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The Effectiveness of Red Fruit Oil (*Pandanus conoideus* Lamk.) Emulgel on The Acceleration of The Incision Wound Healing Process

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ABSTRACT

Incision wounds have a fairly high prevalence in Indonesia. Chemical treatment of incision wounds has adverse side effects, therefore alternative treatment with natural ingredients is needed, namely using red fruit oil as the basic ingredient. The purpose of this study is to determine the effectiveness of red fruit oil (*Pandanus conoideus* Lamk.) gel emulsion on the healing process of incision wounds in males both macroscopically and microscopically. This is an experimental laboratory study. The study design used was true experimental with a post-test-only control group design approach. The population consisted of 25 male mice which were divided into 5 groups, namely: (1) K- was a control group where the incision wound on the back was given a gel emulsion base; (2) K+ was the control group where the incision wound on the back was given Iodine Povidone ; (3) P1 is the treatment group where the incision wound on the back is given a 5% red fruit oil gel emulsion (F1); (4) P2 is the treatment group where the incision wound on the back is given a red fruit oil gel emulsion 10% (F2); (5) P3 was the treatment group where the incision on the back was given a 15% red fruit oil gel emulsion (F3). The treatment was given for 14 days. The data were then analyzed using the ANOVA test. The result showed that the administration of red fruit oil emulgel had a significant effect on the size of the incision wound on the 7th day (p=0.035) and the 14th day (p=0.005). Giving red fruit oil emulgel also had a significant effect on the thickness of the epithelium (p=0.000) and the number of fibroblasts (p=0.000). It can be concluded that the administration of red fruit oil emulgel affects the healing process of the incision wound both macroscopically and microscopically.
Keywords: Red Fruit Oil (*Pandanus conoideus* Lamk.); Emulsion Gel; Topical; Incision Wound; Wound Healing

INTRODUCTION

Wounds are damage to the integrity of body tissues or loss of tissue anatomical unity caused by trauma (Bakkara, 2012). Based on their cause, wounds have several categories, including incisions, burns, bruises, stabs, abrasions, and lacerations (Wombeogo and Kuubire, 2014). Wounds need attention because they can cause complete or partial loss of organ function, sympathetic stress response, bacterial contamination, bleeding and blood clotting, and cell death (Sussman, *et al*., 2012).

The prevalence of wounds in Indonesia is quite high. Incisions have the second-highest prevalence after bruises, which is 20.1 million (Ministry of Health of the Republic of Indonesia, 2018). Incisions can occur intentionally (surgical wounds) or unintentionally (accidental wounds) due to sharp objects (Nabella, 2017). The chemical treatment for incisions often used by the public is iodine povidone. Povidone-Iodine is a local antibacterial compound that is effective in killing bacteria and spores and is widely used for skin antiseptics. Unfortunately, these antiseptic ingredients have several side effects, including irritation of the wound (Frederick, 2003), irritating and more toxic when entering the blood vessels, the use of 10% iodine Povidone can inhibit the formation of fibroblasts (Nurdiantini, *et al*., 2017).

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The use of traditional medicine is generally considered safer than the use of modern medicine. This is because traditional medicine has relatively fewer side effects plus several other advantages such as being cheaper and easier to obtain (WHO, 2003). One alternative traditional medicine that can be used in the treatment of incisions is the red fruit plant. The red fruit plant (*Pandanus conoideus* Lamk) is included in the Pandanus family. This plant is found in Papua and Papua New Guinea (Limbonga, 2009).

The chemical content of the red fruit plant that is widely used by the community is red fruit oil. Red fruit oil has good prospects to be developed, especially as an incision wound treatment. Red fruit oil is a red fruit extract containing various active components, namely -α-carotene, β-carotene, α-tocopherol, vitamin C, and unsaturated fatty acids, especially linoleic, oleic acid (Rohman, 2012). Red fruit oil is known to have anti-inflammatory effects and can increase the number of immune cells. When there is damage to skin tissue due to injury, increased immunity, inactivation of free radicals in the skin, as well as the synthesis of new collagen fibers are very important to accelerate the restoration of skin tissue integrity and accelerate the healing process and all of that can be obtained from the active components of red fruit oil. (Rohman, 2012).

