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Original Research Article

Ameliorative Effect of Ethanol Extract Gel of Kirinyuh (*Chromolaena odorata* L.) on Aphthous Stomatitis in Wistar Rats (*Rattus novergicus*)

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ABSTRACT

Aphthous stomatitis is a self-limiting condition, but its presence interferes with chewing, swallowing, and speaking. Kirinyuh (*Chromolaena odorata* L.) leaves are natural ingredient that is used traditionally as a wound healing medicine. This study aimed to evaluate the ameliorative effect of ethanol extract gel of kirinyuh on aphthous stomatitis in rats. Twenty-five (25) Wistar rats were divided into five groups of 5 animals each: Group I (HPMC), Group II (Hyaluronic Acid), Groups III - V (2%, 4%, and 8% *C. odorata* ethanol extract gel, respectively). A wound was made on the ventral tongue of the rats with a heated burnisher. Following wound induction, the rats were administered HPMC, hyaluronic acid, 2%, 4%, and 8% *C. odorata* leaves ethanol extract gel according to the grouping. The body weights of the rats were monitored, the wound healing, and inflammation were assessed on days 3, 5, and 7. Histopathological examination of the tongue tissues was also carried out. The results showed that the treatments had no significant influence on the body weight of the rats. *C. odorata* ethanol extract gel resulted in a concentration-dependent increase in the percentage wound healing and inflammation recovery, with the 8% *C. odorata* gel exhibiting the highest activity (100% on day 7). Histopathological examination showed that the mean epidermal thickness, the number of fibroblasts and neurovasculature were highest in the 8% *C. odorata* ethanol extract gel treated group. Therefore, *C. odorata* ethanol extract gel is effective in the treatment of aphthous stomatitis wounds.

Keywords: Ameliorative effect, Aphthous stomatitis, *Chromolaena odorata*, Ethanol extract gel.

Introduction

The prevalence of aphthous stomatitis in the general population varies from 5% to 66% with a mean of 20%,and it is one of the most common oral diseases in Indonesia, with a prevalence rate of 12%.[1,2] Canker sores or recurrent aphthous stomatitis is the most common type of ulceration that occurs in the oral cavity and is characterized by persistent loss or destruction of the oral epithelium.[3] Aphthous stomatitis is self-limiting or can heal by itself within 10 to 14 days, but its presence is very disturbing to the process of chewing, speaking and even interferes with the cleaning of the oral cavity. Although aphthous stomatitis can heal on its own, but treatment may still be required because oral wounds are susceptible to bacterial infection due to loss of the innate protective function of the oral mucosa, which can slow down the healing efficiency of oral ulcers.[4,5]Aphthous stomatitis treatment generally uses topical steroids.[6] Long-term and/or repeated use of steroid drugs has side effects such as adrenal suppression, candidiasis, burning sensation, bad taste in the mouth, mucosal atrophy, nausea, sore throat, and xerostomia.[7]Therefore, it is necessary to develop new therapies with higher efficacy and lower side effects.

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Kirinyuh (*Chromolaena odorata*) leaves are natural ingredient traditionally used as medicine for wound healing, they also have anticancer, antidiabetic, anti-hepatotoxic, anti-inflammatory, antimicrobial and antioxidant activity. Among the phytochemicals present in *C. odorata* leaf are flavonoids, tannins, and saponins. These phytochemicals have been shown to facilitate the wound healing process.[8,9] Tannins for example, can promote wound healing through several mechanisms: 1) scavenging of free radicals and reactive oxygen species (ROS), 2) promoting wound contraction, and 3) increasing formation of fibroblast and new capillary vessels which function as transport medium for the supply of food and oxygen needed by cells that are undergoing repair, thereby accelerating wound healing. Tannins also help stimulate epidermal growth because they play a role in the transcription and translation of vascular endothelial growth factor (VEGF). VEGF acts in a paracrine manner not only in the vascular endothelium of the skin, but increases re-epithelialization so that the epidermal layer thickens.[10]Flavonoids can inhibit the enzymes cyclooxygenase and lipooxygenase, thereby limiting inflammatory cells migrating to the wound tissue.[11]

The main goals of aphthous stomatitis treatment are to reduce pain, the number and size of lesions, reduce superinfection, accelerate healing time and increase the disease-free period. The aim of this study was to determine the ameliorative effect of ethanol extract gel of kirinyuh on aphthous stomatitis in Wistar rat.

