

# THE EFFECT OF SUMBAWA FOREST HONEY ON INCREASING THE NUMBER OF FIBROBLAST CELLS (IN VIVO STUDY AFTER WISTAR RAT TOOTH EXTRACTION)

Welmi Liaman<sup>1\*</sup>, Ickman Setoaji Wibowo<sup>2</sup>, Ulfa Yasmin<sup>3</sup>, Galuh Anggraini Adityaningrum<sup>4</sup>, Trisnawaty K<sup>5</sup>

<sup>1</sup>Faculty of Dentistry, University of Sriwijaya, Indonesia

<sup>2</sup>Department of Oral Surgery, Faculty of Dentistry, University of Sriwijaya, Indonesia

<sup>3</sup>Department of Pedodontia, Faculty of Dentistry, University of Sriwijaya, Indonesia

\*Corresponding Author Email: welmiliaman031@gmail.com

**Article info:** Received: 20-10-2024; Revised: 20-11-2024; Accepted: 12-12-2024; Publish: 30-12-2024

## Abstract

**Background:** Fibroblasts play an important role in the process of wound healing in the proliferation phase. Honey contains flavonoids, phenolic acids, vitamins and enzymes that play a role in increasing fibroblasts. The aim of this research was to determine the effect of Sumbawa forest honey on increasing the number of fibroblast cells after Wistar rat tooth extraction on day 7. **Method:** This is a laboratory experimental study with Post Test Only with Control Group design. In this study used 24 male Wistar rats, divided into 4 groups, the negative control (aquadest), the 50% Sumbawa forest honey, the 100% Sumbawa forest honey, and the positive control (hyaluronic acid) were applied topically twice a day for 7 days in dental sockets after tooth extraction in Wistar rats. The number of fibroblast was counted by histopathology preparations under Olympus CX31 microscope and ImageJ software and analyzed using Independent sample t-test and Post Hoc Least Significant Difference (LSD). **Results:** The result of this study showed the group with 100% concentration of Sumbawa forest honey had significantly higher number of fibroblast cells compared to the group with 50% concentration of Sumbawa forest honey and the negative control ( $p < 0.05$ ). **Conclusion:** Sumbawa forest honey concentrations of 50% and 100% have an effect in increasing the number of fibroblast cells after tooth extraction of wistar rats and 100% have an effect in increasing the number of fibroblast cells after tooth extraction of wistar rats and the highest number of fibroblast cells was found in the group with concentration of 100% Sumbawa forest honey.

**Keywords:** Sumbawa forest honey, tooth extraction, fibroblast, wound healing

## INTRODUCTIONS

Tooth extraction is one of the most widely performed procedures in the world of dentistry.<sup>1</sup> Tooth extraction is performed by removing the tooth from the socket in the alveolar bone with an indication that the tooth can no longer be

treated.<sup>2</sup> Data obtained from the 2018 Riset Kesehatan Dasar (RISKESDAS) shows that tooth extraction is second only to medication in overcoming dental and oral problems, with a percentage reaching 7.9%.<sup>3</sup> Tooth extraction will result in the opening of the tooth socket, which has the potential to cause discomfort experienced by the patient.<sup>4</sup>

The occurrence of wounds will be followed by a healing process that takes place physiologically until the wound is completely closed and the tissue returns to normal.<sup>5</sup> Wound healing takes place through a series of interactions between various mediator cells, cytokines, and extracellular matrices that can be grouped into 4 phases, namely the hemostasis phase, the inflammatory phase, the proliferation phase, and the remodeling phase.<sup>6, 7</sup> In the first phase, known as the hemostasis, injured blood vessels will experience bleeding. This bleeding serves to activate intrinsic and extrinsic coagulation factors, which then trigger platelet aggregation and clot formation. In addition, vasoconstriction, retraction at the ends of the severed blood vessels, and hemostasis reactions occur.

Furthermore, the inflammatory phase takes place. with the aim of cleaning dead tissue, preventing bacterial colonization. The next phase is the proliferation phase, which is marked by the transition of the provisional matrix dominated by platelets and macrophages. Furthermore, this process is gradually replaced by fibroblast cell migration and extracellular matrix synthesis. The purpose of this proliferation phase is to create a balance between scar tissue formation and tissue regeneration. The final phase is the remodeling phase, which aims to maximize the strength and structural integrity of the new tissue that fills the wound, as well as supporting epithelial growth and scar tissue formation.<sup>30</sup>

