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Potential of *Muntingia calabura L.* Leaf Extract Cream on the Remodeling Phase of Wound Healing in Diabetic Rats *(Rattus norvegicus)*

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Abstract:- Incision wounds are narrow, elongated wounds caused by sharp objects. One of the factors that hinders wound healing is high blood sugar levels in the condition of diabetes mellitus. This study aims to determine the effectiveness of *Muntingia calabura* L leaf extract cream in accelerating the healing process of incision wounds during the remodeling period on the skin of white rats with diabetes mellitus. The experimental animals used were 12 male white rats (*Rattus norvegicus*) with an average weight of 150-200 grams and were 2-3 months old. The rats were divided into 4 treatment groups with 3 repetitions. The K1 group as a negative control is given a cream base. The K2 group as a positive control was given 0.1% silver sulfadiazine cream and metformin. The K3 group was given a 5% *Muntingia calabura* L leaf extract cream and an oral extract of *Muntingia calabura* L leaves. The K4 group was given a 15% *Muntingia calabura* L leaf extract cream and an oral extract of *Muntingia calabura* L leaves. All treatments were carried out for 14 days. The results of the statistical test on the average number of fibroblast cells showed a real difference (P<0.05) between the four groups. The results of the statistical test on the mean collagen density score in the K3 and K4 treatment groups showed a real difference (P<0.05) compared to the K1 and K2 control groups. It can be concluded that the administration of 5% *Muntingia calabura* L leaf extract cream can reduce the number of fibroblast cells and increase collagen density, thereby accelerating the healing of incision wounds during the remodeling phase on the skin of white rats with diabetes mellitus.

Keywords:- *Muntingia Calabura L Leaves; Incision Wounds; Fibroblast Cells; Collagen Fibers.*

I. INTRODUCTION

The wound is the disconnection of tissue continuity due to damaged or missing tissue (Wintoko and Yadika, 2020). One type of wound is an incision wound, which is an elongated and narrow wound on a surface, especially on the skin that occurs due to sharp objects (Wilantari *et al.*, 2019). The wound healing process is a complex cellular process focusing on restoring tissue integrity. It consists of three phases: the inflammatory phase, the proliferation phase, and the maturation or remodeling phase (Primadina *et al.*, 2019). One of the factors that affect the length of wound healing is high blood glucose levels such as in the condition of diabetes mellitus (Siregar, 2020 and, Nadira *et al*, 2021).

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia, which is an increase in glucose levels in the blood due to impaired insulin production by pancreatic ß cells or due to the body's inability to use insulin effectively (Buraerah *et al.*, 2010). Diabetes mellitus can cause complications because it affects almost all body systems such as the heart, kidneys, liver, eyes, and skin (Kurniati and Alfaqih, 2022).

Histologically, the skin of people with diabetes mellitus has an extracellular matrix and collagen fibers that are more stretched than normal skin (O'Brien *et al.*, 2014). Collagen comes from fibroblast cells so the acceleration of collagen growth is influenced by the development of the number of fibroblast cells (Nanda *et al.*, 2017). Type I collagen, which is the main component of the extracellular matrix, can repair damaged tissues so it plays an important role in the wound healing process (Gunawan *et al.*, 2019). The formation of type I collagen occurs in the last phase of wound healing, namely the remodeling phase which begins on day 14 (Gonzalez *et al.*, 2016).

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One of the plants that can be used to speed up the wound healing process while lowering blood glucose levels is *Muntingia calabura L.* which is widely found in tropical areas (Binawati and Amilah 2013). This plant is a roadside tree that is commonly used as traditional medicine in Indonesia (Surjowardojo *et al.,* 2014). *Muntingia calabura* L leaves are known to have active compounds that can accelerate wound healing while lowering blood glucose levels (Iryani *et al.,* 2017).

Knowledge about the efficacy of *Muntingia calabura L* leaves on wound healing in hyperglycemia is still scarce, so it is the basis for research to determine the effectiveness of giving *Muntingia calabura L* leaf extract cream in the process of wound healing incision remodeling phase on the skin of white rats *(Rattus norvegicus)* diabetes mellitus. The results of this study are expected to be a reference in healing wounds in hyperglycemic conditions traditionally.

