



**Evaluation of Topical Red Dragon Fruit Extract Effect
(*Hylocereus Polyrhizus*) on Tissue Granulation and
Epithelialization in Diabetes Mellitus (DM) and Non-DM
Wistar Rats: Pre Eliminary Study**

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Abstract

The use of natural materials as wound healing is an alternative that is widely used. Red Dragon Fruit Extract (EBNM) has antioxidant and anti-inflammatory content that is needed to accelerate the wound healing, but studies have reported effects on wound healing is still limited. The purpose of this study was to evaluate the effect of topical Red Dragon Fruit Extract on DM wound and Non-DM wound healing in Wistar rats. This research method is an Experimental Study with post-test with control group design. Albino Male Wistar rat (n = 18) with the weight (200-250 grams) were divided into 2 groups (group A (n = 9) Wistar DM + incision divided into 3 groups, each with 3 rats and group B (n = 9) Non-DM Wistar + incision divided into 3 groups of each 3 rats). Furthermore Wistar rat wounded in the back left and right using 8 mm punch biopsy. 7.5% topical Red Dragon Fruit Extract cream was applied to the surface of the wound with the cotton bud. Tissue preparat colored with *Hematoxylin* and *Eosin* (HE) then the wound healing parameters were assessed; the thickness of the granulation tissue and epithelialization with histopathology assessment. Data were analyzed using *independent T test* and *paired T test* (SPSS 21, Chicago Inc.) Granulation scores tend to be better at a concentration of 7.5% in the topical Red Dragon Fruit Extract than the negative control group for DM (p <0.068) and non-DM (p <0.034). Epithelialization Scores are better at concentrations of 7.5% in Topical Red Dragon Fruit Extract group than the negative control group for DM (p <0.034) and non DM (p <0.034). Topical Red Dragon Fruit Extract 7.5% increase the growth of granulation tissue and epithelialization in wound healing of acute non-DM and DM at Wistar rats.

Keywords: *Hylocereus Polyrhizus*; wound healing; granulation tissue; epithelialization tissue; DM wound.

1. Introduction

Wound healing is a complex biological process in which tissue repair can be divided into three phases; wound healing consists of phases of inflammation, proliferation, and remodeling [1-4]. Wound healing requires better integration in the regulation of biological mechanisms and molecular complex, including cell migration, cell proliferation, and deposition of extracellular matrix (ECM) [5].

Wound care problem in Indonesia starts from the high prevalence of both acute wounds and chronic wounds. Basic Health Research (Riskesda, 2013) reported that the proportion of injuries in Indonesia is dominated by scratching / bruises (70.9%), sprains (27.5%) and lacerations (23.2%) [6]. The prevalence of chronic wounds is reported to be high, including the prevalence of diabetic foot wounds (12%) [7] at the hospital and (26%) in the home care setting [8] as well as the prevalence of decubitus sores (4.5-8%) in public hospitals [9] and specialty hospitals (17-28%) [10]. This fact shows the importance of finding and optimizing approaches in the treatment of wounds.

In Indonesia, some research explored about the natural sources as complementary approaches in the process of wound care. Such as, the use of honey [11] and the use of coconut oil [12]. Moreover, Indonesia still saves other natural plant sources that could be an alternative, one of which is the Red Dragon Fruit that often consumed as a beverage or food [13].

One of the natural ingredients contained in the Red Dragon Fruit and potentially used for wound healing is *Hylocereus polyrhizus* [14] which has the phytochemical effect in the form of polyphenols, flavonoids (*kaempferol* and *quercetin*), phytochemical has an important role in the process of regeneration in the wound [15,16]. In addition to the Red Dragon Fruit extract also found β -*amyirin* (23.3%), α -*sitosterol* (19.3%), *octadecane* (9.2%) [17]. Phyto-extracts contribute as antimicrobial, antioxidant free radical scavengers, increased cell proliferation, angiogenesis, increased collagen production and an increase in DNA synthesis [18].

The purpose of this study was to examine the potential of the Topical Red Dragon Fruit Extract to the thickness of granulation tissue and accelerate the growth of epithelialization tissue on the DM Acute wound and Non DM at Wistar rat.