One of the important roles is fibroblasts, especially during the proliferation phase. Fibroblasts are cells with high heterogeneity and plasticity, showing a central role in this phase under macrophage regulation. Macrophages produce growth factors such as PDGF (Platelet-Derived Growth Factor), FGF (Fibroblast Growth Factor), and TGF- $\beta$  (Transforming Growth Factor  $\beta$ ), which stimulate fibroblasts to proliferate, migrate, and form an extracellular matrix. This extracellular matrix will fill the wound space and provide a foundation for keratinocyte movement and become the most important component of skin

wounds. Fibroblasts then differentiate into myofibroblasts, which contribute to wound contraction. Fibroblasts are also the main source of collagen synthesis in wound healing.<sup>8</sup>

The discomfort caused by the slow wound healing process has prompted much research in dentistry to find the right ingredients to speed up the process. Various studies have been conducted on the use of natural ingredients as a source of active substances that can speed up the wound healing process, one of which is honey. The use of natural ingredients as a treatment is widely chosen by the public because it is considered safer for health and has fewer side effects compared to drugs made from chemicals.<sup>63</sup>

Honey is a natural ingredient that is used as a medicine. Honey has several important characteristics, including anti-inflammatory activity, antibacterial effects, and antioxidant properties. Honey can also stimulate the removal of dead tissue, reduce the odor of wounds, and maintain wound moisture so that it can speed up the wound healing process.<sup>11</sup> Honey contains many active compounds that play a role in increasing the wound healing process, namely flavonoids, phenolic acids, enzymes, and vitamins. Honey is divided into two types based on the flower source, namely monofloral honey (for example, longan honey) and multifloral (for example, forest honey). In Indonesia, the types of honey that are marketed are often named according to their origin, for example, Sumbawa honey or Lampung honey.<sup>10</sup>

There are several studies examining the potential of various types of honey in improving the wound healing process. Research by Muhammad et al. (2021) proves that giving honey can accelerate the wound healing process by reducing neutrophil cells.<sup>11</sup> Research by Rupan et al. (2019) showed that 15% concentration of Manuka honey accelerates epithelialization and collagen tissue formation.<sup>14</sup> Another study conducted by Yuslianti et al. (2016) showed that flavonoids contained in rambutan honey accelerate the wound healing process and prevent oxidative stress, thereby inducing TGF- $\beta$ 1 (Transforming Growth Factor  $\beta$ 1) to inhibit the formation of MDA (Malondialdehyde).<sup>16</sup> Based on research by Leila et al. (2021), who studied the therapeutic effects of 80% concentration of Lotus honey on hard palate wounds in mice, it showed that there was an increase in

fibroblasts starting from day 3 and peaking on day 7 to day 14.<sup>16</sup> According to research conducted by Al-Jadi et al. (2014), Malaysian honey can stimulate fibroblast proliferation because it contains hydrogen peroxide.<sup>64</sup>

There are many studies on honey, but studies that specifically examine local honey from native Indonesian honeybees are still relatively few. One of the local honeys produced is Sumbawa honey.<sup>17, 18</sup> The author chose Sumbawa forest honey with concentrations of 50% and 100% because there has been no research on the effectiveness of Sumbawa forest honey on the number of fibroblasts.<sup>62</sup> The author chose an increase in fibroblast cells on day 7 because, based on research by Yuslianti et al. (2016), fibroblast increase peaked on day 7.<sup>16</sup> Currently, there has been no research that discusses the effect of Sumbawa forest honey on increasing fibroblast cells after tooth extraction. Therefore, the author wishes to conduct research on the effect of Sumbawa forest honey on increasing the number of fibroblast cells after tooth extraction in Wistar rats.

## **METHODS**

The research method is an experimental laboratory with a posttest-only control group design. The research sample for each group was determined using the Federer so that 24 male Wistar rats were obtained and divided into 4 groups, namely the negative group (aquadest), the 50% Sumbawa forest honey group, the 100% Sumbawa forest honey group, and the positive group (hyaluronic acid), which was given 2 times a day for 7 days.