II. MATERIALS AND METHODS

This research received an ethical clearance approval letter for experimental animals from the Animal Ethics Committee Faculty of Veterinary Medicine, Universitas Syiah Kuala Banda Aceh Indonesia to perform all trials and procedures of this research.

This study is a laboratory analysis research using a complete random design (RAL) one way. A total of 12 mice were divided into 4 groups and each group consisted of 3 mice. The extraction process starts from drying kersen leaves by aerating. The drying process is continued using an oven. The dried kersen leaves are then mashed using a blender until simplistic powder is obtained. The ratio between simplicia powder and 96% ethanol solvent is 1:5. A total of 600 g of simplicia powder is put into the maser, then 3 liters of 96% ethanol solvent are added until completely submerged and macerated for 5 days with stirring once per day. The mass obtained was concentrated using a vacuum rotary evaporator to obtain a thick extract of *Muntingia calabura L.* leaves (Mokoginta *et al.,* 2020).

The cream is made by dividing the ingredients into two phases, namely the oil phase (stearic acid and cetyl alcohol) is put in a porcelain cup, propyl paraben is added and then dissolved in the water bath and the water phase (glycerin, propylene glycol, TEA, and, aquades) is put into a glass beaker and then added with methylparaben. The fused oil phase is poured into the mortar and stirred until homogeneous. The water phase is added little by little while stirring slowly until a creamy mass is formed. Kersen leaf extract is then added to the cream mass and stirred until homogeneous (Saryanti *et al.,* 2019). The manufacture of oral extract of kersen leaves was carried out by adding kersen leaf extract to 1% CMC-Na solvent. CMC-Na 1% solvent is widely used in oral formulations to improve the viscosity of preparations (Rowe *et al.,* 2006).

The hyperglycemic examination is carried out before streptozotocin (STZ) induction, 3 days after STZ induction, and, before collection by collecting blood at the tip of the tail. Blood glucose checks are carried out using GlucoDR. The blood obtained is dripped on a strip of GlucoDR, after 11 seconds the GlucoDR will display the blood glucose level in mg/dL. When blood glucose levels above 250 mg/dL are defined as diabetic mice (Taher *et al.,* 2016). Before STZ induction, all mice were given a two-week adaptation period. Afterward, all mice were induced intraperitoneally with a single dose of 45 mg/kg body weight because this dose could cause hyperglycemia with a 100% success rate (Zhang *et al.,* 2008).

The incision wound was made by anesthetizing the rats using a combination of ketamine xylazine with a dose of ketamine 40-100 mg/kg BW and xylazine 5-10 mg/kg BW IM in musculus femoralis (Noor *et al.,* 2022). Anesthesia injection is performed by inserting the rat into the strain cage. Before the procedure, the fur in the wound area is shaved and the skin is sterilized using 70% alcohol and 2% iodine tincture. Incision wounds are performed in the paravertebral area using a sterile scalpel with a length of 2 cm and a depth to the subcutaneous. After that, wound care is carried out according to the treatment group. Group 1 (K1) was given a cream base (negative control); group 2 (K2) was given a 0.1% silver sulfadiazine cream and metformin with a dose of 4.5 mg/kg BB (Tuldjanah *et al.,* 2020). (positive control); group 3 (K3) and group 4 (K4) were given oral kersen leaf extract at a dose of 450 mg/kg BB (Andalia *et al.,* 2021) and 5% and 15% *Muntingia calabura L* leaf extract cream, respectively.

All mice were euthanized on day 15 using the cervical dislocation method. After the mice were disinfected, the mice's skin was immediately taken and cleaned with 0.9% NaCl then put into 10% BNF for 18-24 (Febram *et al.,* 2010). The manufacture of histological preparations is based on the guidelines available at the Histology Laboratory, Faculty of Veterinary Medicine, Syiah Kuala University, namely skin specimens that have been fixed and then put into a 70% alcohol solution which is a stopping point. The specimens were then dehydrated using 80%, 90%, 95%, and 100% graded alcohol (absolute alcohol) for 2 hours each. After that, the clearing process is carried out by inserting the specimen into xylol for 30 minutes for 3 replicates, then tissue infiltration is carried out for 30 minutes with 3 replicates, and continued with planting (embedding) in liquid paraffin. Next, blocking is carried out until a paraffin block is formed. The paraffin block is then cut (sectioning) with microtomes 4-6 µm thick transversely. The slices are then placed in a water bath and taken with an object glass then put into a warmer slide, and then hematoxylin-eosin (HE) staining is carried out.