Red fruit oil as an incision wound treatment can be given topically. Gel emulsion formulation is one of the most popular topical dosage forms because of its superior physicochemical properties. An emulsion is a liquid dispersion or suspension in another liquid that does not mix under normal conditions (Winarno, 1997). In the manufacture of emulsions, the principle is mixing or homogenization without involving high temperatures in a relatively short time, so that the active components are relatively stable. The advantages of gel emulsion preparations include a cooling effect on the skin when used; the appearance of the clear and elegant preparation; when applied to the dry skin, it leaves a translucent, elastic, high adhesive film that does not clog pores so that pore breathing is not disturbed; easy to wash with water; drug release is good; and has a good ability to spread on the skin (Wardiyah, 2015).

Macroscopic and microscopic observations need to be made to draw a comprehensive conclusion on whether red fruit oil gel emulsion indeed has a significant effect on the rapidity of wound healing. Macroscopic observations are carried out to determine the activity of using test preparations given topically for signs of inflammation, namely redness, swelling, and the formation of scabs in the wound (Syailindra, 2017). Meanwhile, microscopic observations are carried out to determine wound healing activities through the mechanism of angiogenesis, increased epithelialization, fibrogenesis, and collagen formation (Ariadi, 2016). This study aims to determine the effectiveness of red fruit oil gel emulsion (*Pandanus conoideus* Lamk.) on the healing process of incisions in male mice both macroscopically and microscopically.

METHODOLOGY

Materials

Tools used in this study were centrifuge, dispersive glass, adhesive test equipment, homogenizer, analytical balance, wood tongs, thermometer, glassware, mortar, stemper, tripod, bunsen, asbestos, pH meter, stirring rod, watch glass, parchment paper, spatula, horn spoon, spatula, 10 mL vial, 15 mL centrifugation tube, 200 mL container, 50-gram, 100-gram, and 200-gram weights, ruler, slide, and coverslip. Materials used in this study were red fruit oil (Pandanus conoideus lam), carbomer (carbopol 940), HPMC, TEA, aqua dest, propylene glycol, propylparaben, methylparaben, BHT, tween 80, span 80.

Sample Preparation

The sample used in this study was red fruit oil from CV Made Mulya, Papua, Indonesia.

Methods

Formulation Design

Before making a red fruit oil gel emulsion, first, design a red fruit oil gel emulsion formulation. Fruit oil gel emulsion made used HPMC + Carbomer gel base. The red fruit oil gel emulsion formulation design can be seen in Table I.

Gel Emulsion of Red Fruit Oil

The gel emulsion preparation was made of 3 formulas, namely F1, F2, and F3 which were added with active substances, namely 5%, 10%, and 15% red fruit oil. For the manufacture of red fruit oil gel emulsion, the first step was to make a gel base. The gel bases used were carbomer and HPMC. After that, an emulsion of red fruit oil was made. After the gel base and red fruit oil emulsion had been made, the next step was to mix them both to obtain a red fruit oil gel emulsion formula with a concentration of 5%, 10%, and 15%.

Evaluation of Red Fruit Oil Gel Emulsion

Organoleptic test

The organoleptic test included observation of color, odor, and stability. Preparations had to show the same character both before and after storage.

pH test

The pH test was carried out by dissolving a sample of 1 gram with 10 mL of distilled water and testing using a pH meter (Dipahayu, 2020). pH which corresponded to skin pH was 4.5-6.5 (Kurnia et.al., 2019).

Homogeneity test

The physical homogeneity test was carried out by placing a small amount of preparation (base and elmulgel) on a slide and observing under a microscope, to see if any particles were not homogeneous (Halid and Saleh, 2019).

Dispersion Test

Emulgel as much as 0.5 grams was placed carefully on a transparent glass lined with graph paper, letting the preparation spread to a certain

Table I. Formulation Design Gel Emulsion of Red Fruit Oil

	F1	F2	F3
Red fruit oil	5	10	15
Carbomer	1 40	1 40	1 40
HPMC	0.25 10	0.25 10	0,25 10
TEA	1	1	1
Propylene Glycol	10	10	10
Span 80	0.4675	0.4675	0.4675
Tween 80	4.5325	4.5325	4.5325
Methylparaben	0.18	0.18	0.18
Propylparaben	0.02	0.02	0.02
BHT	0.03	0.03	0.03
Total	22.48	27.48	32.48
Aquadest	77.52	72.52	67.52
Aquadest for emulsion	27.52	22.552	17.52

diameter. Then it was covered with transparent glass and given a load of 200, then the area gain was measured after being given a load after waiting for 5 minutes (Rakhma et.al., 2020).