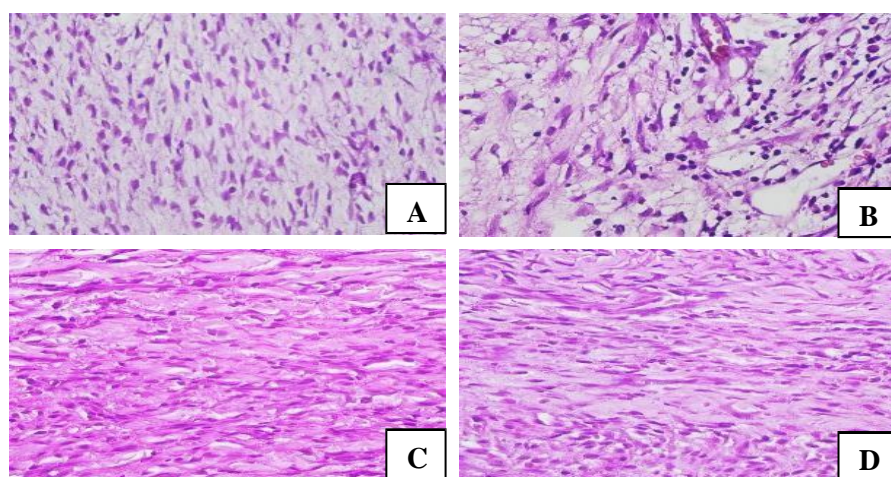
This study used Sumbawa forest honey produced by CV. Honeysia Alamindo Barokah in Kembang Putih, Guwosari, Special Region of Yogyakarta. The preparation of a 50% concentration of Sumbawa forest honey was carried out using a dilution formula so that 5 ml of Sumbawa forest honey was obtained diluted with 5 ml of aquadest. Histopathological preparations were taken from the results of decapitation.

Decapitation is the separation of the jaw of the experimental animal from the head. In this study, the lower jaw was separated from the rat's head with a scalpel and blade and then placed in a 10% formalin. Staining with Hematoxylin Eosin (HE) and the number of fibroblasts were observed under an Olympus CX31

microscope at 400x magnification in 3 fields of view and counted using ImageJ software. Statistical analysis in this study used Shapiro-Wilk for normality testing, Levene's test for homogeneity testing, independent sample T-test for hypothesis testing, and post hoc least significant difference (LSD) test to determine significant differences.

## RESULTS

This study aims to determine the effect of Sumbawa forest honey on the increase in the number of fibroblast cells after tooth extraction of Wistar rats. The histological description of the number of fibroblast cells from each group is shown in Figure 1.



**Figure 1.** Histological Image of Post-Tooth Extraction Socket Tissue in Treatment Groups: (A) Aquadest, (B) Sumbawa forest honey 50% concentration, (C) Sumbawa forest honey 100% concentration, and (D) Hyaluronic acid, for 7 days in one field of view with a microscope at 400x magnification.

The density of fibroblast cells was more visible in the Sumbawa forest honey group with a concentration of 100% and hyaluronic acid compared to aquadest and Sumbawa forest honey with a concentration of 50% (Figure 1.). The 100% Sumbawa forest honey group had the highest average number of fibroblast cells, namely 148.27, while the lowest was in the aquadest group, 64.38 (Table 1).

**Table 1.** Mean Number of Fibroblast Cells After Treatment

<b>Group</b>	<b>Mean Number of Fibroblast Cells ± SD</b>
Sumbawa Forest Honey 50%	97,77 ± 10,28
Sumbawa Forest Honey 100%	148,27 ± 26,29
Aquadest	64,38 ± 41,48
Hyaluronic Acid	115,05 ± 38,74

The research data was continued with the Shapiro-Wilk normality test. This test was conducted to determine whether the research data was normally distributed or not. The four groups showed a significance value (p) > 0.05 (Table 2.), which means that the data collected is normally distributed data.

**Table 2.** Shapiro-Wilk Normality Test Results

<b>Group</b>	<b>Significance Value</b>
Sumbawa Forest Honey 50%	0,632
Sumbawa Forest Honey 100%	0,812
Aquadest	0,063
Hyaluronic Acid	0,180

\*If the p value is greater than 0.05, the data is considered normally distributed.

The next step in processing data using the independent sample t-test is to do a homogeneity test using the Levene test following the completion of the normality test. Table 2. displays the significant value of the Sumbawa forest honey data with a 50% concentration of 0.134 and the Sumbawa forest honey with a 100% concentration of 0.663, according to the Levene test homogeneity test findings. Both groups' results demonstrate a significance value (p) > 0.05, indicating that the collected data is homogeneous. Normal distribution and homogeneity of data are prerequisites for the independent sample t-test hypothesis test. Since these two conditions are satisfied, the hypothesis test may be conducted using the independent sample T-test.

**Table 3.** Independent Sample T-test Results

Group Receiving Treatment	Levene-test	Independent Samples T-test
	Sig.	Sig.
Sumbawa Forest Honey 50%	0,134	0,042
Sumbawa Forest Honey 100%	0,663	<0,001

\* If the p value is less than 0.05, it is considered that there is a significant difference.

