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PENGARUH MADU, *Aloe vera,* DAN MEBO TERHADAP KEPADATAN KOLAGEN PADA LUKA BAKAR DERAJAT II KULIT TIKUS

EFFECT OF HONEY, *Aloe vera,* AND MEBO ON COLLAGEN DENSITY IN HEALING PROCESS OF SECOND DEGREE BURNS IN RATS

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Abstrak

Berbagai penelitian ilmiah telah membuktikan bahwa kolagen merupakan biomaterial ideal dalam aktivitas penyembuhan luka. Senyawa bioaktif pada madu dan *Aloe vera* dapat membantu meningkatkan pembentukan kolagen. Penelitian ini dilakukan untuk membandingkan pengaruh aplikasi topikal madu, gel *Aloe vera*, dan *Moist Exposed Burn Ointment* (MEBO) terhadap kepadatan kolagen pada proses penyembuhan luka bakar derajat dua pada tikus. Luka bakar dibuat pada 28 ekor tikus dan dibagi menjadi empat kelompok yang dipilih secara acak serta dilakukan aplikasi topikal harian dengan NaCl, madu, gel *Aloe vera,* dan MEBO secara berurutan. Biopsi kulit dilakukan pada hari ke-7, kemudian dilakukan pembuatan sediaan histopatologi kulit dan dihitung kepadatan kolagennya. Uji *One Way ANOVA* menunjukkan kepadatan kolagen berbeda secara signifikan antar masing-masing kelompok (p= 0,009). Uji *Post Hoc Bonferroni* menunjukkan terdapat perbedaan yang signifikan antara kelompok NaCl dengan madu (p= 0,024) dan NaCl dengan MEBO (p= 0,024). Penelitian ini menunjukkan bahwa aplikasi madu dan MEBO secara topikal pada luka bakar derajat dua dapat meningkatkan pembentukan kolagen, sehingga dapat mempercepat proses penyembuhan luka. Madu, *Aloe vera,* dan MEBO dapat dijadikan sebagai terapi alternatif dalam penyembuhan luka bakar.

Kata kunci: *Aloe vera;* Kolagen; Luka bakar; Madu; MEBO

Abstract

Various scientific studies have proven that collagen is an ideal biomaterial in wound healing activities. The bioactive compounds in honey and Aloe vera can help increase collagen formation. This study was conducted to compare the effect of topical application of honey, Aloe vera gel, and MEBO (Moist Exposed Burn Ointment) on collagen density in the healing process of second-degree burns in rats. Burns were made on 28 rats which were further randomly divided into four groups to receive daily topical application of NaCl, Aloe vera, honey, and MEBO respectively. Skin biopsy was carried out on the seventh day, then histopathological preparation of the skin was made and collagen density was calculated. Result of One Way ANOVA test showed that collagen density differed significantly between groups (p= 0.009). The Post Hoc Bonferroni test resulted in significant difference between NaCl with honey group (p= 0.024) and NaCl with MEBO (p= 0.024). This study found that topical application of honey and MEBO to second-degree burns could increase collagen formation, thus accelerating wound healing process. Honey, Aloe vera, and MEBO can be used as alternative therapies for healing burns.

***Keywords**: Aloe vera; Burns; Collagen; Honey; MEBO*

INTRODUCTION

Burns occur when the skin comes in contact with a source of heat. Other causes are electricity, friction, chemical, radiation, or radioactive. Thermal burns (heat) occur when some or all cells and tissues in the skin are damaged due to fire, hot objects, or hot liquids (World Health Organization, 2018).

Globally, annual number of deaths from burns reached 180,000, mostly occurred in middle to lower-income countries, two-thirds occurred in Southeast Asia and Africa (World Health

Organization, 2018). In 2013, Basic Health Research data showed there was a 0.7% prevalence of burns in Indonesia. Papua (2.0%), and Bangka Belitung (1.4%) occupied the highest prevalence, while the prevalence for DKI Jakarta and West Java regions accounted for 0.8% and 0.9%, respectively (Badan Penelitian dan Pengembangan Kesehatan Kementerian Kesehatan RI, 2013).