2. Materials And Methods

2.1. Animal Preparation

Adult male albino Wistar (200-250g) were obtained from the Faculty of Veterinary Medicine, University of Gadjah Mada (UGM) in Yogyakarta. Wistar separately placed in a cage made of wire with a floor area size 30 cm x 50 cm x 15 cm. Density cages, each containing three rats. Wistar rats fed 300 gr / day / rat and given sufficiently drink, and the cage is cleaned every day with the temperature around $28 \pm 2^{\circ}\text{C}$ and lighting with 12-hour cycle. Animal management protocol followed the guidelines/protocols of Experimental Animal Laboratory, Faculty of Medicine, Hasanuddin University and has received ethical approval from the ethics committee of the health research Medical Faculty of Hasanuddin University (1684/H4.8.4.5.31/PP36-KOMETIK/2015).

2.2. Wounded Procedure

DM Wistar group, injected Streptozotocin (STZ) 40-50 mg / kg intraperitoneally, then blood was taken from the tail vein 72 hours after injection and glucose level was measured by using Glucose Test Strips (Nesco)[14]. Induction declared successful when the fasting blood glucose tests after 48-72 hours was ≥ 14.0 mmol/L, and the incision would be conducted if the blood glucose level was high (over 250 mg/dL).

Wistar rats anesthetized by inhalation using *isoflurane* (0.01 $\mu\text{g}/\text{kg}$ –0.05 $\mu\text{g}/\text{kg}$) [19]. Furthermore, bristles at the incision area threshed using (VEET[®] size 60 grams Reckitt Benckiser), then the incision area is disinfected with *chlorhexidine* 0.5% solution. Then a biopsy performed using sterile punch disposable biopsy type seamless sharp number, 8.0 mm MILT-33-3 in the hip area to the fascia profunda [20]. Then the wound smeared topical red dragon fruit cream with a cotton bud.

2.3. Red Dragon Fruit Extract (RDFE)

Red Dragon fruit is taken from plantations comes from Samarinda, East Kalimantan, Indonesia, then the dragon fruit is extracted using methanol, and examining the inhibition percentage of free radicals (DPPH) with IC_{50} 314.69 ppm, levels of polyphenols total are 10.62 GAE and levels of flavonoids total as many as 8.3 mg per 1

gram of Red Dragon Fruit Extract. Furthermore, the topical Red Dragon Fruit Extract (RDFE) cream is made by the concentration of 7.5%.

2.4. The process of Wound Care

DM Wistar Group and Non-DM were divided into 3 groups: negative control (NC) spread thin in diameter wound with a *cotton but* as many as 20 mg Vaseline and positive control (PC) spread thin in diameter wound with a *cotton but* as many as 20 mg Bioplacenton[®], Kalbe Farma and the Red Dragon Fruit Extract (RDEFE) group spread thin in diameter wound with a *cotton but* as many as 20 mg Red dragon fruit extract 7.5% topical cream. Wound care was conducted on the 1st day to the 7th day.

2.5. Macroscopic Evaluation

The first day of biopsy set as the day 0, where the wound healing process was observed from day 0 to until the 14th day. The process of wound healing was evaluated macroscopically. Macroscopic evaluation was conducted by calculating the change in diameter of the wound using wound crossbar.

2.6. Histological Evaluation

Skin samples were fixed in formalin normal buffer solution (BNF) 10%, dehydrated in alcohol of various concentrations (70%, 80% and 90%), clearing with *xylol* and *embedded* in paraffin. The tissue was put into liquid paraffin display device and allowed to harden paraffin, cut with microtome to the thickness of 5- μm . Then conducted the rehydration process and the stock stained with hematoxylin and eosin (HE).

Evaluation of wound healing was assessed by the score of epithelialization and granulation tissue thickness using an electron microscope with a magnification of 400. Epithelialization assessment using Semi-quantitative histological evaluation of sections[21]. Where the score 1 = cell migration (<50%), score 2 = cell migration ($\geq 50\%$), 3 Closure + keratinocytes in the entire incision. Thickness assessment of granulation tissue using histological score [22] where the score 1: thin, score 2: moderate, and the score 3: thick.