A significant value of 0.042 ( $p < 0.05$ ) was obtained from the first hypothesis test on 50% concentration Sumbawa forest honey, indicating that  $H_0$  was rejected and  $H_1$  was accepted (Table 3.). These findings suggest that administering 50% Sumbawa honey to Wistar rats on the seventh day following tooth extraction can significantly increase the quantity of fibroblast cells. Due to the significance value of  $<0.001$  ( $p < 0.05$ ) obtained from the second hypothesis test,  $H_0$  was rejected and  $H_1$  was accepted (Table 3.). These results suggest that administering 100% Sumbawa honey can significantly increase the amount of fibroblast cells in Wistar rats on the seventh day following tooth extraction.

To find out if there is a significant difference between the four groups, a post hoc least significant difference test (LSD) is performed (Table 4.). There is a substantial difference between the aquadest and Sumbawa forest honey groups with a 100% concentration, as indicated by their values of ( $p$ )  $<0.001$  ( $p < 0.05$ ) (Table 4.). The value of ( $p$ ) 0.012 ( $p < 0.05$ ) for the aquadest and hyaluronic acid group also suggests that there is a significant difference between the two groups. At a value of ( $p$ ) 0.012 ( $p < 0.05$ ), the results of the Sumbawa forest honey group with a 100% concentration and Sumbawa forest honey with a 50% concentration also demonstrate a significant difference.

**Table 4.** Fibroblast Cell Count Comparison of p Values Between Groups Following Treatment

<b>Sig. Value Between Groups</b>	<b>Aquadest</b>	<b>Honey 50%</b>	<b>Honey 100%</b>	<b>Hyaluronic Acid</b>
Aquadest		0,083	<0,001*	*0,012
Honey 50%	0,083		0,012*	0,356
Honey 100%	<0,001*	0,012*		0,084
Hyaluronic Acid	0,012*	0,356	0,084	

\* If the p value is less than 0.05, it is considered substantially different.

## DISCUSSION

The average value between the treatment group and aquadest was significantly different, indicating that Sumbawa forest honey had an impact on the quantity of fibroblast cells following tooth extraction in Wistar rats on the seventh day. With a 100% concentration of Sumbawa forest honey, the treatment group had the greatest average number of fibroblasts, at 148.278. These findings are consistent with the study by Al-Jadi et al. (2014), which found that honey increases the number of fibroblasts.<sup>44</sup>

Fibroblasts are crucial to the process of wound healing. First the inflammatory phase, which starts migrating to the wound site in response to chemical cues from immune cells. Macrophages generate fibroblasts by producing growth factors such transforming growth factor- $\beta$ , platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF). In the presence of growth factors generated by macrophages, fibroblasts generate extracellular matrix (ECM) and matrix metalloproteinases (MMPs).

Fibroblasts also create type III collagen, which will eventually replace the extracellular matrix. During the remodeling phase, type I collagen will take the place of type III collagen. Matrix metalloproteinases (MMPs), which are released by fibroblasts, endothelial cells, and macrophages, mediate these collagen alterations.<sup>31, 32</sup> These collagen fibers will be positioned, put together, and tidied along the wound line in order to make the two wound edges closely spaced.<sup>7</sup>

An increase in fibroblasts can speed up the healing of damaged tissue and make the entire process run more smoothly. Honey's components, which include pyruvate kinase enzymes, hydrogen peroxide, phenolic acid, flavonoids, and vitamin C, contribute to the growth of fibroblasts and hasten the healing of wounds.<sup>43,44</sup>

Flavonoids were found in Sumbawa honey according to a phytochemical examination conducted by Adalina et al. (2019). The presence of flavonoids can promote tissue regeneration and wound healing processes.<sup>48</sup> This also supports the findings of Yuslianti et al. (2016), who found that flavonoids in honey have antibacterial, anti-inflammatory, and antioxidant qualities. They can also promote the growth of collagen and fibroblasts.<sup>16</sup> According to Suparwitri et al. (2024), flavonoids boost fibroblast activity, which in turn raises TGF- $\beta$ 1 throughout the wound healing process.<sup>64</sup>

The phenolic acid content of honey can promote angiogenesis and neovascularization by inducing VEGF and PDGF and enhancing fibroblast and endothelial cell motility, according to Melguizo et al. (2021).<sup>50</sup> Hydrogen peroxide content promotes the growth of fibroblasts, inflammatory cells, and vascular endothelial cells, according to research by Dunnill et al. (2017).<sup>51</sup> A study by Mohammed et al. (2016) found that vitamin C phagocytoses neutrophils during the inflammatory phase and collagen maturation during the proliferation phase, whereas Kim et al. (2023) demonstrated that the pyruvate kinase enzyme promotes angiogenesis.<sup>52,53</sup>