Hematoxylin-eosin staining begins with soaking the tissue slides into xylol for 2 repetitions, the first repeat for 5 minutes and the second repeat for 2 minutes. The next stage is soaking in absolute alcohol for 2 minutes for 2 repetitions, then 90% alcohol for 2 minutes with 1 repetition.

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After that, it is washed under running water. The next process is to soak the tissue slide in hematoxylin for 5 minutes and pour it with running water. After that, the tissue slide is put in acid alcohol and water once dipped each, then put in the eosin solution for 5 minutes. Next, the dehydration and clearing process was carried out again. The last stage is mounting, which is the closure of the tissue slide using a cover glass with Entellan® adhesive.

Histopathological observations use a computer-connected Olympus light microscope and micrograph photography. Observations were made based on the healing process of incision wounds on the skin of mice in the 14th day period which was the beginning of the remodeling phase. The assessment was carried out based on the number of fibroblast cells and the density of collagen fibers. The scoring parameters for the distribution density of collagen fibers were carried out based on the calculation of 3 fields of view on a 400x magnification object. 0 = No collagen fibers in the wound area; +1 = Low collagen density in the wound area (less than 10% per field of view); +2 = Collagen density in moderate wound areas (10 to 50% per field of view); +3 = Collagen density in the area of close wound (50 to 90 per field of view); +4 = Collagen density in the wound area is very dense (90 to 100% per field of view) (Rizka and Vicky, 2013). The treatment data was analyzed by analysis of variance (ANOVA) and continued with the Duncan test with a significance level of 5%.

III. RESULTS AND DISCUSSION

➢ *Fibroblast Cells*

The statistical test results showed a real difference ($P<0.05$) in the average number of fibroblast cells between the four treatment groups. The K1 group (negative control) had the highest average number of fibroblast cells among other groups, namely 110.22 ± 3.41. In contrast, the K2 group (positive control) had the lowest average number of fibroblast cells, which was 37.56 ± 5.80. In general, the K3 group (5% *Muntingia calabura* L leaf extract cream) 46.00 ± 2.02 and the K4 (15% *Muntingia calabura* L leaf extract cream) 67.00 ± 4.10 had a lower average number of fibroblast cells than the K1 group, but more than the K2 group (Table 1).

Entering the remodeling phase, the number of fibroblast cells in the wound area has decreased as a result of the emigration process and apoptosis of the fibroblast cells themselves (Gonzalez et al., 2016). A high average number of fibroblasts in the K1 group which is a negative control indicates the occurrence of fibroplasia which indicates that the lesion is still in the proliferation phase (Sumbayak, 2015). The wound healing process in the K1 group was slower compared to the other groups due to the longer proliferation phase.

The decrease in the number of fibroblast cells on the 14th day in the K2, K3, and K4 groups indicates an increasingly advanced wound-healing process (Fitri and Wael, 2015). The more perfect healing a wound is, the fewer fibroblast cells there are (Harris *et al.*, 2019). The wound healing process in the K2 group was the fastest among the four treatment groups, as seen from the lowest average number of fibroblast cells. This is because silver sulfadiazine cream 0.1% can stimulate macrophages to produce growth hormone which has a positive effect on the proliferation phase so that it affects the next phase of wound healing (Nugraha and Muhartono, 2013). Silver sulfadiazine cream 0.1% also has an antimicrobial effect, namely it can eradicate bacteria in wounds so that infection control occurs and accelerates the wound healing process (Domenico, 2020).

