THE COMPARISON OF SUMATERA FOREST HONEY AND TRIAMCINOLONE ACETONIDE FOR TRAUMATIC ULCER HEALING IN WISTAR RAT: CLINICAL AND HISTOLOGICAL EVALUATION

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Abstract

Traumatic ulcer is ulcerated lesion on oral mucosa commonly caused by mechanical injury. The clinical picture of a traumatic ulcer is a solitary ulcer, it can be oval or irregular in shape, the center of the ulcer is yellow-gray or white/grey with erythematous edges. Traumatic ulcer cause difficulty in mastication, speech, and swallowing. Forest honey is a traditional medicine that can be used to heal traumatic wounds because of its anti-inflammatory, antimicrobial, antioxidant, and covering agent. The purpose of this study was to determine the effectiveness of Sumatera Forest honey on healing of traumatic ulcer in Wistar rats. This study is a quasi-experimental study. This study involved 32 rats divided into two groups, each containing 16 rats, namely the treatment group (100% forest honey) and the control group (Triamcinolone Acetonide). The animal model was slashed with a scalpel to induce an ulcer. The data collection was done by examining the size of the ulcer and erythema and then observed on the 1, 5, 7, 10 and 14 days. Analysis in this study used the Mann Whitney and Cochran statistical test. The results showed that Sumatera-forest honey significantly reduce ulcer size (p = 0.001) and erythema (p = 0.000). Sumatera forest honey is effective in healing traumatic ulcer.

Keywords: Forest Honey, Healing, Traumatic Ulcer

Introduction

Traumatic ulcer is ulcerated lesion on oral mucosa commonly caused by mechanical injury. Ulcer is a lesion that often appears in the oral cavity (1). The prevalence of ulcer in the world reached 3-24% of the population (2). The etiology of traumatic ulcer can be caused by mechanical, chemical, thermal, and electrical trauma (3).

Traumatic ulcers were more common on buccal mucosa (42%), tongue (25%), and lower labial mucosa (9%) (1). The clinical presentation of a traumatic ulcer is a solitary ulcer, which may be oval or irregular in shape, the center of the ulcer is yellow-gray or white/grey with erythematous edges (1-4). Traumatic ulcer is not a dangerous disease, but their presence can interfere with the oral mucosa. The pain caused can interfere with the function of chewing, speaking, and swallowing (5).

Traumatic ulcer can be cured within a few days to two weeks by eliminating the cause and given treatment aimed at speeding up the healing process (6). Currently, the most commonly used drug on traumatic ulcer is a drug containing corticosteroids (7). The most widely used drug to treat ulceration in the mouth is topical steroids (8). Topical corticosteroids are the main choice in the treatment of traumatic ulcer, but they can cause side effects such as irritation, redness, and burning sensation (9). In addition to chemical-based drugs, traumatic ulcer can also be treated with traditional medicine, such like honey (10).

Forest honey is honey that is harvested directly from the trees in the forest without the bee keping process. Forest

honey is produced by Apis dorsata bees, which is a type of bee that cannot be cultivated because of its aggressive and wild nature (11). Producing forest honey bees offers several advantages over other honey bee varieties (12). This includes the distinctive sweet taste and more robust, pungent aroma of the nectar collected by these bees (13). Forest honey stands out as a nutrient-rich substance due to its therapeutic properties. It contains sugar compounds like fructose and glucose, along with protein acid content, minerals, water, and other elements. These components hold potential as anti-inflammatory, antimicrobial, antioxidant, and protective agents (14).

Subrahmanyam's research findings suggest that the application of forest honey can diminish inflammation in burn injuries (15). Tashkandi conducted a study exploring the efficacy of forest honey in the healing process of wound length and width (16). Research on the use of forest honey for ulcers revealed its effectiveness in promoting wound healing (17). The provided description highlights the numerous benefits of forest honey. Various studies indicate that honey possesses wound-healing properties. Research has consistently demonstrated honey's attributes as an anti-inflammatory, antimicrobial, and antioxidant agent. Currently, there is a lack of investigation into the use of forest honey specifically for the healing of traumatic ulcers in the oral cavity. This gap in knowledge has piqued researchers' interest, prompting them to explore the potential effectiveness of forest honey in the healing process of traumatic ulcers.