At a 100% concentration, Sumbawa forest honey differs significantly from aquadest ( $p < 0.001$  (Table 4.)). These findings demonstrate that, in comparison to aquadest, applying 100% Sumbawa forest honey helps hasten the healing process of wounds. These findings support a study by Nasution et al. (2021) that found that 100% honey administration can hasten wound healing through chemical and physical actions that can boost fibroblastic activity.<sup>13</sup> Masir et al. (2012) also talked about how honey's flavonoid content can promote the growth of Fibroblast Growth Factor (FGF), which in turn can increase the activity of fibroblast cells to produce collagen and form connective tissue, thereby suppressing the inflammatory process and promoting wound healing.<sup>66,67,68</sup>

The difference between aquadest and Sumbawa wild honey at 50% concentration was not statistically significant ( $p = 0.083$ ; Table 4.). These findings suggest that giving 50% Sumbawa forest honey does not effectively increase the number of fibroblast cells in comparison to aquadest. The physical properties of honey, including its acidity, osmotic effects, and chemical effects, result in a higher average number of fibroblast cells in the 100% Sumbawa forest honey group than in the 50% Sumbawa forest honey group. Increased honey concentrations also result in faster wound healing times because honey's increased sugar content and more acidic pH promote better wound healing.<sup>67</sup>

The value ( $p$ )  $<0.001$  of 100% Sumbawa forest honey is higher than the value ( $p$ ) 0.012 of hyaluronic acid (Table 4.). According to these findings, Sumbawa forest honey at a 100% concentration is more effective than hyaluronic acid at promoting the growth of fibroblast cells. The effectiveness of 50% Sumbawa forest honey was found to be similar to that of hyaluronic acid, as evidenced by the fact that there was no significant difference between the two substances ( $p = 0.356$ ; Table 4.).

One of the study's limitations is that the samples were treated for a duration of 12 hours, which is not equivalent to giving them twice a day due to the research location's operational hours (lab operational hours 08.00-17.00). Also, a phytochemical analysis of Sumbawa forest honey at 50% and 100% concentrations was not done in this study; this can be done in the future to see if the concentration content has changed. To find out if it has the same effect and may be used as a medication to treat wounds in dentistry, this research must also be conducted clinically on humans.

## **CONCLUSION**

Based on the research results, it can be concluded that Sumbawa forest honey at 50% and 100% concentrations has an effect on increasing the number of fibroblast cells after tooth extraction in Wistar rats.

## **SUGGESTIONS**

To be used as an alternative wound-healing medication in dentistry, this study must do phytochemical analysis of Sumbawa forest honey at concentrations of 50%, 100%, treatment duration with the same dose, and continued clinically in humans.

## **REFERENCES**

1. Adnan S, Adzakiyah T. Gambaran pencabutan gigi di rumah sakit gigi dan mulut (RSGM) universitas andalas pasca pandemi covid-19. *Andalas Dent J.* 2022;10(1):16-23.
2. Lande R, Kepel BJ, Siagian K V. Gambaran faktor risiko dan komplikasi pencabutan gigi di RSGM PSPDG-FK UNSRAT. *E-Gigi.* 2015;3(2).
3. Domic D, Bertl K, Lang T, Pandis N, Ulm C, Stavropoulos A. Hyaluronic acid in tooth extraction: a systematic review and meta-analysis of preclinical and clinical trials. *Clin Oral Investig.* 2023;27(12):7209-7229.
4. KEMENKES. Laporan Nasional riset kesehatan dasar (RISKESDAS) [Internet]. Indonesia; 2018 [cited 2023 Sep 20]. Available from: <https://layanandata.kemkes.go.id/katalog-data/riskesdas/ketersediaan-data/riskesdas-2018>
5. Santosa AH, Kintawati S, Sugiaman VK. Pengaruh resorbable collagen plug (RCP) terhadap penyembuhan luka ekstraksi. *E-Gigi.* 2022;10(1):81.
6. Ningsih JR, Haniastuti T, Handajani J. Reepitelisasi luka soket pasca pencabutan gigi setelah pemberian gel getah pisang raja (*musa sapientum* l) kajian histologis pada marmut (*cavia cobaya*). *JIKG.* 2019;2(1):1-6.
7. Palumpun EF, Wiraguna AAGP, Pangkahila W. Pemberian ekstrak daun sirih (*piper betle*) secara topikal meningkatkan ketebalan epidermis, jumlah fibroblas, dan jumlah kolagen dalam proses penyembuhan luka pada tikus jantan galur wistar (*rattus norvegicus*). *J E-Biomedik.* 2017;5(1).
8. Moenadjat, Y. Penyembuhan luka: aspek seluler dan biomolekuler. Fakultas kedokteran universitas indonesia. 2023.