Adhesion Test

Emulgel was weighed 1 gram and placed on a glass object that had been determined by the area. Then put another glass object on top of the emulgel. Then pressed with a load of 0.5 kg for 5 minutes. Then the load was lifted and the two attached glass objects were released while recording the time when the two glass objects were released (Puspitasari and Setyowati, 2018).

Treatment of Incisions

Before testing, the mice were acclimatized for 1 week, then the mice were anesthetized before making the wound with a combination of ketamine and xylazine (1:1) (Santos, *et al.*, 2021) intramuscularly. The incision was made 1 cm long with a depth of 0.2 cm or up to the subcutis layer on the back using a sterile scalpel. After that, each group of test animals was given treatment and observed on days 0, 7, 14. All procedures carried out in the study involving experimental animals were declared ethically fit according to 7 WHO standards with certificate numbers that passed the ethical review: Reg.No.:240/KEPK-POLKESMA/2021.

Incision Wound Healing Activity Test of Red Fruit Oil Gel Emulsion

The treatments included: The negative control group (K-) was a control group where the incision on the back was given a gel emulsion base, the positive control group (K+) was a control group where the incision on the back was given 10% Povidone-iodine, Treatment group 1 (P1) in the treatment group where the incision wound on the back is given 5% red fruit oil gel emulsion, Treatment group 2 (P2) is the treatment group where the back incision is given 10% red fruit oil gel emulsion, Treatment group 3 (P3) is the treatment group where the incision wound on the back was given a 15% red fruit oil gel emulsion

Macroscopic and Microscopic Observations

Macroscopic observations included measuring the length of the wound and microscopic observations included epithelial thickness and the average number of fibroblast cells. The length of the wound was measured using a ruler starting on days 0, 7, and 14. Epithelial thickness was measured from the dermis to the tip of the epithelium that grew in each incision with HE staining. Observation of the histology of mouse skin by measuring the thickness of the epithelium with a magnification of 100x, in 5 fields of view each one prepared and then averaged (Suyata, *et al.*, 2020). The number of fibroblast cells was counted by a magnification of 400x in 5 fields of view for each preparation and then averaged (Suyata, *et al.*, 2020). This observation used a light microscope (Olympus BX 53 Microscope) and connected to a camera (OptiLab Microscope Camera) and observations were made via a computer monitor.

Data analysis

The study data were then analyzed using One Way ANOVA SPSS version 21 to find out the differences between the test groups.

RESULT AND DISCUSSION

Organoleptic Test

The organoleptic test of red fruit oil emulgel was carried out by observing the physical shape,

Table II. pH Test Result

Formula	pH			Average
	Day 0	Day 7	Day 14	
F1	6.02	6.03	6.18	6.07
F2	6.20	6.14	6.16	6.16
F3	6.34	6.50	6.50	6.44

Table III. Dispersion Test Result

Formula	Dispersion			Average
	Day 0	Day 7	Day 14	
F1	5	5	5.3	5.1
F2	5	5.1	5.1	5.06
F3	4.8	5.1	5.2	5.03

Table IV. Adhesion Test

Formula	Adhesion			Average
	Day 0	Day 7	Day 14	
F1	1.20 s	1.36 s	2.12 s	1.56
F2	2.35 s	3.68 s	3.29 s	3.10
F3	3.09 s	3.90 s	3.80 s	3.59

color, and smell (Tambunan, *et al*., 2018). The results obtained on F1, F2, F3 days 0, 7, and 14 were an orange color, red fruit oil smell, and stable emulgel.

Homogeneity Test

A physical homogeneity test was carried out by placing a small amount of preparation (base and elmulgel) on a slide and observing under a microscope, to see if there were any particles that were not homogeneous. Homogeneity is indicated by the absence of coarse grains in the preparation (Sayuti, 2015). The results obtained were all formulas, i.e. F1, F2 and F3 were homogeneous on days 0, 7, and 14.

pH Test

The pH test was carried out by dissolving a sample of 1 gram with 10 mL of distilled water and tested using a pH meter (Dipahayu, *et al*., 2014). Based on table 2, the pH test results show that all red fruit oil emulgels were in the pH range of 6.07-6.44, thus the formulated emulgels met the physiological pH range of human skin, i.e. 4.5-6.5 (Garg, *et al*., 2002).