Materials and Methods

This research was a quasi-experimental study to determine the effectiveness of Sumatera forest honey on healing of traumatic ulcer in Wistar rats. This study has been approved by the ethics committee No. 00630/KEPH-FMIPA/2020 of Health Research Ethics Committees/HREC the Faculty of Mathematics and Natural Sciences, Universitas Sumatera Utara.

The inclusion criteria of Wistar rats including healthy rats indicated by healthy hair and active mobilization. Unhealthy rats were excluded from the study. Rats who died during study was drop out from the study. Wistar rat acclimatization was done for 48 hours before experiment. Wistar rats receive normal food two times a day. The traumatic ulcer induction was begun with the administration of an anesthetic of 0.5 ml of ketamine intraperitoneally. A single 5 mm traumatic ulcer made by slashed the labial mucosa of the lower lip. Wistar rats then divided into two groups. The treatment group was given forest honey (n=16) and the control group triamcinolone acetonide (n=16). Sumatra forest honey was applied using a brush on the ulcer lesions twice a day in the treatment group. Meanwhile, the positive control group were treated with triamcinolone Acetonide (Kenalog® In orabase). The treatment was given for 14 days by applying the material topically twice a day.

Sample collection

Ulcer were measured using digital calipers on the 1st, 5th, 7th, 10th and 14th days and erythema was observed. Erythema observation was done using direct visual examination.

Histopathological examination

Both of the treatment groups (honey and triamcinolone acetonide) which had been given treatment on 1st, 5th, 7th, 10th and 14th days of treatment would be taken from the labial mucosa of the lower jaw on each treatment day further preparations to be made with the Hematoxylin-Eosin (HE) staining method. Samples of the mandibular labial mucosa were taken and cut 1x1x1 cm, then immersed in 10% neutral buffer formalin (NBF) solution. The organ sample was further reduced with thin slices to be stored in a tissue cassette and fixed in an NBF solution. After fixation, the dehydration and clearing process was carried out with one solution session consisting of 70% alcohol, 80% alcohol, 90% alcohol, absolute alcohol, toluene, and paraffin, gradually over one day. The tissue samples were blocked with an embedding set filled with liquid paraffin and then cooled. The cooled blocks were sectioned using a microtome with a thickness of ±4–5 microns. The final process was staining with the Harris Hematoxylyin-Eosin method and mounting media. The histopathological preparations were observed under a 100-objective magnification. For the examination results, the degree of inflammation was given a score of 1 (mild < 20%), 2 (moderate=20-50%), and 3 (severe > 50%).

Results

Based on Table 1, the results showed that the mean size of traumatic ulcer in the sample after being given forest honey on day 1st, 5th, 7th, 10th and 14th was 4.80±0.08 mm, 1.74±0.49 mm, 0.54±0.61 mm, 0.16±0.20 mm, and 0.00±0.00 mm. While the mean size of traumatic ulcer after being given Triamcinolone Acetonide on day 1st, 5th, 7th, 10th and 14th was 4.81±0.07 mm, 3.99±0.06 mm, 3.40±0.08 mm, 0. 94±0.37 mm, and 0.00±0.00 mm.

Table 1: Mean Size of Traumatic Ulcer After Being Given Forest Honey and *Triamcinolone Acetonide* on day 1, 5, 7, 10, 14

Day	Mean Size of Traumatic Ulcer (mm)			
	Forest Honey		*Triamcinolone Acetonide*	
	Mean	SD	Mean	SD
1	4.80	0.08	4.81	0.07
5	1.74	0.49	3.99	0.06
7	0.54	0.61	3.40	0.08
10	0.16	0.20	0.94	0.37
14	0.00	0.00	0.00	0.00

Based on the table, the mean size of the traumatic ulcer was the most significant on day 5th. The table also shows that on the 10th day, the group that was given forest honey had recovered.

In this study, the normality test was conducted using the Shapiro Wilk statistical test because the number of samples of this study amounted to less than 50. Based on Table 2, the results of the study indicate that the research data is not distributed normally. Analysis can be continued by using the Mann Whitney and Cochran test.