9. Putra ATW, FW WA, Hamidy MY. Tingkat kepadatan fibroblas pada luka sayat mencit dengan pemberian gel lidah buaya (aloe chinensis baker). 2007;(1).
10. Destri C. Potensi jatropa multifida terhadap jumlah fibroblast pada aphthous ulcer mukosa mulut tikus. J Biosains Pascasarj. 2017;19(1):14.
11. Tashkandi H. Honey in wound healing: an updated review. Open Life Sci. 2021;16(1):1091-1100.
12. Shalih MF, Monica WS, Sari DK, Jamaluddin W. Description of neutrophil cells of giving sugar and honey in incision wound of domestic cat (felis domestica). Jurnal Riset Veteriner Indonesia. 2021;5(1):27-33.
13. Nasution MFW, Muslimdjas Y. Uji efektivitas madu konsentrasi 50% dan 100% dibandingkan dengan povidone iodine terhadap penyembuhan luka sayat pada mencit (mus musculus). J Ilm Mhs Kedokt Indones. 2021;8(3):47-53.
14. Suhandy D, Yulia M, Kusumiyati K. Klasifikasi madu berdasarkan jenis lebah (apis dorsata versus apis mellifera) menggunakan spektroskopi ultraviolet dan kemometrika. J Ilmu Pertan Indonesia. 2020;25(4):564-573.
15. Poojar B, Ommurugan B, Adiga S, Et Al. Comparative evaluation of wound healing potential of manuka and acacia honey in diabetic and nondiabetic rats. Asian J Pharm Clin Res. 2017;7(10):1-5.
16. Yuslianti ER, Bachtiar BM, Suniarti DF, Sutjiatmo AB, Mozef T. Effect of rambutan-honey and its flavonoid on tgf- $\beta$ 1 induce fibroplasia oral wound healing. Res J Med Plant. 2016;10(8):435-442.
17. Golpasandhagh L, Salehi P, Karimi B, Moghimipour E. Therapeutic effect of ziziphus lotus honey on hard palate ulcers in rats. Med Stud. 2021;37(1):58-64.
18. Saputri DS, Putri YE. Aktivitas antioksidan madu hutan di beberapa kecamatan di kabupaten sumbawa besar. J Tambora. 2017;2(3).
19. Sumarlin LO, Muawanah A, Wardhani P. Aktivitas antikanker dan antioksidan madu di pasaran lokal indonesia (anticancer and antioxidant activity of honey in the market local indonesia). J Ilmu Pertan Indonesia. 2014;19(3):136-144.

20. Ludfiyaningrum SD, Gustari S. Pengaruh penggunaan madu sumbawa dan madu olahan berbagai konsentrasi terhadap kualitas spermatozoa epididimis domba setelah penyimpanan dalam refrigerator. *Ovozoa J Anim Reprod.* 2021;10(1):1.
21. James RH, Edward E MR. *Contemporary Oral And Maxillofacial Surgery* 7th Ed.; 2015. P.107-8.
22. Mehrota D. *Fundamentals of oral and maxillofacial surgery.* 2020.
23. Balaji S. *Oral And Maxillofacial Surgery* 2nd Ed. 2013:337-355.
24. Bonanthaya K, Panneerselvam E, Manuel S, Et Al. *Oral and maxillofacial surgery for the clinician.* 2021.
25. Fragiskos FD. *Oral surgery.* 2007. P.181-200
26. Soviana RA, Dian Femala DF, Susatyo JH, Suryana B. Pengetahuan pengunjung tentang instruksi pasca pencabutan gigi di pusat pengobatan mata dan gigi. *Dent Ther J.* 2021;3(1):41-49.
27. Samantha, Elshendro Tandrya, Ngo Viet Nhan MS Dan F. Potensi pemberian cold pressed vco secara oral dalam mengakselerasi penyembuhan soket alveolar paska pencabutan gigi pada tikus jantan strain wistar secara klinis. *Syntax Idea.* 2020;14(2):1-4.
28. Syam IA, Hatta R, Ruslin M. Potensi dari ceker ayam kampung (*gallus domesticus*) untuk mempercepat penyembuhan soket pascaekstraksi gigi. *Makassar Dent J.* 2015;4(2):50-55.
29. Zulkefli N, Che Zahari CNM, Sayuti NH, Et Al. Flavonoids as potential wound-healing molecules: emphasis on pathways perspective. *Int J Mol Sci.* 2023;24(5).
30. Primadina N, Basori A, Perdanakusuma DS. Proses penyembuhan luka ditinjau dari aspek mekanisme seluler dan molekuler. *Qanun Med - Med J Fac Med Muhammadiyah Surabaya.* 2019;3(1):31.
31. Parrish W, Breana R. Physiology of blood components in wound healing: an appreciation of cellular co-operativity in platelet rich plasma action. *Journal Of Exercise, Sports And Orthopedics.* 2017: 1-14.
32. Sumbayak EM. Fibroblas: struktur dan peranannya dalam penyembuhan luka. *J Kedokt Meditek.* 2015;21(6):1-6.