Materials and Methods

Collection and identification of plant materials

C. odorata leaves were collected in May 2023 from Tabanan Bali, precisely at geographical coordinates 114°54'52" - 115°12'57" W and 8°14'30" - 8°30'70" S.The plant materials were identified and authenticated at UPT Laboratorium Herbal Materia Medica Batu Malang with voucher number 000.9.3/ 2423/102.20/ 2024.

Plant preparation and extraction

C.odorata leaves were washed under running water, then dried using an oven at 50ºC for 24 h. The dried leaves were ground into powder form using an electric blender. The powdered leaves (200 g) was macerated with 2 L of ethanol at room temperature for 72 h. The extract was filtered using Whatman No.1 filter paper, then evaporated using a vacuum rotary evaporator at 40ºC to obtain a crude extract of *C.odorata* leaves. The extract obtained was made into a gel at 2%, 4% and 8%concentrations with Hydroxy Propyl Methyl Cellulose (HPMC).

Animals

This study was approved by the ethical committee Politeknik Kesehatan Denpasar, Bali-Indonesia, with ethical clearence reference number: LB.02.03/EA/KEPK/0441/2023.

Male Wistar rats were acclimatized to the laboratory condition for one week. The animals were fed with standard rodent feed and allowed access to drinking water *ad libitum*. The body weights of the rats were monitored, and maintained within 150-200 g during the period of acclimatization.The health status of the animals was assessed by physical examination, and animals that met the following criteria were selected for the study: clean white fur, bright red eyes, no hair loss, no secretions or fluidfrom the eyes or ears, normal behavior or activities, and good appetite.

Wound induction and administration of C. odorata leaf ethanol extract gel

Twenty-five (25)male Wistar rats that met the selection criteria were randomly divided into five groups, of 5 rats each. The rats were anaethesized by intraperitoneal administration of ketamine and xylazine. Wound induction was carried out thermally using a burnisher. A burnisher that has been heated for 60 seconds in a spirit lamp was attached to the ventral part of the tongue for one second up to a depth reaching one third of the burnisher. Stomatitis wounds presenting as peripheral erythema with a yellowish white center, were formed after 2 days. On days 1, 3, and 5 following wound induction, the rats were treated as follows; Group I –administered HPMC 2%, Group II – administered hyaluronic acid (HA) 0.2%, Groups III, IV, and V – administered0.1 mg each of ethanol extract gel of *C. odorata* leaves 2%, 4%, and 8%, respectively. On day 7, the wound diameter was measured, and observed for signs of inflammation, which were measured as Inflammation Score Sign (ISS). The ISS value was obtained from observing signs of inflammation such as edema, tissue necrosis, erythema and lesions with a minimum score of 0 and a maximum score of 4. In each of the treatments and observation period, the rats were anaesthesized to facilitate treatment and observation. The percentage weight loss, percentage would healing, and percentage ISS recovery were calculated using the formulas below.

$$\text{Percentage weight loss} = \frac{\text{Weight on day 7} - \text{Weight on day 1}}{\text{Weight on day 1}} X\ 100$$

$$\text{Percentage wound healing} = \frac{(Wound\ diameter\ day\ 1)^2 - (Wound\ diameter\ day\ 7)^2}{(Wound\ diameter\ day\ 1)^2} X\ 100$$

$$\text{Percentage ISS Recovery} = \frac{\text{ISS day 1} - \text{ISS day 7}}{\text{ISS day 1}} X\ 100$$

Preparation of tongue samples for histological examination

On day 7, the animals were euthanized using ketamine and xylazine. The tongues of the wounded animals were removed, washed with sodium chloride and placed in 10% formaldehyde solution for 24 h. Thereafter, the tongue tissues were trimmed and placed on the embedding cassette of the tissue processing machine. The tissues were dehydrated by immersion in increasing concentration of ethanol. Following dehydration, the tissues were cleared by immersion in xylene. The embedding cassette was removed from the tissue processor, and placed in a paraffin bath. The specimen were removed from the embedding cassette with tweezers, placed into a clean, and neatly cut 4 microns thick brass block. Liquid paraffin was poured into the block. The preparations were placed in an incubator overnight, followed by staining with Harris-Haematoxyllin-eosin (HE) dye.Histological observations were made at 400x magnification.The thickness of the epidermis, the number of fibroblasts, and the number of neovasculature as parameters for wound healing was determined.