Dispersion Test

Emulgel as much as 0.5 grams was placed carefully on a transparent glass lined with graph paper, letting the preparation spread to a certain diameter. Then covered with transparent glass and given a load of 200 g. Then the increase in the area after being given a load after waiting for 5 minutes was measured. Based on table 3, the results of the dispersion test showed that all red fruit oil emulgels were in the range of 5.03-5.1cm, thus the formulated emulgel met the normal dispersion range was 5-7 cm (Nurlaela, et.al., 2012).

Adhesion Test

Emulgel was weighed 1 gram and placed on a glass object that had been determined by the area. Then put another glass object on top of the emulgel. Then pressed with a load of 0.5 kg for 5 minutes. Then the load was lifted and the two attached glass objects were released while recording the time when the two glass objects were released (Yusuf, *et al*., 2017). Based on table 4, the results of the adhesion test showed that all red fruit oil emulgels were in the adhesion range of 1.56-3.59 s, thus the formulated emulgels met the normal range of adhesion, i.e. more than 1 s (Yusuf, dkk., 2017).

Effect of Giving Red Fruit Oil Emulgel on Incision Wound Size

The data on the average day of wound healing on day 7 and day 14 have been tested for normality and homogeneity. The results of the normality test on day 7 and day 14 obtained values of $p = 0.87 > 0.05$ and $p = 0.22 > 0.05$, which meant the data was normally distributed. The results of the homogeneity test obtained successive values of $p = 0.46 > 0.05$ and $p = 0.62 > 0.05$, which meant the two data were homogeneous. The data were tested by One Way ANOVA and significant results were obtained both on day 7 and day 14, i.e 0.035 ($p < 0.05$) and 0.005 ($p < 0.05$).

Then, a multiple comparison test (Post Hoc Test) was conducted using the LSD test from the 2 observations, i.e day 7 and day 14. The results showed that the red fruit oil emulgel treatment group with a concentration of 15% (P3) was the most influential treatment group for the length of the wound. Wounds treated with 15% red fruit oil emulgel concentration (P3) gave a faster healing effect when compared to other treatments and the K- treatment gave the longest healing effect of all treatments.

The increase in wound closure both in the late inflammatory stage (day 7) and in the proliferative stage (day 14) indicated that topical application of MBM emulgel, in general, could accelerate the wound closure process without causing clinically visible negative effects. Red fruit oil is a red fruit extract that contains various active components, namely α-carotene, β-carotene, α-tocopherol, vitamin C, and unsaturated fatty acids, especially linoleic, oleic acid (Rohman, *et al*., 2012)

The function of ascorbic acid is as a co-enzyme and co-factor in several biochemical pathways of the body. In connective tissue, vitamin C is required for the synthesis of collagen fibers, which is an important process in tissue repair and healing. Vitamin C is a water-soluble antioxidant that is very important for our body (Mohammed, 2016). Lin, *et al* (2012) explained that tocopherol stimulates the production of cyclic adenosine monophosphate (cAMP) which is often associated with immunomodulatory effects by modulating the inflammatory response of various types of immune cells including macrophages. Tocopherols have also been shown to have anti-inflammatory effects by attenuating the production of pro-inflammatory cytokines and chemokines. Thus, the application of tocopherol is useful for wound healing, probably due to its antioxidant and anti-inflammatory properties. α-Tocopherol contained in vegetable oil is a natural antioxidant. The content of α-tocopherol in red fruit oil is 145.12 ug/g.[10] The content of α- tocopherol in red fruit oil was higher when compared to corn oil (116-172 ug/g), palm oil (129-215 ug/g), and olive oil (63-135 ug/g) (O'Brien, 2009).

The content of fatty acid in form of Oleic and linoleate plays role in the proliferative phase. According to Silva, *et al*., (2018) and Ferreira, *et al*. (2012), Oleic and linoleate can initiate fibroblasts to the wound area to synthesize growth factors by transforming growth factor-β (TGF-), so that more fibroblasts in the wound area will increase extracellular matrix (ECM) synthesis and accelerate wound closure. Furthermore, Silva, *et al*., (2018) and Ferreira, *et al*., (2012) explained that Oleic and linoleate components can help fibroblasts to synthesize type I and type III collagen, which according to Sabirin *et al*. (2013) that type III collagen in the form of fibers begins to be synthesized in the proliferative phase by fibroblasts stimulated by growth factor (TGF-β) from fibroblast cells and macrophages themselves.