33. Ulya I. Pengaruh pemberian gel ekstrak daun melati (jasminum sambac L. Ait) terhadap jumlah fibroblas kulit dalam penyembuhan luka bakar derajat ii a pada tikus putih (rattus norvegicus) galur wistar. *J Ilmu Keperawatan* .2016;4(1):1-11.
34. Cialdai F, Risaliti C, Monici M. Role of fibroblasts in wound healing and tissue remodeling on earth and in space. *Front Bioeng Biotechnol*. 2022;10:1-18.
35. Rizkia D, Taufiqurrahman I, Dewi RK. The effect of ramania leaf (bouea macrophylla griff) extract gel on collagen fibers density in incisional wound of male wistar rats. *Dentino J Kedokt Gigi*. 2021;6(1):96.
36. Guo S, Dipietro LA. Critical review in oral biology & medicine: factors affecting wound healing. *J Dent Res*. 2010;89(3):219-229.
37. Rosylianti, Puspita Sari I, Humardewayanti Asdie R. Faktor risiko infeksi luka operasi (ilo) dan rasionalitas antibiotik profilaksis bedah di RSUP Dr. Sardjito Yogyakarta. *Maj Farm*. 2021;17(3):265-274.
38. Silalahi KI, Sartika Munthe D, Suchayo D, Et Al. faktor-faktor yang mempengaruhi lama penyembuhan luka DM. *JKJ Persat Perawat Nas Indonesia*. 2022;10(3):519-526.
39. Triyani Y, Wittiarika ID, Hardianto G. Factors influencing the process of perineal wound healing in postpartum women in serui hospital, papua. *Indonesia Midwifery Heal Sci J*.2021;5(4):398-405.
40. Azizah A, Mardiana A. Stres dan penyembuhan luka periodontal. *BDent J Kedokt Gigi Univ Baiturrahmah*. 2021;8(3):202-209.
41. Himammi AN, Hartono BT. Ekstraksi gigi posterior dengan kondisi periodontitis kronis sebagai persiapan pembuatan gigi tiruan lengkap pada pasien diabetes mellitus. *J Kesehat Gigi*. 2021;8(1):6-10.
42. Anderson K, Hamm RL. Factors that impair wound healing. *J Am Coll Clin Wound Spec*. 2012;4(4):84-91.
43. Sakri F. Madu dan khasiatnya suplemen sehat tanpa efek samping. Diandra Pustaka Indonesia; 2015.