Table 2: Data Normality Test Results of Forest Honey and Triamcinolone Acetonide

Day	Normality			
	Forest Honey		*Triamcinolone Acetonide*	
	p value	Information	*p value*	Information
1	0.004	Abnormal	0.004	Abnormal
5	0.100	Usual	0.001	Abnormal
7	0.002	Abnormal	0.005	Abnormal
10	0.001	Abnormal	0.350	Usual

Based on Table 3, the results showed that the size of traumatic ulcer after being given forest honey on the 1,5,7,10,14 day was 4.80±0.08 mm, 1.74±0.49 mm, 0.54±0.61 mm, 0.16±0.20 mm, and 0.00±0.00 mm while the size of traumatic ulcer after administered Triamcinolone Acetonide on the day 1,5,7,10,14 is 4.81±0.07 mm, 3.99±0.06 mm, 3.40±0.08 mm, 0.94±0.37 mm, and 0.00±0.00 mm. On that table seen that the size of traumatic ulcer was most significant reduced on the 7th day on the treatment of forest honey. The results showed that there were significant differences in the size of traumatic ulcer between the treatment group and the control group on days 1,5,7,10 and 14 (p=0.001, p<0.05).

Table 3: Effectiveness of Traumatic Ulcer Size Reduction Between Forest Honey group and Triamcinolone Acetonide group.

Day	Average size of Traumatic Ulcer (mm)				*p value*
	Forest Honey		*Triamcinolone Acetonide*		
	Mean	SD	Mean	SD	
1	4.80	0.08	4.81	0.07	0.001
5	1.74	0.49	3.99	0.06	
7	0.54	0.61	3.40	0.08	
10	0.16	0.20	0.94	0.37	
14	0.00	0.00	0.00	0.00	

Based on Table 4, forest honey is effective against erythema in traumatic ulcer with a value of p=0.000 (p<0.05).

Table 4: Effectiveness of Loss of Traumatic Ulcer Erythema between Forest Honey and Triamcinolone Acetonide

Day	Erythema				p value
	Forest Honey		*Triamcinolone Acetonide*		
	Exist	None	Exist	None	
1	16	0	16	0	0.000
5	12	4	16	0	
7	16	10	14	2	
10	0	16	7	6	
14	0	16	0	16	

Based on Table 5 and Figure 1, On histological examination showed that not significant reduction in the degree of inflammation, but forest honey groups obtained faster healing process than triamcinolone groups.

Table 5: Data Analysis of Reducing Degree of Inflammation in Each Group.

Groups	Degree of inflammation				Total		*p-value*
	Mild (20%)		Moderate (20-50%)				
	n	%	n	%	n	%	
Honey	5	35.7%	2	14.3%	7	50%	
Triamcinole Acetonide	3	21.4%	4	28.6%	7	50%	0.592
Total	8	57.1%	6	42.9%	14	100%	

Discussion

In this study, forest honey that was used was already following the phytochemical screening. The forest honey contains secondary metabolites flavonoids (18). Flavonoids in honey have many elements and are strongly influenced by geography, flower nectar sources, climate, processing, and environmental condition (19). Therefore, honey taken from different flower sources will provide different flavonoids, as well as honey from different flowers, the same but from different regions can provide different levels of flavonoids. Flavonoids are known to have an effect as an antibiotic, anti-inflammatory and antioxidant. The mechanism of action of anti-inflammatory and antioxidant flavonoids by inhibiting the release of inflammatory mediators such as TNα (Tumor Necrosis Alpha) and IL (Interleukin) also inhibits prostaglandin biosynthesis (20-21).

