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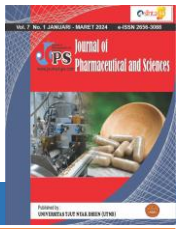

Assessment of collagen density in second-degree burns of white rats (*Rattus norvegicus*) treated with melinjo leaf (*Gnetum gnemon* L.) extract cream

Penilaian densitas kolagen pada luka bakar derajat II tikus putih (*Rattus norvegicus*) yang diterapi dengan krim ekstrak daun melinjo (*Gnetum gnemon* L.)

Leonardo Reza Srimaryanto [a]*, Nove Hidajati [b], Nusdianto Triakoso [c], Eduardus Bimo Aksono Herupradoto [b], Mochamad Lazuardi [b], Boedi Setiawan [c]

[a] *Master of Disease and Veterinary Public Health, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia.*
[b] *Division of Basic Veterinary Medicine, Faculty of Veterinary Medicine, Universitas Airlangga, Airlangga, Surabaya, East Java, Indonesia.*
[c] *Division of Veterinary Clinic, Faculty of Veterinary Medicine, Universitas Airlangga, Surabaya, East Java, Indonesia.*

Corresponding Authors: leonardoreza55@gmail.com

Abstract

Second-degree burns are complex traumatic conditions requiring optimal tissue healing interventions. This experimental study investigated the impact of *Gnetum gnemon* L. leaf extract cream on collagen density in burn wounds. The research was conducted using 20 male Wistar rats (*Rattus norvegicus*), divided into five groups: negative control, positive control (silver sulfadiazine), and three treatment groups with varying leaf extract concentrations (2.5%, 5%, and 10%). Burn induction was performed on the right gluteal area using a thermostat at 85°C for 5 seconds. Collagen density was evaluated through histopathological analysis using ImageJ with density scores ranging from 0 to 4. Research results demonstrated significant collagen density increases in treatment groups, with the 10% concentration displaying the highest density (score +4). Significant differences between groups were confirmed by statistical analysis ($p<0.05$). Findings indicate the potential of *Gnetum gnemon L.* extract as an alternative therapy for improving burn wound healing through collagen density optimization.

Keywords: Burns, Gnetum gnemon l., Collagen, Wound Healing, Alternative Therapy

Abstrak

Luka bakar derajat dua adalah kondisi traumatis kompleks yang membutuhkan intervensi optimal untuk penyembuhan jaringan. Tujuan penelitian eksperimental ini adalah untuk mempelajari bagaimana krim ekstrak daun melinjo (*Gnetum gnemon* L.) mempengaruhi densitas densitas kolagen pada luka bakar. Penelitian dilakukan dengan menggunakan 20 ekor tikus putih jantan (*Rattus norvegicus*) dari strain Wistar, dibagi menjadi lima kelompok: kontrol negatif, kontrol positif (silver sulfadiazine), dan tiga kelompok perlakuan dengan konsentrasi ekstrak daun melinjo yang bervariasi antara 2,5%, 5%, dan 10% . Induksi luka bakar dilakukan di area gluteus kanan tikus dengan termostat pada suhu 85°C selama 5 detik. Evaluasi densitas kolagen dilakukan melalui analisis histopatologis menggunakan ImageJ dengan skor densitas dari 0 hingga 4. Hasilnya menunjukkan peningkatan densitas kolagen yang signifikan pada kelompok perlakuan, dengan konsentrasi 10% menunjukkan kepadatan tertinggi (skor +4). Hasil analisis statistik menunjukkan bahwa ada perbedaan yang signifikan antar kelompok tersebut ($p<0,05$). Temuan menunjukkan potensi ekstrak daun melinjo sebagai terapi alternatif dalam meningkatkan proses penyembuhan luka bakar melalui optimalisasi densitas kolagen.