44. Al-Jadi AM, Kanyan Enchang F, Mohd Yusoff K. The effect of malaysian honey and its major components on the proliferation of cultured fibroblasts. *Turkish J Med Sci.* 2014;44(5):733-740.
45. SNI. SNI 8664:2018 Standar nasional indonesia badan standardisasi nasional madu [Internet]. Jakarta; 2018 [cited 2023 Sep 25]. Available from: [https://jogja.bsilhk.menlhk.go.id/wp-content/uploads/2023/09/13.-SNI-8664-2018\\_Madu.pdf](https://jogja.bsilhk.menlhk.go.id/wp-content/uploads/2023/09/13.-SNI-8664-2018_Madu.pdf)
46. Gunawan NA. Madu : efektivitasnya untuk perawatan luka. *IAI.* 2017;44(2):138-142.
47. Mardhiati R. Karakteristik dan beberapa kandungan zat gizi pada lima sampel madu yang beredar di supermarket. *Gizi Indonesia.* 2017;40(1):35-44.
48. Yelin A, Kuntadi. Phytochemical identification of honey from several regions in Java and Sumbawa. *AIP Conf Proc.* 2019;2120:3-8.
49. Santos TS, Dos Santos IDD, Pereira-Filho RN, Et Al. Histological evidence of wound healing improvement in rats treated with oral administration of hydroalcoholic extract of vitis labrusca. *Curr Issues Mol Biol.* 2021;43(1):335-352.
50. Melguizo-Rodríguez L, De Luna-Bertos E, et al. Potential effects of phenolic compounds that can be found in olive oil on wound healing. *Foods.* 2021;10(7):1-18.
51. Dunnill C, Patton T, et al. Reacative oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. *Int Wound J.* 2017;14(1):89-96.
52. Kim E, Hwang Y, Kim H, et al. Pyruvate kinase M2 accelerates cutaneous wound healing via glycolysis and Wnt/B-Catenin signaling. *Pharmaceutics.* 2023;15(8).
53. Mohammed BM, Fisher BJ, Kraskauskas D, et al. Vitamin C promotes wound healing through novel pleiotropic mechanisms. *Int Wound J.* 2016;13(4):572-584.
54. Halim S, Girsang E, Lister I, et al. Effectivity of gel ethanolic of senggani leaves (*melastoma candidum d.don*) in increasing the number of fibroblast

- cells and thickness of collagen fibers against socket wound after tooth extraction on male white rats. *America Scientific Res J.* 2019;60(1):159-173.
55. Huang H, Feng J, Wismeijer D, Wu G, Hunziker EB. Hyaluronic acid promotes the osteogenesis of BMP-2 in an absorbable collagen sponge. *Polymers (Basel).* 2017;9(8).
56. Pasupuleti VR, Sammugam L, Ramesh N, Gan SH. Honey, propolis, and royal jelly: a comprehensive review of their biological actions and health benefits. *Oxid Med Cell Longev.* 2017.
57. Bisala FK, Fitiyani Ya U, Studi PS, Pelita Mas Palu S. Uji efek antidiabetes ekstrak etanol daun talas pada tikus putih jantan hiperkolesterolemia-diabetes. *Farmakol J Farm.* 2019;(1).
58. Al-Hajj NQM, Algabr M, Sharif HR, Aboshora W, Wang H. In vitro and in vivo evaluation of antidiabetic activity of leaf essential oil of *pulicaria inuloides-asteraceae*. *Journal Food Nutr Res.* 2016;4(7):461-470.
59. Rully M. Pengaruh pemberian buah pepaya (*carica papaya l.*) terhadap kadar trigliserida pada tikus sprague dawley dengan hiperkolesterolemia. *J Nutr Coll.* 2012;1(1):192-198.
60. Mushlih M, Rosyidah R. Buku ajar mata kuliah statistika “Aplikasi Di Dunia Kesehatan”. Umsida Press; 2020.
61. Febia A, Mukarlina, Rahmawati. Aktivitas antifungi ekstrak methanol daun bandotan (*ageratum conyzoides*) terhadap *phytophthora sp.* Secara invitro. *J Protobiont.* 2020;9(2):167-174.
62. Fahriza M, Yenita. Uji Efektivitas Madu Dibandingkan Dengan Povidone Iodine Terhadap Penyembuhan Luka Sayat Pada Mencit (*Mus Musculus*). *JIMKI.* 2020;8(3):47-53.
63. Iswanto H, Sri Kuswandari, Putri K. Pengaruh aplikasi topikal propolis 10% terhadap penyembuhan luka pasca pencabutan gigi desidui persistensi (kajian pada anak usia 6-10 tahun). *J Ked Gi.* 2016;7(2)80-25.
64. Suparwitri S, Paramita N. Effect of honey administration on transforming growth factor beta-1 levels during orthodontic tooth movement in young and older rats. *Journal Of Orofacial Sciences.* 2024;16(1):11-16.
65. Gartner P, James L. *Color of atlas and text of histology.* Sixth Edition. 2014.

66. Lasito B. Honey therapy can decrease the wound healing process in diabetes mellitus patients. *Journal of complementary nursing*. 2021;1(1):19-26.
67. Kristian H. Topical clover flower honey administration accelerated wound healing in swiss webster mice. *Journal of medicine and health*. 2018;2(2):788-797.
68. Masir GO, Manjas M, Putra AE, Agus S. Pengaruh cairan kultur filtrate fibroblast (CFF) terhadap penyembuhan perimental pada *Rattus norvegicus* galur wistar. *Jurnal Andalas*. 2012;1(3):112-7.