2.7. Data Analysis

Difference analysis of wound diameter among negative control groups, positive control, and Red Dragon Fruit Extract 7.5% in DM Wistar and Non-DM using *Mann-Whitney* test. While differences in tissue granulation and epithelialization among negative control groups, positive control, and Red Dragon Fruit Extract 7.5% using the Kolmogorov-Smirnov test. In this research, did not compare between groups DM and non-DM.

3. Results

3.1. Wound Diameter Size

Wound Diameter size after the 7th day treatment was found that the diameter of the wound was better in RDFE groups (Non-DM group $p = 0.047$; DM Group $p = 0.061$) and PC (Non-DM group $p = 0.047$; DM Group $p =$

0.061) compared with Negative Control group DM and non-DM. RDFE groups tend to have the same effect with Positive Control in reducing the diameter of the wound (Non-DM group $p = 0.754$; DM Group $p = 1.000$) (Figure 1 and Table 1).

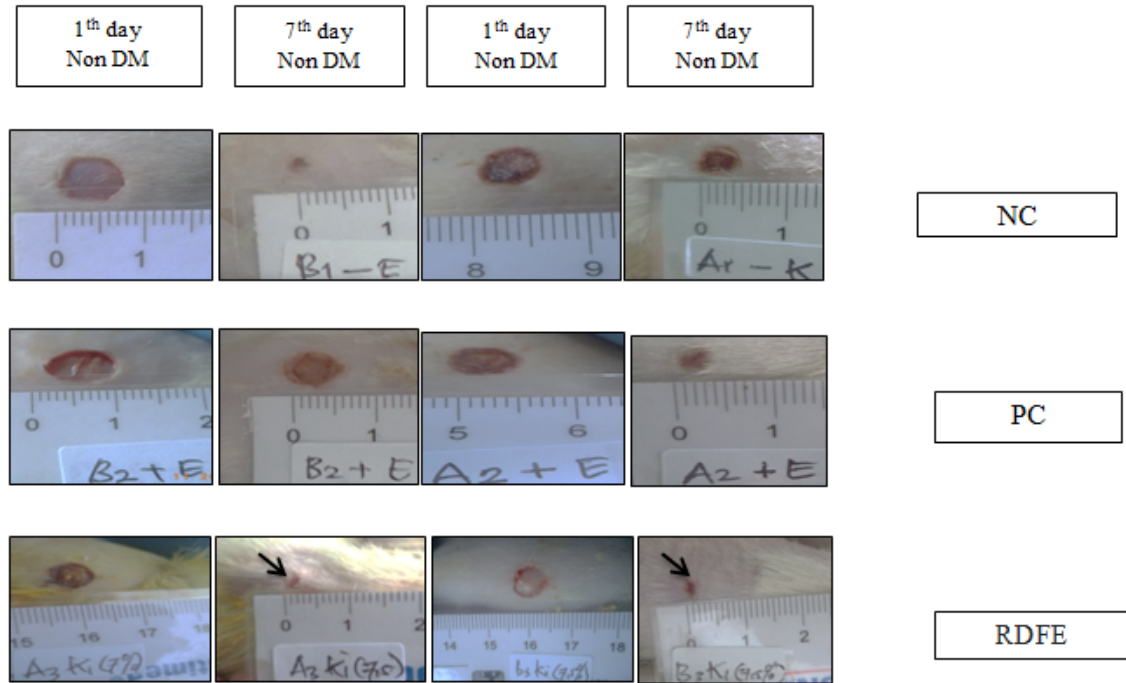


Figure 1: Macroscopic appearance on the wounds on 1th day and 7th day post wounding in the Negative Control (NC) group, Positive Control(PC) group, and Red Dragon Fruit Extract (RDFE) group in Wistar Non-DM and DM groups. Diameter of wounds area at RDFE group smaller than the NC and the PC group DM and non-DM.