The body will carry out biological processes normally by healing when a wound occurs. There are four very precised and programmed phases occur sequentially in wound healing, those are hemostasis, inflammation, proliferation, and remodeling. The process of hemostasis consists of narrowing of the arteries followed by platelet aggregation, degranulation, and formation of fibrin (thrombus). The inflammatory process consists of neuthropil, infiltration and differentiation of monocytes into macrophages, and lymphocyte infiltration. The proliferation process consists of re-epithelization, angiogenesis, collagen synthesis, and the formation of the extracellular matrix. The final stage is a remodeling which consists of collagen remodeling followed by vasular maturation and regression (Guo & DiPietro, 2010).

Extracellular matrix (ECM) is known as a chronic wound healing factor. Collagen is the main protein in ECM. Many say the benefits of collagen-based biomaterials in promoting cell growth and modulating matrix of metalloproteinase (Gould, 2016). Collagen is a fibrous protein that is a major component of connective tissue and as the most abundant protein in mammals (Marks, Marks, & Smith, 2014). Numerous scientific research have been carried out to find ideal biomaterials with wound healing activities for clinical and collagen use that have been proven to be suitable biomaterials candidates (Felician et al., 2019).

Hashemi, Madani, and Abediankenari (2015) reported that *Aloe vera* has a beneficial effect on wounds, especially healing wound on the skin. Wound healing can be accelerated by compounds contained in *Aloe vera* including saponins, flavonoids, gibberellins, tannins, terpenoids, and steroids (Priscilla, 2017). *Aloe vera* can modulate inflammation, increase wound contraction and epithelialization processes, reduce the size of scar tissue, and improve the alignment and regulation of scar tissue that is regenerating (Oryan, Mohammadalipour, Moshiri, & Tabandeh, 2016). *Aloe vera* has a significant stimulating effect on cell proliferation, and the migration of fibroblasts and keratinocytes. Research showed that *Aloe vera* could accelerate wound healing (Teplicki et al., 2018). *Aloe vera* heals the skin by forming an angiogenesis process, increasing blood flow, stimulating fibroblast proliferation, moisturizing, also activating anti-inflammatory, and antimicrobial (Farzadinia et al., 2016).

Honey has been used as a medicine in wound care for a long time. It has been proven by several studies and experiments on animals showing that honey accelerates wound healing (Jull et al., 2015). The beneficial effect of honey especially that provides anti-microbial activity, makes honey a useful option for the management of various wound healings. A large amount of honey content consists of minerals, amino acids, lipids, carbohydrates, vitamins, and proteins that play an important role in wound healing with minimum trauma during recovery (Oryan, Alemzadeh, & Moshiri, 2016). The efficacy of honey has scientifically proven through preclinical studies and clinical trials where honey could accelerate wound healing, including burns, surgical wounds, infected surgical wounds, and malignant wounds. Other studies have shown that honey modulates the release of cytokines such as TNF-α and IL-10, stimulates proliferation, collagen matrix production, and fibroblast migration. In addition to being a strong immunomodulator (pro and anti-inflammatory activity), honey can neutralize oxidative cell stress that occurs in various stages of wound healing due to its anti-oxidative abilities (Ibrahim et al., 2018).

Moist Exposed Burn Ointment (MEBO®) is a topical agent that is widely used in burned skin (El-Hadidy, El-Hadidy, Bhaa, Asker, & Mazroa, 2014). The formation of granulation tissue increased was found to increase significantly in skin excision wounds treated with MEBO. Also, MEBO can shorten wound healing time and increase neovascularization and the number of fibroblasts. Besides increasing protein expression, the use of MEBO also increases the expression of Vascular Endothelial Growth Factor (VEGF) and Basic Fibroblast Growth Factor (BFGF) genes, MEBO, therefore, has the potential as a healing drug for delayed skin lesions (Tang et al., 2014).