Kata Kunci: Luka Bakar, Gnetum gnemon L, Kolagen, Penyembuhan Luka, Terapi Alternatif

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Introduction

Burns are one of the most complex and challenging traumatic conditions in medicine, with significant implications for individual health and the burden on the global health economy. This thermal injury not only causes superficial tissue damage but also triggers a complex biological cascade involving the processes of inflammation, proliferation, and tissue remodeling. [1]. In second-degree burns, the damage reaches the dermal layer, requiring comprehensive interventions to support the optimal healing process. Collagen density is a critical indicator in wound healing evaluation, where the quality and quantity of collagen determine the integrity and strength of the reconstructed tissue. [2]. The healing process of burns involves complex cellular and molecular mechanisms, in which collagen production plays a fundamental role in tissue reconstruction. Disruption of collagen synthesis can result in abnormal scarring, decreased skin elasticity, and potential long-term complications [3]. Therefore, interventions that can modulate and optimize collagen production are the main focus of burn management [4].

Indonesian plants, especially melinjo (*Gnetum gnemon L.*), have long been known to have pharmacological potential that has not been fully explored. Recent pharmacognostic studies reveal that melinjo leaves contain bioactive compounds, such as flavonoids, tannins, and polyphenols, with significant antioxidant and anti-inflammatory activities [5]. This ability can support the wound healing process through inflammatory modulation mechanisms and stimulation of cell proliferation. Previous research has shown that phytochemical compounds can affect the dynamics of collagen formation. [6]. The molecular mechanisms involved include activation of transcription factors, modulation of collagen gene expression, and stimulation of fibroblast proliferation [7]. However, specific evidence regarding the direct effects of melinjo leaf extract on collagen density in burns is still limited, creating a significant research gap. A natural product-based approach to burn management offers a comparative advantage over conventional interventions. Plant extract creams have the potential to provide a safer, more economical therapy with minimal side effects. [8]. This characteristic is particularly relevant in the context of burn treatment, where the complexity of therapy often limits treatment options [9].

The white rat (*Rattus norvegicus*) has proven to be a representative experimental model in wound healing studies. Its physiology allows extrapolation of results to more complex biological systems. The similarity of wound healing mechanisms between mice and humans makes it a valid research subject to explore the potential of innovative therapies [10]. This study aims to fill the knowledge gap by comprehensively investigating the effect of melinjo leaf extract cream on collagen density in second-degree burns. Using a systematic experimental approach, we will evaluate the potential of alternative therapies based on Indonesian natural products, which can significantly contribute to developing more effective and sustainable burn management strategies [11]. This study's significance lies in exploring the melinjo leaf's pharmacological potential and its contribution to a deep understanding of wound healing mechanisms and plant-based intervention strategies. By combining modern pharmacological approaches and local wisdom, this research has the potential to open up new avenues in more innovative and integrated burn therapy.

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Research Methods

This research method uses a laboratory experimental approach to systematically investigate the effect of melinjo (*Gnetum gnemon* L.) leaf extract cream on collagen density in second-degree burns. It uses a purely experimental approach with a Post-Test Only Control Group Design. This research methodology was developed by considering strict ethical protocols and international standards in laboratory animal research to produce comprehensive and accountable scientific data. [12].

Materials and Apparatus

The materials used included melinjo leaves (*Gnetum gnemon* L.), 70% ethanol, aquades, glycerin, triethanolamine, stearic acid, nipagin, sodium borate, melinjo leaf extract, silver sulfadiazine, ketamine, and xylazine. The apparatus used in this study included glass jars, rotary vacuum evaporator, erlenmeyer, beaker glasses, mortar, water bath, modified thermostat, microscope, and ImageJ software.

Preparation of Test Animals

The research subjects consisted of 20 male white rats (*Rattus norvegicus*) of the Wistar strain, with inclusion criteria including a body weight of 150-200 grams and an age range of 2-3 months. The selection of white mice as an experimental model was based on physiological and genetic fit that allowed extrapolation of the results of the study to a more complex biological system [10]. Before the implementation of the experiment, all test animals underwent environmental adaptation for 7 days, with strict supervision of health conditions and nutritional status. The research protocol has obtained ethical approval from the Animal Ethics Commission, which ensures the fulfillment of ethical rules in laboratory animal experimentation. The ethical approval in this study was issued by the Animal Ethics Commission (*Animal Care and Use Committee*) Faculty of Veterinary Medicine, Airlangga University, Surabaya, with number 1.KE.147.12.2021.