Table 1: Rates of diameter (in millimeters) of wounds area after 7th day post wounding

Groups	Diameter of wounds area (mm)					
	DM			Non-DM		
	Mean	SD	p	Mean	SD	p*
NC	5.67	1.528	0.047	4.00	1.000	0.061
PC	3.33	0.577		2.67	0.577	
NC	5.67	1.528	0.047	4.00	1.00	0.061
RDFE	3.67	0.577		2.67	0.577	
PC	3.33	0.577	0,754	2.67	0.577	1.000
RDFE	3.67	0.577		2.67	0.577	

*Mann-Whitney

3.2. Granulation tissue

At DM Wistar group after the 7th day of treatment showed that the scores of granulation tissue thickness were thinner on Experiment group (66.7%). The same was found in the Positive Control group (66.7%), but the Negative Control group was not found any Wistar experienced the thin granulation tissue. As at non-DM Wistar, the score of granulation tissue in the RDFE group is thinner (100%) and Positive Control (66.7%). Statistical test results found that in the Non-DM Wistar has difference granulation tissue between the RDFE group and Negative Control of non-DM Wistar ($p = 0.034$) while in DM Wistar has not ($p = 0.068$). As for the Positive Control group found has no difference with Negative Control ($p = 0.068$) (Figure 2 and Table 2).

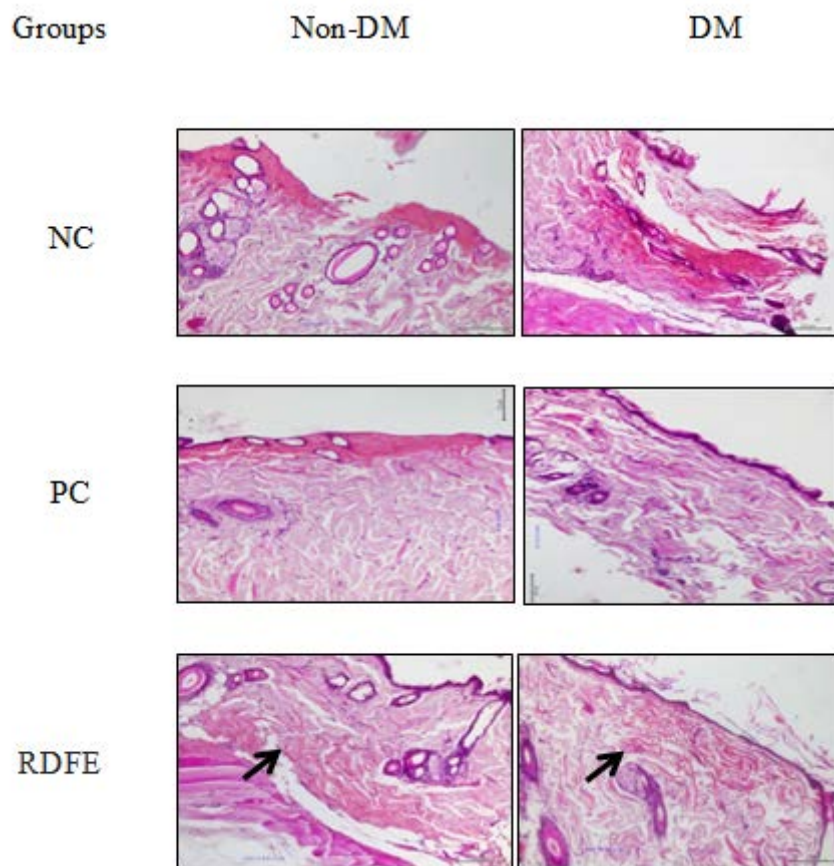


Figure 2: Granulation Tissue on 7th day after wounding in the Negative Control (NC) group, Positive Control(PC) group, and Red Dragon Fruit Extract (RDFE) group in Wistar Non-DM and DM groups. The results showed that tissue granulation at the RDFE group had thinner than the NC group and PC group

3.3. Epithelialization Tissue

In DM Wistar group after the 7th day of treatment showed that keratinized epithelialization tissue score in Experiment group (66.7%) and Positive Control (66.7%), but in the negative control group was not found Wistar who have not keratinized (0.0%). As for the non-DM group had keratinized in Experiment group (100%) and Positive Control (66.7%). Statistical test results found that there are differences in the epithelialization tissue

between Experiment groups and Negative Control (DM group $p = 0.034$; Non-DM group $p = 0.025$). Similarly, the Positive Control group found differences in the epithelialization tissue with Negative Control (DM group $p = 0.034$; Non-DM group $p = 0.034$) (Table 3 and Figure 3).