Based on table 4, the results of the Mann Whitney test to see the effectiveness of reducing the size of traumatic ulcer in the treatment group and the control group, it is stated that there is a significant difference (p=0.001, p<0.05) so it can be concluded that forest honey is effective in reducing the size of traumatic ulcer. The results of this study are in accordance with a study conducted by Chamani et al regarding the effectiveness of honey as a topical therapy

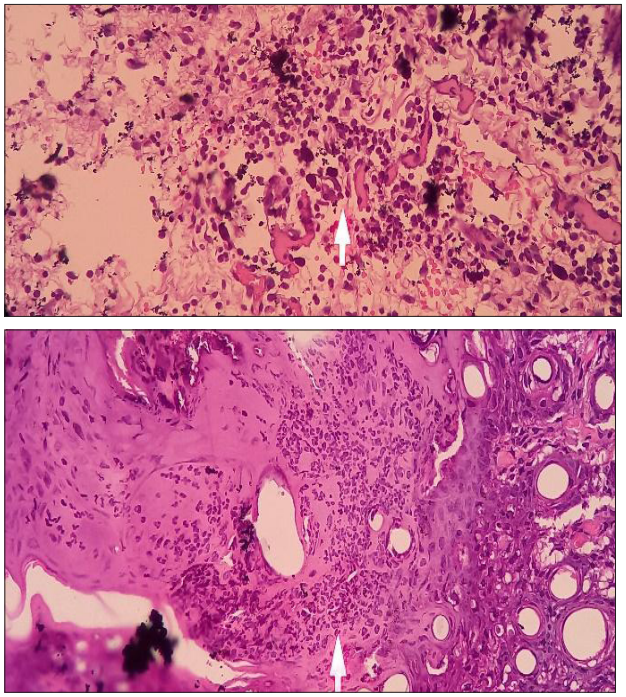

Figure 1: The difference in the results of histological examination of the reduction in the degree of inflammation on the 7-th day of treatment which it showed that the forest honey group reached a mild degree/score 1 indicated by smaller number of immune cells, **(a)** while the triamcinolone acetonide group still had a moderate degree/score 2 indicated by large number of immune cells, **(b)** Histological observation using H&E with 400X magnification, scale bar = 20 µm.

for healing intraoral ulcer in rats which showed that there was a significant difference between honey and the placebo control group with a value ($p<0.05$). Wound size was smaller in the honey group compared to the control group (22).

Another study conducted by Mohamed et al looked at the effectiveness of honey on reducing ulcer diameter in patients with recurrent aphthous stomatitis compared to Triamcinolone Acetonide and found a significant p-value ($p=0.001$, $p<0.05$)(21). Research by Nakajima et al show that honey treatment on acute phase of burn wound show lower number of neutrophils and necrotic cell compared to untreated wound (23).

Ulcer can heal without treatment; the goal of treatment is to speed up the healing process. Reduction in the diameter of the ulcer is one sign of the effectiveness of the wound healing process. The wound healing process is a process related to the growth or regeneration of tissue. The wound healing process is generally divided into several phases, namely, the inflammatory, proliferative, and remodeling phases (24).

In the inflammatory phase, the bioactive content contained in forest honey, flavonoids, can inhibit the inflammatory process (25). This inflammatory mechanism can be attributed to its antioxidant capacity. Flavonoids as antioxidants can reduce free radicals generated in the inflammatory process. Flavonoids can induce cellular antioxidant, inhibits the action of the enzyme xanthine oxidase and protein kinase Co-producing anion radical superoxide (O2) also inhibit the enzyme cyclooxygenase, lipooxygenase that play a role in the inflammatory process (26, 27).

The role of flavonoids that inhibit the process of fat peroxidation is to reduce free radicals so that they can inhibit tissue death, increase vascularity, prevent cell damage, and increase DNA synthesis (28, 29). Flavonoids are recognized for their ability to hinder nucleic acid synthesis, impede energy metabolism, disrupt cell membrane function, inhibit biofilm synthesis, and suppress pathogenic processes. As a result, they play a role in mitigating infections by attenuating these various essential aspects (30)