The decrease in the number of fibroblast cells in the K3 and K4 groups is caused by flavonoid compounds contained in the *Muntingia calabura* L. leaf extract cream. Flavonoids trigger macrophage activation. Macrophages secrete TGF-β so the increase in the number of macrophages increases TGF-β levels. TGF-β functions to trigger the proliferation of fibroblasts and epithelium (Suharto and Etika, 2019). Epithelial cells at the edge of the wound in the proliferation phase begin to migrate and form a layer of basal cells accompanied by an increase in mitosis of epithelial cells in the wound area. When the basal cell layer between the two edges of the wound touches and closes each other, the proliferation phase ends (Velnar et al., 2009). The sooner the proliferation phase begins, the sooner this phase ends is characterized by a decrease in the number of fibroblasts.

There was a difference in the average number of fibroblast cells between the K3 and K4 groups. The K3 group had an average number of fibroblast cells less than the K4 group, indicating that wound healing in K3 was more advanced. This is due to the influence of different concentrations of cream preparations. The K4 group had a higher concentration of cream of kersen leaf extract than the K3 group. The higher the concentration of a cream, the lower the spread of the cream. The low spread of the cream results in the active substances contained in the cream not being distributed properly (Lumentut et al., 2020). The K3 and K4 groups had a better effect on wound healing than the K1 group, but not better than the K2 group as seen from the small average number of fibroblast cells (Fig. 1).

➢ *Collagen Density*

The results of the statistical test showed that the average value of collagen density score in the K1 group (negative control) was 55.90 ± 3.95, significantly different ($P<0.05$) from the K3 group (5% *Muntingia calabura* L leaf extract cream) 48.03 ± 3.95 and K4 (15% *Muntingia calabura* L leaf extract cream) from 29.57 ± 3.95, but there was no significant difference ($P>0.05$) from the K2 group (positive control) from 59.83 ± 3.95. The K2 group was significantly different ($P<0.05$) from the K3 and K4 groups and the K3 group was significantly different ($P<0.05$) from the K4 group (Table 2).

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The largest average collagen density score was found in the K2 group and the smallest was found in the K4 group. The K1 group had the largest average collagen density score after the K2 group. Although K1 had a high average collagen density score, the large average number of fibroblast cells and unorganized collagen fibers in this group indicated that the wound had not fully entered the remodeling phase. Normally, in the remodeling phase, the number of fibroblast cells decreases because the fibroblast cell proliferation process has been completed and type III collagen fibers switch to thicker, more organized type I collagen, resulting in tissues with strong tension (Gonzales *et al*., 2016).

The K2 group had the highest average score of collagen density compared to the other three groups followed by a small average number of fibroblast cells. The more perfect healing a wound is, the fewer fibroblast cells there are (Harris *et al*., 2019). This is because the 0.1% silver sulfadiazine cream used in the K2 group can stimulate macrophages to produce *growth hormone* which has a positive effect on the proliferation phase so that it affects the next wound healing phase (Nugraha and Muhartono, 2013). Silver sulfadiazine cream 0.1% also has an antimicrobial effect, namely it can eradicate bacteria in wounds so that infection control occurs and accelerates the wound healing process (Domenico, 2020).

The saponins contained in *Muntingia calabura* L. leaf extract cream have been proven to increase the density of collagen fibers in wounds. Saponins were reported to improve the wound healing process in *in vivo* experiments in diabetic mice and old mice (Morisaki *et al*., 1995). Saponins affect the wound healing process by modifying the expression of TGF-β receptors in fibroblast cells and stimulating the metabolism of extracellular matrix such as fibronectin and collagen from fibroblast cells (Kanzaki *et al*., 1998).

The K3 group had a larger average collagen density score than the K4 group, indicating that wound healing in the K3 group was more advanced. This is due to the influence of different concentrations of cream preparations. The K4 group had a higher concentration of cream of kersen leaf extract than the K3 group. The higher the concentration of a cream, the lower the spread of the cream. The low spread of the cream results in the active substances contained in the cream not being distributed properly (Lumentut *et al*., 2020). The K3 and K4 groups had a better effect on increasing collagen density in the remodeling phase than the K1 group, but not better than the K2 group as seen from the high collagen density score and the thick and organized arrangement of collagen fibers (Fig. 1).