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences v.23 software (IBM Corp., Armonk, NY, USA). Univariate and bivariate analysis were done. Two Way Repeated Measures Anova statistical tests were used to analyze differences in the percentage of weight loss and the percentage of wound healing. Analysis of Percentage of ISS Recovery was done using Kruskal Wallis test. Differences between the treatment groups for epithelial thickness, number of fibroblasts and neovasculature were analyzed using one-way ANOVA test.

Results and Discussion

The body weights of the rats were measured before stomatitis wound induction and on the third, fifth and seventh day following wound induction. Then the percentage of weight loss was calculated by comparing the body weight on day 7 to the body weight on first day prior to induction. The results showed that there was a significant difference in the percentage weight loss among the different groups on the 3rd, 5th and 7th day (p=0.001), but within each group, the treatments (HPMC, HA, *C. odorata* gel) had no significant influence on the body weight of the rats throughout the treatment period (p=0.110) (Table 1). However, from the descriptive analysis, it was observed that in group V (*C. odorata* 8% gel), the percentage weight loss in the rats increased steadily from days 3, 5 and 7 (Figure 1).

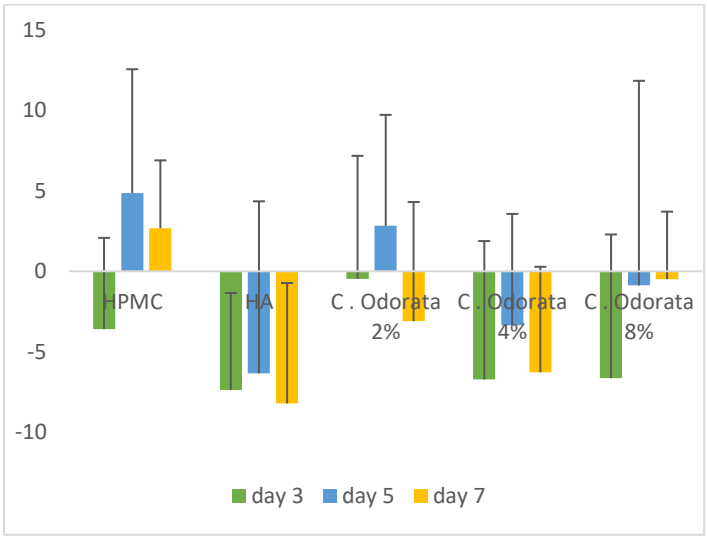

Figure 1: Percentage weight loss within the groups

Stomatitis wounds cause serious discomfort, including pain when eating, swallowing, talking, and also cause stress. Stress and difficulty eating caused by stomatitis wounds have an impact on overall health. Decreased appetite can occur due to acute stress which causes the release of stress hormones. This sudden surge in stress hormones has an appetite suppressing effect due to the release of the hormone corticotropin (CRF) which affects the digestive system.[12-14]Pain in an injury occurs due to an increase in pain mediators such as prostaglandins E2 (PGE2) which are formed as a result of damaged mucous membrane.[15] Pain in acute stomatitis is also caused by damage to the deeper membrane which extends to the lamina propria resulting in the stimulation of pain nerve endings and transmission of pain impulses.[16] On day 3, none of the treatments has resulted in the healing of the stomatitis wound as only a minimal percentage wound healing was recorded for all the treatment groups. From day 5 to day 7, there was a progressive and significant (p = 0.023) increase in the percentage wound healing across all the treatment groups.