The research experiment was aimed to test the potential topical administration of honey, *Aloe*

vera gel, and MEBO for skin burns. The rat skin burns were used as animal model to see the effect of topical administration of honey, *Aloe vera* gel, and MEBO by assessing the density of collagen in these burns.

MATERIALS AND METHOD

Experimental Design

This study applied experimental research and researchers provided interventions on the research objects. Research with true experiment type and post-test only control the group design. Experimental research aims to determine the effect of certain treatments on the subject. In this type of true experiment, randomization will be carried out by allocating the subjects into the control group and the treatment group randomly, thus making each group comparable. The post-test that only controls group design is a design using two or more groups where each group is treated differently. In the final analysis, post-test was conducted on each group (Syahdrajat, 2015).

Location

The study was conducted at The Pharmacology and Therapy Laboratory, Faculty of Medicine, University of Padjajaran. Reading for results was carried out at the Histopathology Laboratory, Faculty of Medicine, UPN Veteran Jakarta.

Animals

The subjects in this study were 28 male rats (*Rattus norvegicus*) of Wistar strain aged between 8–10 weeks old. Samples were taken by simple random sampling technique. Subjects were divided into four groups consisted of 0.9% NaCl group (negative control), *Aloe vera* gel group, honey group, and MEBO group (positive control). All groups were given standard feed and distilled water for drinking during the study period and kept in standard cage.

Inclusion criteria were male rat, healthy during acclimatization period, and body weight between 150–250 g. Exclusion criteria included: if there is any abnormality found especially on the back region, rat has been treated or has been used for research before, and rat is not adaptable to research environment. Drop-out criteria were met if the rat dies or has an infection during the study period.

Experimental Protocol

Before burns were created, rats were acclimatized for three days. Acclimatization was carried out to equate physiological condition of rats before and after they were kept in the laboratory. After acclimatization, burns were made on each rat. Anaesthesia was carried out using 10% Ketamine. Afterwards, the rat's hair on the back side was shaved. Burn induction was done using electric solder that has been electrified by heating electric solder for 10 minutes at maximum temperature of 100 °C. The electric solder side was placed on the back of the rat for 16 seconds under constant pressure. Burn area created was approximately 2–3 cm^2. Immediately after the rats had burns, each group was treated by topically applying 0.9% NaCl for first group, *Aloe vera* gel for second group, honey for third group, and MEBO for fourth group on the surface of the burned skin twice a day for six days. During the study, rats were kept in separated containers, one container for each rat, given distilled water for drinking and standard rat feed for six days.

Almayra *Aloe vera* gel, Madu Murni Nusantara honey, and MEBO were used in this study. Almayra *Aloe vera* gel contains 100% pure *Aloe vera* extract without alcohol and parabens. The species of *Aloe vera* is *Aloe barbadensis*. Madu Murni Nusantara honey contains 100% pure honey without any addition of artificial sweeteners. The honey obtained from the nectar of original randu tree flowers produced by *Apis mellifera* bees. MEBO is an oil-based ointment containing sesame oil, β-sitosterol, berberine, and a small amount of other Chinese herbal plant ingredients.

Surgery was performed on the seventh day. Rats were anesthetized using 10% Ketamine. Skin biopsy of 2–3 mm^2 was taken from the edge of the burn. Hematoxylin-eosin staining was performed to observe the collagen density of each group.

Skin preparations were observed under an Olympus E5 3B light microscope with 100x magnification and photographed using Motic Images Plus 3.0 ML application. Pictures were processed using ImageJ application. The collagen density was calculated quantitatively by measuring the color absorption of RGB (Red, Green, Blue).

Data Analysis

Data were processed statistically using One Way ANOVA test and Post Hoc test. Prior to One Way ANOVA test, normality and homogeneity tests were performed. If normal and homogenous result is obtained, One Way ANOVA test will be performed and followed by Post Hoc Bonferroni test. The value of $P < 0.05$ is considered as statistically significant.