For the results of measuring the length of the wound in the positive control group, different results were obtained from the treatment groups P1, P2, and P3. This is following Kaur *et al*. (2014) that povidone-iodine only contains antiseptic ingredients and does not have anti-inflammatory properties. These antiseptic ingredients have the iodine element which will interact with enzymes and proteins in cell membranes to affect cell structure which leads to cell death (Kaur *et al*., 2014) and according to Pratiwi *et al*. (2015), povidone-iodine not only selects microbial cells as targets but also normal cells which result in disruption of collagen synthesis and affects the migration of epithelial cells to the wound site (Pratiwi, *et al*., 2015). This is what causes wound healing in the positive control group to be slower when compared to groups P1, P2, and P3.

Effect of Giving Red Fruit Oil Emulgel on Mice Epithelial Thickness

The average thickness of the epithelium in the control and treatment groups is shown in the following histogram (Figure 2).

Figure 2 shows the epithelial thickness average for all control and treatment groups. Starting from the K- group, it was seen that the epithelial thickness average increased in all treatment groups with red fruit oil emulgel treatment. Based on the results of the analysis using the ANOVA test, the p-value was 0.000, smaller than $\alpha = 0.05$ ($p < 0.05$). Therefore, from this test, it can be concluded that there was a significant effect of giving red fruit oil gel emulsion on Epithelial Thickness

From the histogram above, it was found that the epithelial thickness in the negative control group had a low value, possibly due to the absence of substances that could inhibit bacteria in the area around the wound. In the positive control group, due to the absence of nutrients from povidone-iodine, could accelerate the wound healing process. Treatment groups P1, P2, P3 showed a fairly high epithelial thickness. Epithelial thickness could indicate the process of re-epithelialization faster so that it affected the rapidity of wound healing. The rapid re-epithelialization process in

Figure 1. Wound Closure of Mice on Days 0, 7 and 14 in Groups K-, K+, P1, P2, P3

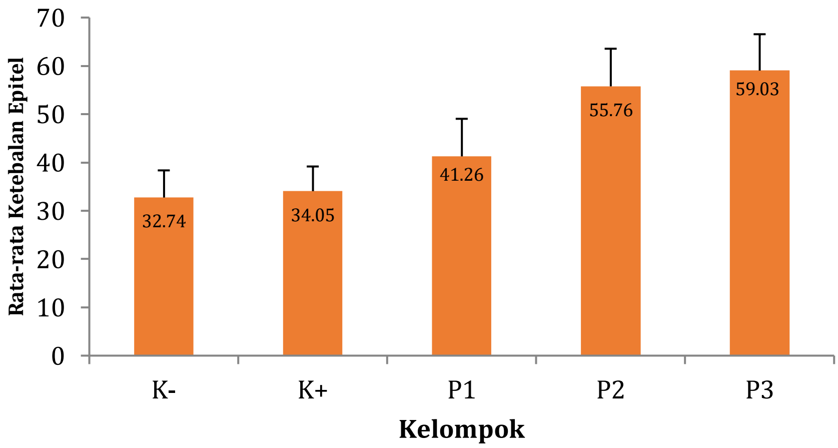

Figure 2. Epithelial Thickness Average Histogram

the treatment group was probably influenced by the content of α-tocopherol in red fruit oil.

Vitamin E is one of the fat-soluble antioxidants and the most commonly used to protect the effects of free radicals on the skin. Vitamin E has an important effect on wound healing due to its natural properties which can penetrate the layers of the skin very easily. Vitamin E plays an important role in reducing free radicals in wounds. The most studied form of vitamin E is α-Tocopherol, which has a strong antioxidant effect to inactivate free radicals by providing electrons to stabilize these free radicals (Hobson, 2016).

α-Tocopherol will encourage the process of reepithelialization, neovascularization, fibroblast proliferation, and the synthesis and maturation of the extracellular matrix. Thus, red fruit oil which has a fairly high content of α-Tocopherol is used as an antioxidant to increase reepithelialization.