Moreover, flavonoids can inhibit the biosynthesis of prostaglandins, which serve as inflammatory mediators. This ability can influence the process of diminishing ulcer size. As research conducted by Scepankova et al that honey can stimulate the release of inflammatory agents such as TNF α which functions to support the wound healing phase and can stimulate inflammatory cells, fibroblasts, and epithelial cells so that the bioactive flavonoid content can support the process of wound healing and tissue regeneration (17). In addition, honey also has a high sugar content, enzyme effectiveness, and a low pH level of honey, between 3.2-4.5 (very acidic) so that it can inhibit bacterial growth. The effect of this antibacterial activity can prevent secondary infection and accelerate ulcer healing (31, 32). After the inflammatory phase, the proliferative phase occurs. In the proliferative phase, the content of vitamins A, B, C in honey can help fibroblasts in synthesizing collagen (33). Fibroblasts begin to lay down ground substance and collagen fibers and new blood vessels (angiogenesis) to infiltrate the wound. After an injury occurs, fibroblasts will be active and move from the tissue around the wound into the wound area, then will proliferate and release several substances that play a role in the reconstruction of new tissue. Signs of inflammation begin to subside and granulation tissue is formed, which formed from new capillary loops, which support collagen and ground substance (34) The last phase of epithelialization, contraction, and tissue reorganization is called the remodeling phase. The purpose of this phase enhances the formation of new tissue. The mineral content of zinc in honey has an important role in protein synthesis and the replication process of body cells and plays a special role in skin and connective tissue metabolism (33). Forest honey can not only reduce the size of traumatic ulcer but also affects erythema.

Based on table 4, Erythema occurred in the rats in the treatment group on days 1st, 5th, 7th which the amount were 16 rats, 12 rats, 7 rats. Meanwhile, there were no found that on 10th days. Contrastly in the control group

it was still found the presence of erythema on days 1st, 5th, 7th, 10th were 16 rats, 16 rats, 14 rats, 7 rats. Overall erythema disappeared on day 14th in the both group. Based on the table, the results of the Cochran test to see the effectiveness of the loss of erythema in traumatic ulcer between the treatment group and the control group stated that there was a significant difference p=0.000 (p<0.05) (Table 4).

The clinical presentation of a traumatic ulcer that can usually be seen is erythema (35) Injured tissue will release histamine and mast cells that cause vasodilation, where this vasodilation results in increased blood flow and local blockage resulting in erythema of the wound (36). Honey as an anti-inflammatory, antibacterial, antioxidant can reduce edema in the tissue so that it will reduce the suppression of blood capillaries (37) . Blood flow that carries oxygen and nutrients (vitamin C) runs smoothly through the blood capillaries in the tissues (38).

Table 5 and Figure 1 indicate that the histological examination did not reveal a significant reduction in the degree of inflammation. However, it is noteworthy that in the honey group, the reduction commenced earlier, specifically on the 7th day of treatment. Overall, the samples in the forest honey group showed recovery by the 11th day of treatment. In contrast, the triamcinolone acetonide group began to reduce the degree of inflammation on the 10th day of treatment, with overall sample recovery observed on the 14th day of treatment.

Honey can increase fibroblasts so that new tissue formation becomes faster. Hydrogen peroxide in honey can also increase blood flow to ischemic tissue and stimulate the formation of cytokines by leukocytes as a healing process. Honey contains the enzyme glucose-oxidase which stimulates the release of hydrogen peroxide which facilitates the increase of lymphocytes, phagocytes and helps monocytes to release cytokines and interleukins, thereby eliminating erythema and stimulating the healing process (39, 40). This causes the treatment group given forest honey groups showed mild inflammation level or even no erythema on the 10th compared with the triamcinolone groups on the 14th day. For that reasons forest honey proved to be effective in the treatment of traumatic ulcer. Further studies are needed to assess the effective minimal dose of forest honey and to examine the quantitative histological assessment.

Conclusion

Sumatera forest honey was more effective in reducing the mean size of traumatic ulcer compared to Triamcinolone Acetonide since day 5th. Forest honey was also effective in removing erythema in Wistar rats since the 10th day. The histological examination evaluated that the reduction in the degree of inflammation was not significant, but showed that the inflammation degree reduced since 7th-day treatment of forest honey.

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Competing interests

There is no conflict of interest in this journal publication.

Ethical Clearance

This research has been approved by the ethics committee No. 00630/KEPH-FMIPA/2020 of Health Research Ethics Committees/HREC the Faculty of Mathematics and Natural Sciences, University Sumatera Utara.