Ethics

Rats were treated according to ethical guidelines. Experiment protocol was approved by the Health Research Ethics Committee of University of Pembangunan Nasional Veteran Jakarta (number B/2373/1/2020/KEPK).

RESULTS

This study compared collagen density of each group in the healing process of second degree burns in rat model. Collagen density was observed using light microscope and assessed using ImageJ application. Histopathological features of rat skin burn are shown in Figure 1. Microscopic images were analyzed quantitatively by measuring the absorption of light red color of each picture using ImageJ application. The unit of color absorption was shown in pixel. The measurement results for each group were averaged.

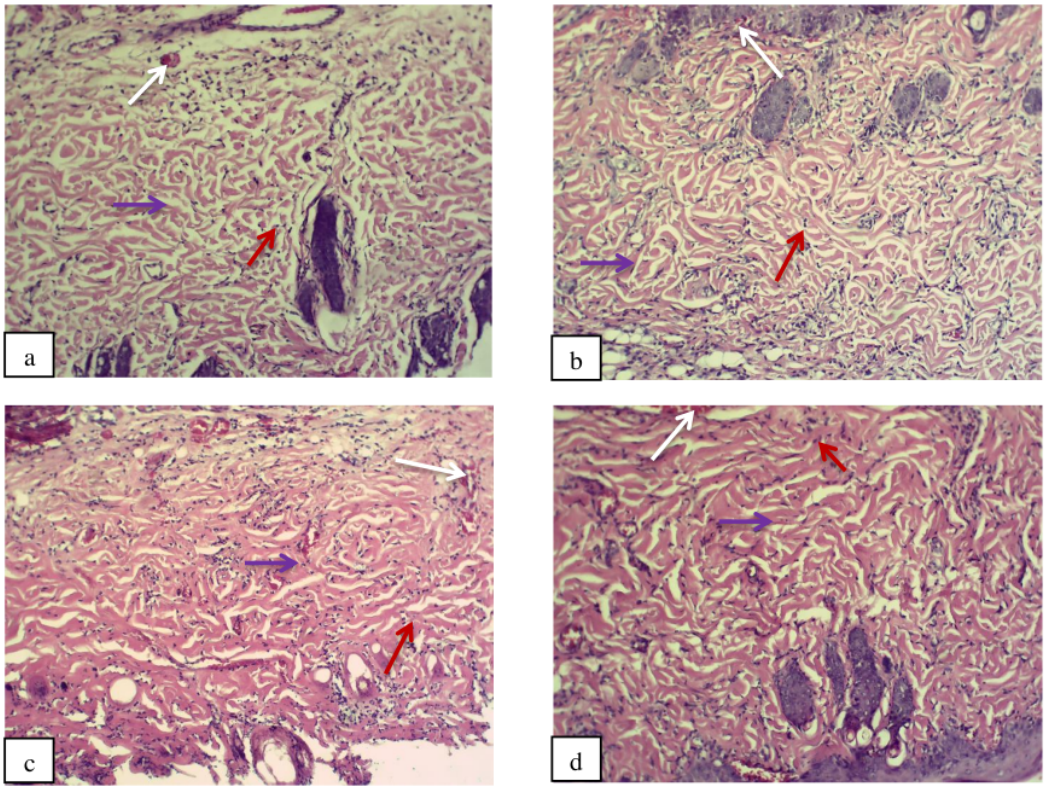


Figure 1. Histopathological features of rat skin burns (purple arrow showing collagen fibers, red arrow showing fibroblasts, and white arrow showing neovascular) treated with 0.9% NaCl