Table 1. Average and Standard Deviation of Fibroblast Cell Count in the Remodeling Phase

Treatment Groups	Average number of fibroblast cells
K1 (Control -)	110.22 ± 3.41a
K2 (Control +)	37.56 ± 5.80d
K3 (5% cream extract)	46.00 ± 2.02c
K4 (15% extract cream)	67.00 ± 4.10b

Remarks: the mean value ± the standard deviation followed by different superscript letters showed a noticeable difference (P<0.05), K1: negative control; delivery base grant, K2: positive control; administration of silver sulfadiazine cream 0.1% and metformin, K3: administration of *Muntingia calabura* L. leaf extract cream and oral extract 5%, K4: administration of *Muntingia calabura* L. leaf extract cream and oral extract 15%.

Table 2. Average and Standard Deviation of Collagen Density Score in the Remodeling Phase

Treatment Groups	Average of collagen density score
K1 (Control -)	$55{,}90 \pm 3{,}95^{a}$
K2 (Control +)	$59{,}83 \pm 3{,}95^{a}$
K3 (5% cream extract)	$48{,}03 \pm 3{,}95^{b}$
K4 (15% cream extract)	$29{,}57 \pm 3{,}95^{c}$

Remarks: the mean value ± the standard deviation followed by different superscript letters showed a noticeable difference (P<0.05), K1: negative control; delivery base grant, K2: positive control; administration of silver sulfadiazine cream 0.1% and metformin, K3: administration of *Muntingia calabura* L. leaf extract cream and oral extract 5%, K4: administration of *Muntingia calabura* L. leaf extract cream and oral extract 15%.

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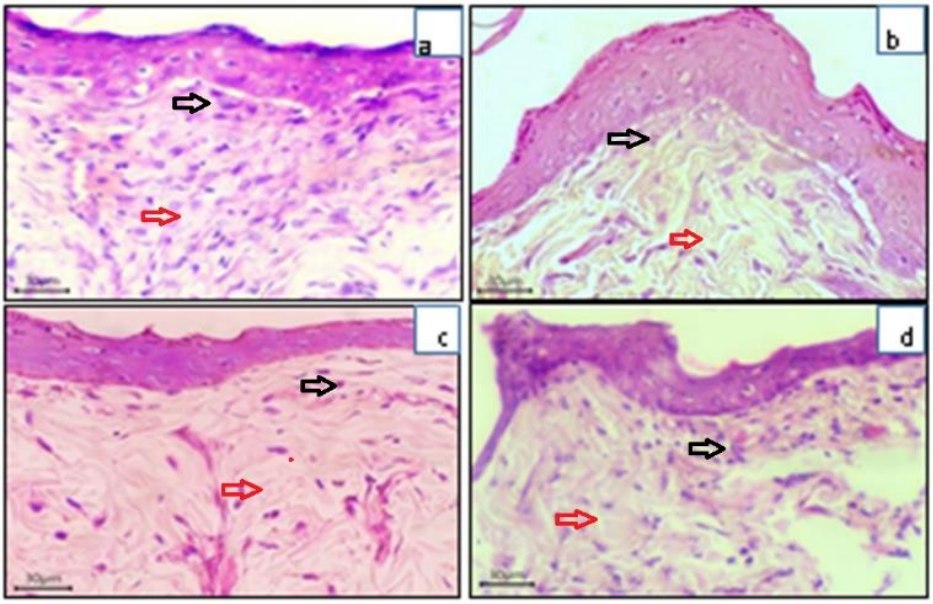

Fig 1. Description of Fibroblast Cells (black arrows) and Collagen Fibers (red arrows) in the wound Area of the Remodeling Phase: a) Negative control group (K1) given cream base: fibroblast cells is very abundant and solid collagen fibers; b) Positive control group (K2) given silver sulfadiazine cream: very little fibroblast and very dense collagen fibers; c) Given *Muntingia calabura* L. leaf extract cream 5% (K3): few fibroblast cells and medium density collagen fiber; d) Given *Muntingia calabura* L. leaf extract cream 15% (K4): few fibroblast cells and non-solid collagen fibers. HE staining, 400x magnification.

IV. CONCLUSION

Topical administration of 5% *Muntingia calabura L.* leaf extract cream can reduce the number of fibroblast cells and increase collagen density, thereby accelerating the healing of incision wounds during the remodeling period in the skin of diabetic white rats.

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