In a recent study, incorporation of α-Tocopherol into tissue fibroblasts may help prevent the breakdown of newly formed collagen and glycosaminoglycans due to oxidation. This is particularly important because the breakdown of collagen and glycosaminoglycans during the proliferative phase of wound healing can delay or interfere with proper tissue healing. There is also some evidence that protecting collagen and glycosaminoglycans from oxidative stress can lead to faster wound closure rates. α-Tocopherol can increase wound reepithelialization (Lin, *et al.*, 2012).

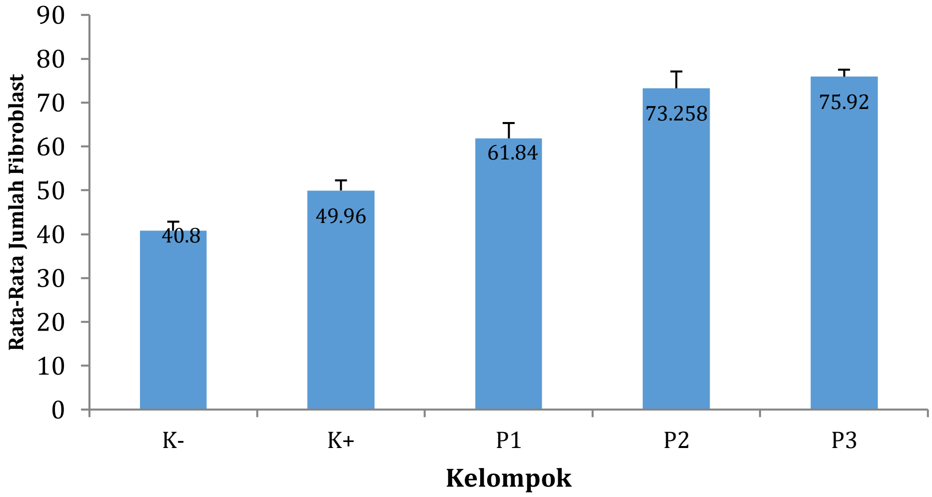

Figure 3. Epithelial Thickness Average Histogram

The Effect of Giving Red Fruit Oil Emulgel on the Fibroblasts Number Thickness

The average number of fibroblasts in the control and treatment groups in full is shown in the following histogram (Figure 3).

Figure 3 shows the histogram of the average number of fibroblasts in all control and treatment groups. Starting from the K- group, it was seen that the average number of fibroblasts increased in all treatment groups given red fruit oil gel emulsion. Based on the results of the analysis using the ANOVA test, the p-value was 0.000, smaller than $\alpha = 0.05$ ($p < 0.05$). Therefore, from this test, it can be concluded that there is a significant effect of giving red fruit oil emulgel on the number of fibroblasts.

From the histogram above, it can be seen that the treatment groups P1, P2, and P3 had a higher average number of fibroblasts compared to the average number of fibroblasts in the control group. Emulgel administration may affect the addition of nutrients to the wound area which can optimize wound healing by increasing the number of fibroblasts. The low number of fibroblasts in the control treatment was probably due to the absence of additional nutrients needed for the wound healing process.

The content of fatty acid in form of Oleic and linoleate plays role in the proliferative phase. According to Silva, et. al., (2018) and Ferreira, et. al. (2012), the Oleic and linoleate process can initiate fibroblasts to the wound area to synthesize growth factor of transforming growth factor-β (TGF-β), so that more fibroblasts in the wound area will increase extracellular matrix (ECM) synthesis and accelerate wound closure. Furthermore, Silva, et. al., (2018) and Ferreira, et. al. (2012) explained that Oleic and linoleate components can help fibroblasts to synthesize type I and type III collagen, in which type III collagen in the form of fibers begins to be synthesized in the proliferative phase by fibroblasts stimulated by growth factor (TGF-β) from fibroblast cells and macrophages themselves.

CONCLUSION

The physical and chemical characteristics of red fruit oil gel emulsion include organoleptic test, homogeneity test, pH test, dispersion test and adhesion test all meet the predetermined standards. There is an effect of red fruit oil gel emulsion on the length of the incision wound on day 7 and day 14 with a p-value of 0.035 ($p < 0.05$). There is an effect of red fruit oil gel emulsion on the thickness of the skin epithelium with a p-value of 0.000 ($p < 0.05$). There is an effect of red fruit oil gel emulsion on the average number of fibroblast cells with a p-value of 0.000 ($p < 0.05$).

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