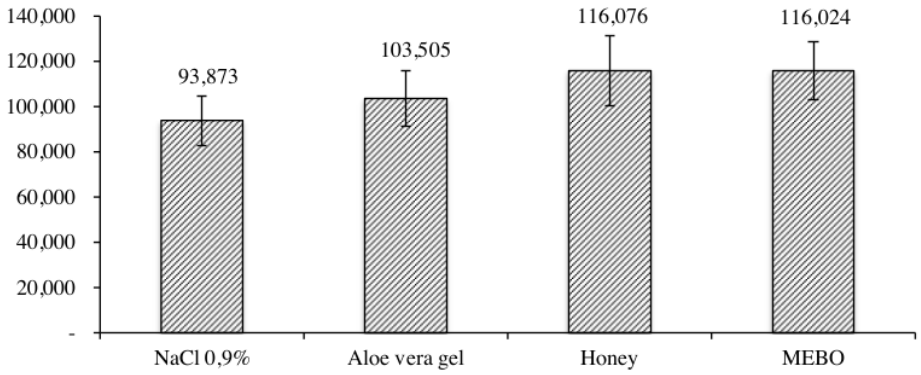
(a), *Aloe vera* gel (b), honey (c), and MEBO (d), respectively.

Table 1. Mean and standard error of collagen density

Group	Mean ± Standard error
0.9% NaCl	93.873 ± 4.150
Aloe vera gel	103.505 ± 4.625
Honey	116.076 ± 5.853
MEBO	116.024 ± 4.884

Table 1 and Graph 1 show that honey group obtained the highest collagen density. Result of normality and homogeneity test showed that data of this study were normally distributed and homogenous, therefore One Way ANOVA test was performed and P-value of 0.009 was obtained. To conclude, "there were at least two groups that had different means of collagen densities" or "there was a significant difference between collagen density in the model treated with NaCl, honey, *Aloe vera* gel, and MEBO groups".

Graph 1. Results of collagen density of each group



Post Hoc Bonferroni test was applied to analyze which treatment groups that will have significant difference. The results of Post Hoc Bonferroni test showed no significant differences of the means of collagen density between NaCl versus *Aloe vera* gel, honey versus *Aloe vera* gel, MEBO versus *Aloe vera* gel, and honey versus MEBO. However, there were significant differences of the means of collagen density between NaCl versus honey and NaCl versus MEBO. The results are shown in Table 2.

Table 2. The results of post hoc Bonferroni test analysis

	0.9% NaCl	*Aloe vera* gel	Honey	MEBO
0.9% NaCl	-	1.000	*0.024	*0.024
Aloe vera gel	1.000	-	0.500	0.508
Honey	*0.024	0.500	-	1.000

MEBO	*0.024	0.508	1.000	-

(*) = a significant difference or significance ($p < 0.05$)

DISCUSSION

Damage to the entire epidermis and part of the dermis will occur in second degree burns (Pencle, Mowery, & Zulfiqar, 2019). This was seen in microscopic observation of Wistar strain rats used as samples in this study. Extracellular Matrix (ECM) is known as wound healing factor, while collagen is the main protein in ECM (Gould, 2016). Collagen has been shown to be an ideal biomaterial in wound healing activity (Felician et al., 2019). Increased collagen synthesis might occur during the proliferation phase (Zhou, Salisbury, Preedy, & Emery, 2013).

Observations in this study compared the collagen density that was affected by the topical administration of honey, *Aloe vera* gel, MEBO (positive control), and NaCl (negative control) on second-degree burns in rat model. The effect was seen from the amount of collagen density through microscopic observation of the skin in each treatment group.

The administration of 0.9% NaCl on first group resulted in the lowest collagen density among the other groups. This finding was acceptable since 0.9% NaCl solution functions as an isotonic fluid and physiological salts. The NaCl solution will not irritate body tissues because the concentration of body fluids is almost the same as the concentration of fluid possessed by NaCl. But in principle, NaCl can help the wound healing process (Purnomo, Dwiningsih, & Lestari, 2014).