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References

1. Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic features of common oral ulcerative lesions: an updated decision tree. Int J Den. 2016; 1-14.
2. Arundina I, Diyatri I, Kusumaningsih T, Surboyo MDC, Monica E, Afanda NM. The role of rice hull liquid smoke in the traumatic ulcer healing. Eur J Dent. 2021; 15(01):033–8.
3. Ouaabbou H, Bahbah S, Chbicheb S. Traumatic ulcer of the tongue mimicking a malignant lesion: Case report. Int J Surg Case Rep. 2023; 109:108460.
4. Fitzpatrick SG, Cohen DM, Clark AN. Ulcerated lesions of the oral mucosa: clinical and histologic review. Head and Neck Pathol. 2019; 13:91–102.
5. Idrus E, Hartanti PD, Suniarti DF, Prasetyo SR, Wimardhani YS, Subarnbhesaj A. An experimental model of chemically-induced ulceration of the buccal mucosa of Mus musculus. Makara J Health Res. 2019; 23(3):181–187.
6. Rosa DE, Hapid MH, Hidayat W. Non-healing chronic traumatic ulcer, an entity that can resemble other chronic ulcers. Int Med Case Rep J. 2023; 16:585–90.
7. Altenburg A, El-Haj N, Micheli C, Puttkammer M, Abdel-Naser MB, Zouboulis CC. The treatment of chronic recurrent oral aphthous ulcers. Dtsch Arztebl Int. 2014; 111(40):665–73..
8. Belenguer-Guallar I, Jiménez-Soriano Y, Claramunt-Lozano A. Treatment of recurrent aphthous stomatitis. A literature review. J Clin Exp Dent. 2014; 6(2):e168–e174
9. Gabros S, Nessel, TA, Zito M. Topical corticosteroids. Treasure Island (FL): StatPearls. 2023.