Table 2: Score of granulation tissue on DM and Non-DM groups after 7th day post wounding

Groups	DM						p*	Non-DM						p*
	Thick		Moderate		Thin			Thick		Moderate		Thin		
	n	%	n	%	n	%		n	%	n	%	n	%	
NC	2	66.7	1	33.3	0	0.0	0.068	2	66.7	1	33.3	0	0.0	0.068
PC	0	0.0	1	33.3	2	66.7		0	0.0	1	33.3	2	66.7	
NC	2	66.7	1	33.3	0	0.0	0.068	2	66.7	1	33.3	0	0.0	0.034
Exp	0	0.0	1	33.3	2	66.7		0	0.0	0	0	3	100	
PC	0	0.00	1	33.3	2	66.7	1.000	0	0.0	1	33.3	2	66.7	0.317
Exp	0	0.0	1	33.3	2	66.7		0	0.0	0	0	3	100	

*Kolmogorov-Smirnov Test

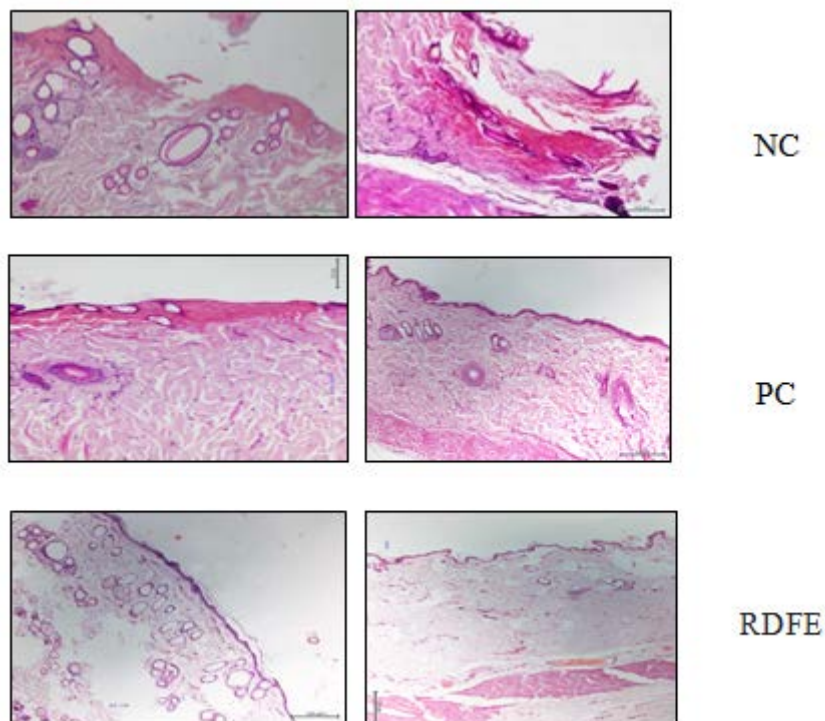


Figure 3: Epithelialization Tissue on the 7th day after wounding in the Negative Control (NC) group, Positive Control (PC) group, and Red Dragon Fruit Extract (RDFE) group in Wistar Non-DM and DM groups. The results showed that Epithelialization Tissue at the Exp group had keratinization stage

Table 3: Score of Epithelialization on DM and Non-DM groups after 7th day post wounding

Groups	DM						p*	Non-DM						p*
	Migration of cells ≥50%		Bridging the excision		Keratinization			Migration of cells ≥50%		Bridging the excision		Keratinization		
	n	%	n	%	n	%		n	%	n	%	n	%	
NC	3	100	0	0.0	0	0.0	0.034	2	66.7	1	33.3	0	0.0	0.034
PC	0	0.0	1	33.3	2	66.7		0	0.0	1	33.3	2	66.7	
NC	3	100	0	0.0	0	0.0	0.034	2	66.7	1	33.3	0	0.0	0.025
Exp	0	0.0	1	33.3	2	66.7		0	0.0	0	0.0	3	100	
PC	0	0.0	1	33.3	2	66.7	1.000	0	0.0	1	33.3	2	66.7	0.317
Exp	0	0.0	1	33.3	2	66.7		0	0.0	0	0.0	3	100	

*Kolmogorov-Smirnov Test

4. Discussion

4.1. The diameter of the wound in DM and non-DM Wistar group

The average diameter wound on a group of Wistar DM between topical red dragon fruit extract 7.5% and the positive control has the same tendency as good in reducing the diameter size of the wound, while in the non DM experienced the same thing, where the diameter cuts between groups topical red dragon fruit extract 7.5% in the positive control was smaller. Macro wound closure can be a simple parameter, for assessing the quality of wound healing needs to measured histopathologically (Figure 1 & 2).