Burn Induction Procedure

Second-degree burns are induced using a precisely calibrated modified thermostat. The right gluteus area of the rats was shaved in an area of 3 cm x 3 cm and then exposed with a 1 cm diameter thermostat at 85°C for 5 seconds [13]. Burn depth is validated through a comprehensive clinical evaluation, including systematic observation of clinical manifestations such as bull formation, erythema, and vascular variation. [14]. This technique allows for consistent reproducibility of burn conditions between research specimens.

Experimental Treatment Design

The test animals were divided into five experimental groups, each consisting of four replicates:

1. Negative Control Group (K-): Extract-free cream-based therapy
2. Positive Control Group (K+): Silver sulfadiazine therapy
3. Group P1: Melinjo leaf extract cream 2.5%
4. Group P2: Melinjo leaf extract cream 5%
5. Group P3: Melinjo leaf extract cream 10%

The wound care process is carried out periodically for 14 days, with a frequency of application twice daily, following the proliferation phase of wound healing [15]. Each group received the treatment according to the protocol set by paying attention to the variation in the concentration of melinjo leaf extract.

Cream Extraction and Formulation

Melinjo leaf extraction was done using the silent maceration method with 70% ethanol. The procedure involves soaking 200 grams of melinjo leaf powder in 600 ml of ethanol for 24 hours, with the extraction process repeated until a clear solution is obtained. The concentrated extract is produced through a rotary vacuum evaporator at a temperature of 70°C. The cream formulation uses the Oil in Water (O/W) type, with a composition that includes equates, glycerine, triethanolamine, stearic acid, nipagin, and sodium borate. [16].

Collagen Density Analysis

Collagen density evaluation was carried out through histopathological analysis using ImageJ software. Microscopic assessment refers to a standard protocol with quantitative criteria:

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1. Score 0: No collagen fibers
2. Score +1: Low collagen density (25%)
3. Score +2: Medium collagen density (50%)
4. Score +3: Density of dense collagen (75%)
5. Score +4: Very dense collagen density (100%)

Observations were made on four viewing fields with 400x magnifications, using an observation pattern in the direction of the letter S to ensure the sample's representativeness. [17].

Statistical Analysis

The data from the study were analyzed using the non-parametric Kruskal-Wallis statistical test and then the Mann-Whitney test to identify significant differences between the treatment groups. The analysis was conducted using SPSS for Windows software, with a significance level of $p < 0.05$ as a meaningful difference criterion. [18]This comprehensive methodological approach is designed to provide in-depth insights into the potential of melinjo leaf extract cream to improve collagen density in second-degree burns while maintaining the highest ethical and scientific standards in experimental research.

Results and Discussion

The experimental research aimed to explore the effect of extract cream of melinjo leaf (*Gnetum gnemon L.*) on collagen density in second-degree burns in white rats (*Rattus norvegicus*) showed significant and interesting findings. Histopathological analysis of collagen density provides in-depth insights into wound healing dynamics and the potential of plant-based therapies in burn management. The microscopic observations showed significant variations in collagen density between the treatment groups. The negative control group (K-), given only a cream base, displayed collagen density with a score of +2, indicating moderate density levels and a relatively slow wound healing process. This aligns with research by Sagaradze *et al.* (2020), which emphasizes the importance of active intervention in stimulating tissue regeneration [19].

The positive control group (K+) treated with silver sulfadiazine showed the highest collagen density with a score of +4, reflecting the effectiveness of standard therapy in accelerating the wound healing process. These findings are consistent with studies that emphasize the role of antimicrobial components in optimizing tissue regeneration [20]. The treatment group with melinjo leaf extract cream showed an interesting pattern of increasing collagen density. The P1 group with a concentration of 2.5% achieved a collagen density score of +3, indicating significant tissue density compared to negative controls. This increase can be attributed to the activity of bioactive compounds in melinjo leaf extract, such as flavonoids and polyphenols that have anti-inflammatory and proliferative abilities [5].