10. Khounganian R, Auda S, Al-Zaqzouq R, Al-Zaqzouq R, Al-Semari H, Shakeel F. Effect of two different delivery systems of honey on the healing of oral ulcer in an animal model. J Food Sci Technol. 2020; 57(11):4211–9.
11. Kahono S, Peggie D, Sulistyadi E. Diversity of the closed-nested honey bees (Apidae: Apis Spp.) and the traditional honey collecting and beekeeping in four islands of Indonesia. Treubia. 2021; 48(2):141–52.
12. Hill DB. Pollination and honey production in the forest and agroforest. In N. Amer. Conf. on Enterprise Development through Agroforestry: Farming the Forest for Specialty Products. Center for Integrated Natural Resources and Agricultural Management, Univ. of Minnesota, St. Paul. 1998.
13. Septiani A, Suryati T, Apriantini A, Endrawati YC. Characteristics of forest and Manuka Honey as well as their application as herbal honey drinks with the addition of Qusthul Hindi and turmeric. JITEK. 2022; 17(3):183–96.
14. Kieliszek M, Piwowarek K, Kot AM, Wojtczuk M, Roszko M, Bryła M, Petkoska AT. Recent advances and opportunities related to the use of bee products in food processing. Food Sci Nutr. 2023; 11:4372–4397.
15. Subrahmanyam M. Topical application of honey for burn wound treatment - an overview. Ann Burns Fire Disasters. 2007; 20(3):137-139.
16. Tashkandi H. Honey in wound healing: an updated review. Open Life Sci. 2021; 16(1):1091–1100.
17. Scepankova H, Combarros-Fuertes P, Fresno JM, Tornadijo ME, Dias MS, Pinto CA, Saraiva, JA, Estevinho LM. Role of honey in advanced wound care. Molecules. 2021; 26(16): 4784.
18. Yelin A, Kuntadi. Phytochemical identification of honey from several regions in Java and Sumbawa. In: AIP Conference Proceedings. AIP Publishing. 2019; 2120(1).
19. Subrahmanyam M. respective randomised clinical and histological study of superficial burn wound healing with honey and silver sulfadiazine. Burns. 1998; 24(2): 157-161.
20. Al-Khayri JM, Sahana GR, Nagella P, Joseph B V., Alessa FM, Al-Mssallem MQ. Flavonoids as potential anti-Inflammatory molecules: a review. Molecules. 2022; 27(9):2901.
21. Mohamed SS, Al-Douri AS. The effect of honey on the healing of oral ulcers. Al-Rafidain Dent J. 2008; 8(2):157-160.
22. Chamani G. Evaluation of Honey as a Topical Therapy for Intraoral Wound Healing in Rats. Wounds. 2017; 29(3):80–86.
23. Nakajima Y, Mukai K, Nasruddin, Komatsu E, Iuchi T, Kitayama Y, Sugama J, Nakatani T. Evaluation of the effects of honey on acute-phase deep burn wounds. J Evid Based Complementary Altern Med. 2013; 2013:784959.
24. Fauziah M, Soniya F. Potensi tanaman zigzag sebagai penyembuh luka. Jurnal Penelitian Perawat Profesional. 2020; 2(1):39-44.
25. Rishika D, Sharma R. An update of pharmacological activity of Psidium Guajava in the management of various disorders. Int J Pharm Sci. 2012; 3(10):3577–3584.
26. Zhang Y, Wang JZ, Wu YJ, Li WG. Anti-inflammatory effect of recombinant human superoxide dismutase in rats and mice and its mechanism. Acta Pharmacol Sin. 2002; 23(5):439–444.
27. Dutta S, Das S. A study of the anti-inflammatory effect of the leaves of Psidium guajava Linn. on experimental animal models. Pharmacognosy Res. 2010; 2(5):313.
28. Michalak M. Plant-derived antioxidants: significance in skin health and the ageing process. Int J Mol Sci. 2022; 23(2):585.
29. Domaszewska-Szostek A, Puzianowska-Kuźnicka M, Kuryłowicz A. Flavonoids in skin senescence prevention and treatment. Int J Mol Sci. 2021; 22(13):6814.
30. Al-Khayri JM, Sahana GR, Nagella P, Joseph B V., Alessa FM, Al-Mssallem MQ. Flavonoids as potential anti-Inflammatory molecules: a review. Molecules. 2022; 27(9):2901.
31. Abeshu MA, Geleta B. Medicinal uses of honey. Biol Med. 2016; 8(2):1.
32. Albaridi NA. Antibacterial potency of honey. Int J Microbiol. 2019; 2019:1–10.
33. Santosa WRB, Riyono R. Perbandingan efektifitas pemberian kompres madu dan kompres gula kristal terhadap penyembuhan luka pada tikus putih. Strada Jurnal Ilmiah Kesehatan (SJIK). 2018; 7(1):28–35.
34. Schultz GS, Chin GA, Moldawer L, Diegelmann RF. Principles of wound healing. Mechanisms of vascular disease: a reference book for vascular specialists; Adelaide (AU): University of Adelaide Press. 2011.
35. Minhas S, Sajjad A, Kashif M, Taj F, Alwadaani H, Khurshid Z. Oral ulcers presentation in systemic diseases: an update. Open Access Maced J Med Sci. 2019; 7(19):3341–7.
36. Rastogi V, Singh D, Mazza JJ, Parajuli D, Yale SH. Flushing disorders associated with gastrointestinal symptoms: part 1, neuroendocrine tumors, mast cell disorders and hyperbasophila. Clin Med Res. 2018; 16(1–2):16–28.
37. Yaghoobi R, Kazerouni A. Evidence for clinical use of honey in wound healing as an anti-bacterial, anti-inflammatory anti-oxidant and anti-viral agent: A review. Jundishapur J Nat Pharm Prod. 2013; 8:100–104.
38. Pullar JM, Carr AC, Vissers M. The roles of vitamin C in skin health. Nutrients. 2017; 9(8):866.
39. Zbuchea A. Up-to-date use of honey for burns treatment. Ann Burns Fire Disasters. 2014; 27(1):22–30.
40. Alam F, Islam MA, Gan SH, Khalil ML. Honey: a potential therapeutic agent for managing diabetic wounds. J Evid Based Complementary Altern Med. 2014; 2014:1–16.