The Red dragon fruit is very popular with the active substance, such as, antioxidants, flavonoids and polyphenols[16]. Red dragon fruit also contains phytochemicals that are good for the body, such as flavonoids. The content of flavonoids in red dragon fruit as much as 7.21 ± 0.02 mg CE / 100 gram [23] The results of this study showed that each 1 gram Red Dragon Fruit contains about 8.3 mg total flavonoid levels and 10.62 mg GAE total phenol content. Anti-free radical activity of Red Dragon Fruit extract and vitamin C obtained IC₅₀ values, respectively 314.69 ppm and 3.28 ppm.

4.2. Topical Red Dragon Fruit extract and Granulation Tissue

The Red Dragon Fruit extract also has a good effect on wound healing granulation phase. Red Dragon Fruit extracts 7.5% is believed to work diluting the granulation tissue in proliferation phase. The result in this study indicated that the granulation score on Topical Red Dragon Fruit extract group obtained the thin categories on

the 7th day on Wistar non DM group and positive control group also experienced a similar trend. While at the Wistar DM group found granulation tissue as much thinned in the Red Dragon Fruit extract 7.5% group and positive control.

One of Red Dragon Fruit extract content is polyphenol, flavonoids and antioxidants[24]. Polyphenol role in activating the production of NO and improve endothelial function capabilities that facilitate the formation of vascular (angiogenesis) which is an important structure formation of granulation tissue. In addition, the content of the Red Dragon Fruits affluent with the antioxidant *anthocyanin* type, in which the anthocyanin thought to accelerate the growth of macrophage cells and inhibits cell proliferation [25].

Wound healing begins with the formation of a good granulation followed by depletion of granulation tissue to prepare the epithelium tissue formation. Quercetin contained in the Red Dragon Fruit help wound healing through the modulation of cytokines and growth factors on proliferation phase that play a role in forming granulation tissue [26,27]. Quercetin function inhibits ROS and the excessive tissue inflammation.

4.3. Topical Red Dragon Fruit Extract and Re-epithelialization Tissue

The Results of this study showed that, Red Dragon Fruit Extract 7.5% has better ability to the process of re-epithelialization. It can be proved that the wound closure on day 7 at the Non DM Wistar group has keratinized (100%), while the positive control group has keratinized (66.7%). If compared with DM Wistar group found that Red Dragon Fruit Extract 7.5% and the positive control has keratinized 66.7% and both the positive and negative group level of epithelialization closure only ($\geq 50\%$) and no keratinized on day 7 of treatment.

A previous study that evaluating period of the epithelialization using extract *rhizomes of Rumex abyssinicus* found that average period of epithelialization that uses the extract was 13.3 days compared with *simple oitmen based* (SO) [28]. Several studies have been conducted using similar active substance (*polyphenolic*) which has the same content on the dragon fruit in the treatment of wound healing in rats induced with alloxane[29]. Similar research was also conducted to assess the effect of the dragon fruit extract as a topical cream to granulation tissue, collagen growth and hexosamine shown to accelerate wound healing [14].

Similar research using the application use of topical *Sadat-Habdan Mesenchymal Stimulating Peptide* (SHMSP) in rabbits showed that there is a significant improvement in wound healing, blood vessel proliferation and collagen deposition, and a significant reduction in inflammatory cell infiltration in the group of peptides compared with the control group[29,30]. One of the compounds that are also found dragon fruit extract in (*H.polyrhizus*) is *anthocyanin*, the amount of *Anthocyanin* found 658 mg contained in 1000 grams *polyrhizus* of fresh fruits (both on the skin and its flesh). *Anthocyanins* supposed to accelerate the growth of macrophage cells and also inhibit the cancer cell proliferation [25].

5. Conclusion

The use of topical concentration red dragon fruit extract 7.5% proved better in repairing the granulation tissue and epithelialization tissue in the Wistar Non DM group compared with the DM Wistar, so red dragon fruit

extract potential to be used as a therapy in wound healing.

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