The P2 group, with a concentration of 5%, displayed a similar pattern of collagen density to P1, with a score of +3. Interestingly, increasing concentration does not linearly increase collagen density, hinting at a complex mechanism in the interaction of bioactive compounds with wound-healing processes. [21]. The P3 group with a concentration of 10% showed the highest collagen density after a positive control, with a score of +4. These findings indicate the significant potential of melinjo leaf extract in modulating collagen production in burns. Molecular mechanisms that may be involved include transcription factor activation, stimulation of fibroblast proliferation, and collagen gene expression modulation [7]. Statistical analysis using the Kruskal-Wallis and Mann-Whitney tests confirmed significant differences between groups ($p<0.05$). Table 1 displays the average collagen density and the coefficient of variation, which provides a quantitative perspective on the variation of the results.

The relatively high variation of coefficients (CVs) in the P2 and P3 groups indicates the complexity of the biological response to melinjo leaf extract. This confirms the need for further research to understand the underlying interaction mechanisms.

This study provides empirical evidence about the potential of melinjo leaf extract cream as an alternative therapy to increase collagen density in burns. This natural product-based approach offers innovative solutions and opens up new research paths in more sustainable and integrated burn management.

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Table 1. Average collagen density in each treatment group

Observation Group	Mean ± SD	CV (%)
K-	$2.13^{a} \pm 0.144$	6,8%
K+	$3.81^{c} \pm 0.125$	3,2%
P1	$3.19^{b} \pm 0.125$	3,9%
P2	$3.31^{bc} \pm 0.473$	14,2%
P3	$3.56^{bc} \pm 0.590$	16,5%

Description: Different superscripts show significant differences ($p<0.05$).

The microscopic images in Figure 1 provide an in-depth morphological visualization of burn healing and collagen deposition dynamics in various treatment groups. Each microscopic panel with Hematoxylin Eosin staining at 400x magnification revealed significant structural and quantitative variations in collagen tissue formation.

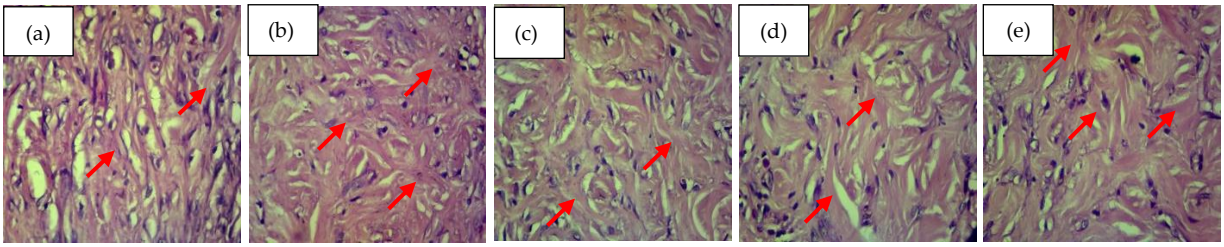

Figure 1. A microscopic collagen density (red arrow) image with Hematoxylin Eosin staining was observed with 400x magnification. (a) Negative control group (therapy with oil in water cream base); (b) Positive control group (therapy with silver sulfadiazine); (c) Treatment group P1 (therapy with 2.5% EDM cream); (d) P2 treatment group (therapy with 5% EDM cream); (e) P3 treatment group (therapy with 10% EDM cream).

Panel (a), representing the negative control group, shows the characteristics of relatively low collagen density and unevenly dispersed. The tissue structure looks looser with a wider spacing between collagen fibers, indicating a tissue regeneration process that is not yet optimal. This can occur because the negative control group was only given a cream base, without any therapeutic agents or active compounds, resulting in no accelerated wound healing. Additionally, since collagen formation was minimal, the wound entered the proliferative phase, forming the extracellular matrix [22].