The density of collagen on second group treated with *Aloe vera* gel showed an increase, because *Aloe vera* has a variety of biologically active compounds such as flavonoids, saponins, amino acids, vitamins, and minerals. The effect of *Aloe vera* on increasing collagen provides strength and integrity to tissue matrix and plays an important role in homeostasis along with epithelialization (Akgun, Aydemir, Ozkan, Yuksel, & Sardas, 2017). *Aloe vera* has a significant stimulating effect on cell proliferation, migration of fibroblasts and keratinocytes, and research showed that *Aloe vera* can accelerate wound healing (Teplicki et al., 2018). *Aloe vera* stimulates fibroblasts which will produce new collagen during the wound healing process (Nimma et al., 2017) as confirmed by Alam (2019) that *Aloe vera* gel could affect the formation of wound collagen.

On the third group, honey resulted in the highest mean of collagen density among other groups. It is expected due to the efficacy of honey that has been scientifically proven through pre-clinical studies and clinical trials, showing that honey could accelerate the healing of many wounds. Honey modulates the release of TNF-α and IL-10. Furthermore, honey also stimulates proliferation, collagen matrix production, and fibroblasts migration. In addition to being a strong immunomodulator (pro and anti-inflammatory activity), honey is able to neutralize oxidative stress cells for its anti-oxidative abilities (Ibrahim et al., 2018). Based on the research of Biondo-Simões et al. (2019), topical use of honey can increase collagen, specifically type I collagen and accelerate healing.

Collagen density in fourth group was the second highest after honey. In 1989, MEBO was developed at China National Science and Technology Centre Beijing as an oil-based ointment that has been proposed as an ideal burn treatment (Prasetyo & Heridadi, 2013; Tang et al., 2014; Biondo-Simões et al., 2019). MEBO was found to significantly promote granulation tissue formation in skin excision wounds, shortens wound healing time, increase neovascularization and the number of fibroblasts, and help fibroblasts migrate from surrounding connective tissue to the wound site (Tang et al., 2014; Li, Ma, Yang, Pan, & Meng, 2017).

Statistical tests showed that the comparison between first group (NaCl), second group (*Aloe vera* gel), third group (honey), and fourth group (MEBO) resulted in significant effect, indicating that topical administration of honey, *Aloe vera* gel, MEBO, and NaCl could increase collagen density and speed up the healing process. The result of study by Ananda (2018) confirmed that *Aloe vera* gel and honey were able to accelerate burn healing in rats.

Aloe vera can improve healing through several mechanisms. *Aloe vera* may increase collagen synthesis and cross-linking collagen caused by the increasing aldehyde content and the decreasing acid solubility. The content of Acemannan (mannose-6 phosphate) in *Aloe vera* accelerates the rate of epithelialization (Ashkani-Esfahani et al., 2019). Manose and glucose contained in Acemannan

(glucomannan) will bind to the mannose receptor and will activate TGF-β directly which plays a role in inducing collagen deposition (Yuza, Wahyudi, & Larnani, 2014). Glucomannan compounds found in *Aloe vera* can influence fibroblast growth factor receptors, which will stimulate fibroblast activity and proliferation to further increase collagen production, while also being able to change collagen composition, and increase collagen cross-linkages (Hekmatpou, Mehrab, Rahzani, & Aminiyan, 2019). *Aloe vera* is also able to accelerate the rate of expression of TGF β-1 and VEGF (Hashemi et al., 2015). To say, *Aloe vera* provides a beneficial effect on the proliferative phase of wound healing. The saponin compounds found in *Aloe vera* also affect the expression of procollagen type I (Yuza et al., 2014).

According to some researchers, low pH of honey can help create and maintain optimal conditions for fibroblasts since fibroblasts require an acidic environment for their activities, such as migration and organizing collagen (Martinotti & Ranzato, 2018). Takzaree et al. (2017) revealed that the acidic pH in honey will also release oxygen from hemoglobin and increase fibroblast activity, hence collagen will quickly form. Honey can also increase angiogenesis and make nutrients (Takzaree et al., 2017). Ascorbic acid in honey that has been proposed as a conjugate to strengthen the healing effect of honey is an enzymatic co-factor needed for the collagen synthesis and fibroblast proliferation (Schencke et al., 2016). This process supports that honey can promote the proliferative phase of wound healing. Moreover, honey has a phenolic content that can act as a binder and form a cross bond, thus affecting mechanical stability. Phenols act both on fibrils that have formed and on the polyphenols of the flavonoids type could affect the assembly of type I collagen fibrils, which independently either increase or completely stop it (Kim, Gaidin, & Tarahovsky, 2018).

