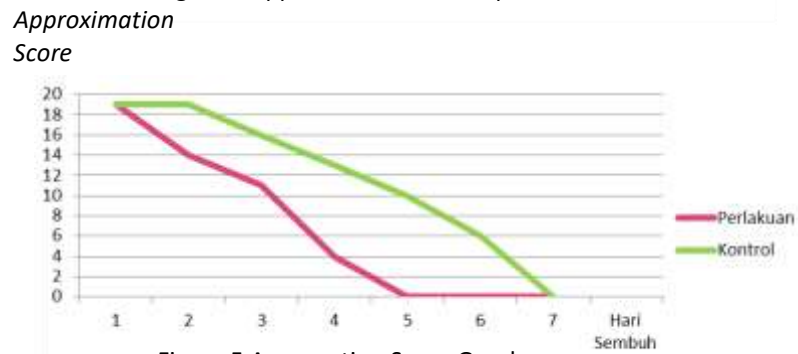


Figure 5 Approxation Score Graph

**Graph of Accelerated Healing of Perineum Wounds REEDA score = 0**

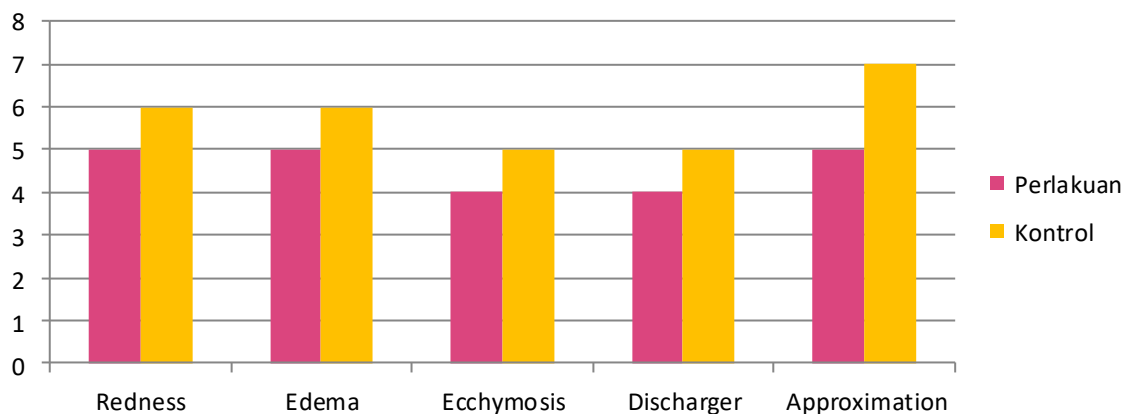


Figure 6 Graph of Accelerated Healing of Perineum Wounds REEDA score = 0

The results of this study are in line with Karimah 2019 research entitled the period of perineal wound healing in postpartum mothers between the decoction of water

treatments of binahong leaves with red betel leaves with the type of quasy experiment post test only without group control design. Sample 32 post partum



mothers. The results of the mann whitney test showed a p value of 0.0001 (p value <0.05) so that there was a difference in the duration of perineal wound healing between the treatment of binahong leaf cooking water and the red betel leaf cooking water. From the results of this study, it is expected that midwives advise postpartum mothers to treat perineal wounds using boiled red betel leaf water (Karimah, N, Khafidhoh N, 2019).

Fitriyani 2011 research on the anti-inflammatory test of methanol extract of red betel leaf (*piper crocatum ruiz & pav*) in white rats namely red betel leaf has been made in a more effective form, namely extract and has been proven to cure inflammation in the wounds of test animals with the result that inflammation as natural response that occurs in tissue damage has been using NSAID (non-steroidal anti-inflammatory) treatment which specifically has a long history and caused a lot of controversy and side effects. One of the medicinal plants used empirically for traditional medicine is red betel. This plant has the potential to be developed into a drug for anti-inflammatory because it contains flavonoids, saponins, tannins, and

alkaloids. Using caragenin induction method in mice. From the results of the study it was found that the extract with a dose of 50mg/kg weight showed an effective anti-inflammatory effect. These results indicate that the red betel extract provides a promising anti-inflammatory effect (Fitriyani A, Winarti L, Muslichah S, 2011).

Supported by the results of the 2016 Cahyanti study entitled the utilization of red betel leaf decoction (*piper crocatum*) against the inhibition of the bacteria *Streptococcus agalactiae* and *Streptococcus uberis*. *Streptococcus agalactiae* is a gram-positive bacteria in the vagina. The completely randomized design (RAL) experimental research method consisted of 4 treatments and 5 replications of the well diffusion method. The results showed that there was no significant difference in each concentration of red betel leaf with iodips used as a comparison in inhibiting the bacteria *Streptococcus agalactiae* and *Streptococcus uberis*, meaning that the red betel leaf decoction in all treatments had the same ability as iodips in inhibiting the bacteria *Streptococcus agalactiae* and *Streptococcus uberis* (Cahyanti, 2016).

Furthermore, the results of Maslikah 2018 entitled red betel leaf extract as an anti-inflammatory agent in rheumatoid arthritis mice. Extracts of red betel leaf on healing inflammation using TNF Alfa as an indicator shows that using 24 test animals of RA mice. Mice were then divided into 6 groups namely normal, RA (K-), RA + aspirin (K +), RA + EDSM dose of 100 mg / kgBB (P1), 200 mg / kgBB (P2), and 400 mg / kgBB (P3) . The results showed that the length of intestinal villi of mice treated with red selh leaf extract were close to normal. Based on the research results, red betel leaf extract can be used as a candidate drug for inflammation with an effective dose of 400 mg / kg (Maslikah Hospital., 2018).

Thus research using red betel leaf extract is proven to be one of the strong alternatives for the treatment of

### **Conclusion**

The application of red betel leaf simplicia extract to increase the effectiveness of antibiotic use in postpartum mothers with perineal wounds performed by episiotomy and stitched for 1-7 days 2x1 per day at a dose of 400 mg / capsule has an effect on:

inflammation and infection prevention. This is due to the superiority of the flavonoid and tannin content in the red betel extract which in this study was tested using the UV-VIS spectrophotometer analysis method with the results of nutritional content, namely flavonoids consisting of flavones and flavonols with test results of 2535, 880 mg / 100g and un-nutritional content, namely tannins with a yield of 908, 645mg / 100g. Making extracts and determining dosages are in accordance with the toxicity test and the conversion results of test animals to humans. This research has a limitation that is uncontrolled intake of nutrition / food consumed by mothers during implementation interventions that allow influence on the process of wound healing and absence *matching* between group.

1. The acceleration of perineal wound healing in the treatment group was more optimal on day 5 compared to the control group on day 7.
2. Increasing the effectiveness of antibiotic use in accelerating the healing of perineal wounds.

The next researcher can explore that is by adding a recall menu of mothers food during the intervention, randomizing sampling and matching between groups and also adding the dependent variable.

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