Panel (b) of the positive control group with silver sulfadiazine showed a very dense and structured collagen density. Collagen fibers appear tight, aligned, and have a uniform distribution, reflecting a superior wound healing process; this explains that standard therapies such as silver sulfadiazine can optimize tissue remodeling through inflammatory modulation and stimulation of cell proliferation [23-24].

The treatment group with melinjo leaf extract showed an interesting gradient of increased collagen density. Panel (c) in the P1 group with a concentration of 2.5% showed an increase in collagen density compared to the negative control. Collagen fibers look tighter and more organized, indicating the potential of bioactive compounds to improve the healing process. [25].

Panel (d), representing the P2 group with a concentration of 5%, shows a similar pattern to P1 but with a slight increase in the density and regularity of collagen fibers. Vaou *et al.* (2022) explain that complex interactions between phytochemical compounds and biological systems are not always linear, which can explain the variation in responses at various concentrations [26].

Panel (e) of the P3 group with a concentration of 10% displayed the highest collagen density after positive control. Collagen fibers appear very dense and structured and have almost the same distribution as silver sulfadiazine, emphasizing that plant extracts' optimal concentration can activate cellular mechanisms that support tissue regeneration to the maximum [27].

Quantitatively, the color and density variation of collagen fibers on each microscopic panel confirms the statistical findings in Table 1. Significant differences between groups ($p<0.05$) were numerically confirmed and visualized through this histopathological analysis. Based on microscopic characteristics such as those shown

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in Figure 1 provide direct evidence of the molecular mechanisms underlying wound healing. The variation in collagen fiber density and organization reflects the complexity of the biological response to therapeutic interventions, particularly in the context of natural product-based therapies. These findings present empirical evidence about the potential of melinjo leaf extract and open up space for further exploration regarding the specific mechanisms involved in increasing collagen density in burns. A comprehensive approach that combines quantitative and qualitative analysis provides in-depth insights into innovative intervention strategies in burn management.

Conclusion

This experimental research presents significant findings related to the potential of innovative therapies based on Indonesian natural products, especially melinjo leaf extract (*Gnetum gnemon L.*), in increasing collagen density in second-degree burns. This study successfully uncovered complex molecular mechanisms in the wound healing process with profound clinical implications through a systematic Post Test Only Control Group research design. Histopathological analysis showed significant variation in collagen density between treatment groups. The negative control group that used only the cream base displayed the lowest collagen density, while the positive control group with silver sulfadiazine achieved the highest collagen density. Interestingly, the treatment group with melinjo leaf extract showed a progressive increase in collagen density, with a concentration of 10% close to the performance of silver sulfadiazine. Statistically, the difference between the groups was significant ($p<0.05$), indicating the obvious effect of melinjo leaf extract on collagen density. This increase is related to the activity of bioactive compounds such as flavonoids, tannins, and polyphenols that can activate transcription factors, stimulate the proliferation of fibroblasts, and modulate collagen gene expression. The variation in coefficients in the treatment groups revealed the complexity of the biological response that required further investigation. Fundamentally, this research presents alternative therapeutic approaches for burns and opens innovative research paths in wound management based on Indonesian natural products. The resulting scientific contribution provides a new perspective on the potential of local plants in wound healing therapy interventions, focusing on optimizing the healing process through increasing collagen density. The implications of this study are very broad. A comprehensive approach that combines local wisdom with modern scientific methodologies shows that melinjo leaf extract has significant prospects as a wound-healing therapeutic agent. This plant-based therapy offers a safer, more economical alternative and potentially lowers the risk of complications compared to conventional therapy.

Conflict of Interest

All authors stated that this study was free from conflicts of interest. The research and writing of the article are carried out independently, without outside interference, and no personal, financial, or professional interest affects the objectivity or integrity of the research.

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Reference

[1] Jeschke, M. G., M. E. van Baar., M. A. Choudhry., K. K. Chung., N. S. Gibran and S. Logsetty. 2020. Burn injury. Nature reviews. Disease primers. 6(1): 11. https://doi.org/10.1038/s41572-020-0145-5.