Isrofah, Sagiran, and Afandi (2015) said that higher collagen density in the proliferation phase will fasten wound healing process and reduce the potential of bad scars formation. In this study, the rate of collagen density on third group (honey) obtained the highest value compared to second group (*Aloe vera* gel). Yet, Tomo, Dachlan, and Purnomosari (2015) were not in line with the results of this study as they found that on the fourth day of decapitation, the rate of collagen in *Aloe vera* group was higher than that in the honey, saliva, egg white, and NaCl groups. However, some studies confirmed this study, such as Novitasari, Setiyajati, and Haris (2015) who found that administration of honey group resulted in faster wound healing compared to *Aloe vera* gel group.

Honey contains antioxidant, that is vitamin C (Dewi & Susanto, 2013) which can inhibit MMP-1 expression in fibroblasts, thus accelerating the process of maturition of collagen fibers (Rosanto, Handajani, & Susilowati, 2012). Honey also has antibacterial activity because it contains flavonoids (Aftria, 2014). In addition to honey, *Aloe vera* also contains flavonoids (Akgun et al., 2017) which has the ability to increase the viability of collagen fibers by reducing lipid peroxidation (Palumpun, Wiraguna, & Pangkahila, 2017).

Flavonoids can increase collagen, but this study showed different result on honey and *Aloe vera* groups which might be related to other studies that explain explained IL-6 and IL-10 as wound healing factors. Honey can modulate the release of TNF-α cytokines and IL-10 (Ibrahim et al., 2018). Study conducted by Linangkung, Dachlan, and Purnomosari (2017) found that egg white and *Aloe vera* caused less IL-10 expression compared to honey, NaCl, and saliva groups. Furthermore, the study stated that IL-10 is a cytokine that functions as a potential anti-inflammatory and antifibrotic. Therefore, IL-10 can affect healing skin incision wounds of rats.

Another study by Indrawan, Dachlan, and Purnomosari (2016) showed that IL-6 serves as an indicator of wound healing. A small amount of IL-6 can accelerate inflammation, which can fasten wound healing. This research found that honey expressed lower amount of IL-6 rather than egg white, saliva, NaCl, and *Aloe vera,* allowing the increasing speed of incision wound healing in rat skin.

From these two studies, it is concluded that high IL-10 expression and low IL-6 compared to *Aloe vera*. Conversely, the administration of *Aloe vera* caused lower IL-10 expression and higher IL-6 expression compared to honey. Both IL-6 and IL-10 are cytokines but have different roles where IL-6 is a pro-inflammatory cytokine, while IL-10 is an anti-inflammatory (Masfufatun, Tania, Raharjo, & Baktir, 2018).

The high IL-10 and low IL-6 were affected by honey application can reduce the inflammatory phase and increase the proliferation phase. During proliferation phase, formation and activation of fibroblasts cells occurs. Fibroblast cells will secrete collagen, and subsequently granulation tissue begins to form. This explains that honey has more collagen yields rather than *Aloe vera* due to IL-6 and IL-10 factors.

CONCLUSION

Topical application of 0.9% NaCl, honey, *Aloe vera* gel, and MEBO significantly affected the healing process of second-degree burns of rats and collagen density. The highest collagen density was obtained by honey group (116.076 ± 5.853 pixels) and followed by MEBO group (116.024 ± 4.884 pixels), *Aloe vera* gel group (103.505 ± 4.625 pixels), and NaCl group (93.873 ± 4.150 pixels).

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