[2] Sucita, R. E., I. S. Hamid., F. Fikri and M. T Elziyad. 2019. Secang Wood Ethanol Extract (Caesalpinia sappan L.) Topically Effective on Collagen Density During Wound Healing in Albino Rats. Jurnal Medik Veteriner. 2(2): 119-126.

[3] Xue, M. and C. J. Jackson. 2015. Extracellular matrix reorganization during wound healing and its

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

impact on abnormal scarring. Advances in wound care. 4(3): 119-136.

[4] Fischer, M., P. Olbrich., J. Hadjadj., V. Aumann., S. Bakhtiar., V. Barlogis., P. von Bismarck., M. Bloomfield., C. Booth., E. P. Buddingh., D. Cagdas., M. Castelle., A. Y. Chan., S. Chandrakasan., K., Chetty., P. Cougoul., E. Crickx., J. Dara., A. Deyà-Martínez., S. Farmand and C. Speckmann. 2024. JAK inhibitor treatment for inborn JAK/STAT signaling errors: An ESID/EBMT-IEWP retrospective study. The Journal of allergy and clinical immunology. 153(1): 75–286.e18. https://doi.org/10.1016/j.jaci.2023.10.018.

[5] Taroreh, T. N. C., J. Rumampuk and K. V. Siagian. 2016. Melatho Leaf Extracts (Gnetum gnemon L.) Strength Against Growth of Streptococcus mutans' Bacteria. Pharmacon. 5.

[6] Rømer, A. M. A., M. L. Thorseth and D. H. Madsen. 2021. Immune Modulatory Properties of Collagen in Cancer. Frontiers in immunology. 12: 791453. https://doi.org/10.3389/fimmu.2021.791453.

[7] Kohlhauser, M., M. Mayrhofer., L. P. Kamolz and C. Smolle. 2024. An Update on Molecular Mechanisms of Scarring-A Narrative Review. International journal of molecular sciences, 25(21): 11579. https://doi.org/10.3390/ijms252111579

[8] Michalak, M. 2023. Plant Extracts as Skin Care and Therapeutic Agents. International Journal of Molecular Sciences. 24(20): 15444. https://doi.org/10.3390/ijms242015444

[9] Hamzelou, S., V. J. Melino., D. C. Plett., K. S. Kamath., A. Nawrocki., M.R. Larsen., B. J. Atwell and P. A. Haynes. 2021. The phosphoproteome of rice leaves responds to water and nitrogen supply. Molecular Omics. 17(5): 706-718. https://doi.org/10.1039/d1mo00137j.

[10] Masson-Meyers, D. S., T. A. M. Andrade., G. F. Caetano., F. R. Guimaraes., M. N. Leite., S. N. Leite and M. A. C. Frade. 2020. Experimental models and methods for cutaneous wound healing assessment. International journal of experimental pathology. 101(1-2): 21–37. https://doi.org/10.1111/iep.12346.

[11] Chapman, K. M., A. Pudasaini., M. N. Vanderbeck, and F. K. Hamra. 2023. Rattus norvegicus Spermatogenesis Colony-Forming Assays. Methods in molecular biology (Clifton, N.J.). 2677: 233–257. https://doi.org/10.1007/978-1-0716-3259-8_14.

[12] Kocaman Kalkan, K. and M. Kekeçoğlu. 2024. Ethical Principles and Rules in Experimental Animal Studies: A Comprehensive Review. Duzce Medical Journal. 26(S1): 1-13. https://doi.org/10.18678/dtfd.1497730

[13] Abdeldjelil, M. C., A. Messai., A. Boudebza and S. Beghoul. 2017. Practical Aspects to Generate Cutaneous Experimental Burns in A Rat Model Scholars. Der Pharmacia Lettre. 9(1): 70-84.

[14] Anggowarsito, J. L. 2014. Luka Bakar Sudut Pandang Dermatologi. Jurnal Widya Medika. Surabaya. 2(2): 115-120.

[15] Primadina, Nova, Basori, Achmad, Perdanakusuma dan David. 2019. Proses Penyembuhan Luka Ditinjau dari Aspek Mekanisme Seluler dan Molekuler. Qanun Medika - Medical Journal Faculty of Medicine Muhammadiyah Surabaya. 3: 31. 10.30651/jqm.v3i1.2198.

[16] Lazuardi, M. 2019. Bagian Khusus Ilmu Farmasi Veteriner. 1st Ed. Airlangga University Press (AUP). Surabaya. 84-154.

[17] Lazuardi, M. 2008. Struktur Histopatologi Ginjal dan Hati Kambing Penderita Tripanosomiasis Pasca Pengobatan Barenil. Media Peternakan. 14-21.

[18] Mardiyantoro, F., N. Prasetyaningrum and H. T. Rahmastuti. 2019. Histopathological characteristics of dental socket healing on collagen density following use of pangas catfish (Pangasius djambal) gelatin. Majalah Kedokteran Gigi Indonesia. 5(3): 117-123.

[19] Sagaradze, G. D., N. A. Basalova., A. Y. Efimenko and V. A. Tkachuk. 2020. Mesenchymal Stromal Cells as Critical Contributors to Tissue Regeneration. Frontiers in cell and developmental biology. 8: 576176. https://doi.org/10.3389/fcell.2020.576176.

[20] Adhya, A., J. Bain., O. Ray., A. Hazra., S. Adhikari., G. Dutta., S. Ray and B. K. Majumdar. 2014. Healing of Burn Wounds by Topical Treatment: A Randomized Controlled Comparison Between Silver Sulfadiazine And Nano-Crystalline Silver. Journal of Basic and Clinical Pharmacy. 6(1): 29-34.

[21] Kining, E. 2015. Aktivitas Antibiofilm Ekstrak Air Daun Melinjo, Daun Singkong Dan Daun Pepaya Terhadap Bakteri Pseudomonas aeruginosa Secara In Vitro. Institut Pertanian Bogor. Bogor.

[22] Gurtner, G. C. 2007. Wound healing, normal and abnormal In: Thorne CH, Beasly, R.W., Aston, S.J., Bartlett, S.P., Gurtner, G.C., Spear, S.L. (Eds), Grabb and Smith's plastic surgery. 6th. Philadelphia: Lippincott Williams and Wilkins. 15-22.

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

[23] Adhya, A., J. Bain., O. Ray., A. Hazra., S. Adhikari., G. Dutta., S. Ray and B. K. Majumdar. 2014. Healing of Burn Wounds by Topical Treatment: A Randomized Controlled Comparison Between Silver Sulfadiazine And Nano-Crystalline Silver. Journal of Basic and Clinical Pharmacy. 6(1): 29-34.

[24] Pratiwi, L., S. Prasetyawan dan D. Vidiastuti. 2020. Pengaruh pemberian salep kolagen hidrolisat ikan sebagai penyembuhan luka bakar derajat IIB berdasarkan ekspresi fibroblast growth factor 2 (FGF-2) dan fibroblas pada tikus putih (Rattus norvegicus). Jurnal MKH. 31(2): 52-63.

[25] Indraswary, R. 2014. Efek konsentrasi Ekstrak Buah Adas (*Foeniculum vulgare Mill*.) Topikal Pada Epitelisasi Penyembuhan Luka Gingiva Labial Tikus Sprague Dawley In Vivo. Fakultas Kedokteran Gigi Universitas Islam Sultan Agung. Semarang.

[26] Vaou, N., E. Stavropoulou., C. C. Voidarou., Z. Tsakris., G. Rozos., C. Tsigalou and E. Bezirtzoglou. 2022. Interactions between Medical Plant-Derived Bioactive Compounds: Focus on Antimicrobial Combination Effects. Antibiotics (Basel, Switzerland). 11(8): 1014. https://doi.org/10.3390/antibiotics11081014.

[27] G u r t n e r , G. C. and V. W. Wong. 2014. Wound healing: normal and abnormal. In: Thorne C.H., Chund K.C., Gosain A.K., et al. eds. Grabb and Smith's Plastic Surgery. Philadelphia: Lippincott Williams and Wilkins. 13-19.

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