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Table 1: Mean Percentage Weight Loss among the Treatment Groups

	HPMC	HA	*C. odorata* 2%	*C. odorata* 4%	*C. odorata* 8%	Sig
Day 3	-3.60 ± 5.68	-7.39 ± 6.04	-0.47 ± 7.65	-6.73 ± 8.61	-6.65± 8.94	0.001
Day 5	4.86 ± 7.71	-6.35 ± 10.70	2.83 ± 6.90	-3.37 ± 6.94	-0.88 ± 12.73	
Day 7	2.67 ± 4.23	-8.22 ± 7.49	-3.11 ± 7.42	-6.28 ± 6.56	-0.49 ± 4.20	
Sig	0.110					

This observation indicates that the treatments have an effect on the healing process of aphthous stomatitis wound in Wistar rats. It is important to note that *C. odorata* ethanol extract gel had the most potent wound healing effect compared to the other two treatment groups (HPMA and HA), and this effect was highly significant (p = 0.001). In addition, *C. odorata* ethanol extract gel resulted in a concentration-dependent increase in the percentage wound healing, with the 8% *C. odorata* gel exhibiting the highest percentage wound healing (100% on the seventh day) (Table 2, Figure 2). According to Fourie and Boy, aphthous stomatitis can heal in 10-14 days.[4] Healing increases greatly on day 5 because the healing process has entered the proliferation phase. In the proliferation phase, there is a decrease in the number of inflammatory cells and signs of inflammation. This proliferation phase is characterized by the appearance of proliferating fibroblast cells, the formation of new blood vessels (neovascularization), epithelialization and wound contraction.[17]

Table 2: Percentage wound healing among the treatment groups

Group	Wound Healing			Sig
	Day 3	Day 5	Day 7	
HPMC	-22.85 ± 23.07	1.25± 15.90	26.77 ± 21.60	0.023
HA	4.78 ± 7.02	38.46± 9.49	72.76 ± 6.21	
*C.odorata*2%	2.03 ± 17.40	63.61 ± 10.42	84.13 ± 4.36	
C.odorata 4%	3.61 ± 27.69	61.78± 23.83	87.93 ± 12.73	
C.odorata 8%	11.05± 11.62	72.35 ± 17.74	100.00 ± 0,00	
Sig		0.001		

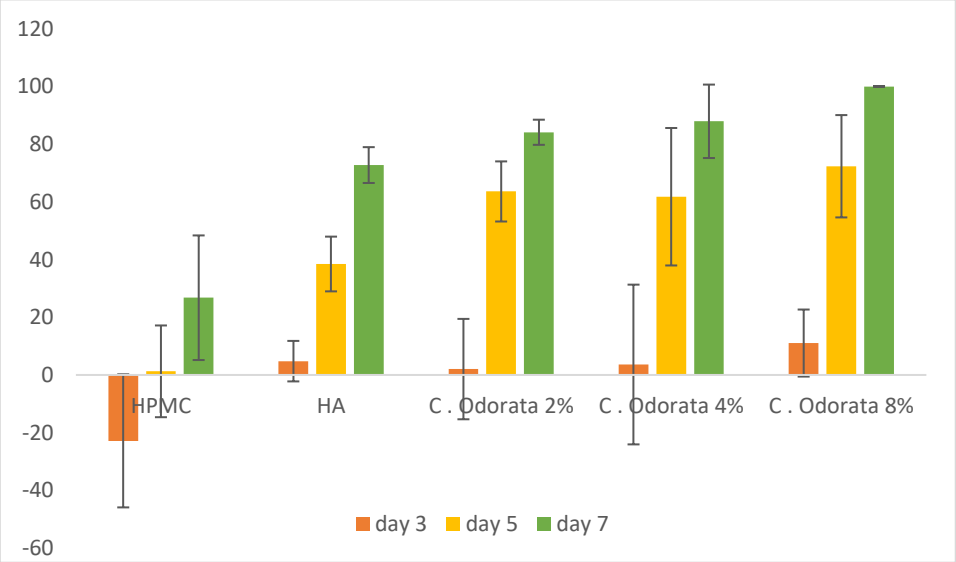

Figure 2: Percentage wound healing

The potent wound healing effect of *C. odorata* might be attributed to its tannin and flavonoid contents. Tannins have astringent properties which are used to heal aphthous stomatitis wounds, so they have immunomodulatory properties. According to Antonia*et al.*, tannins form complexes with proteins in the saliva,providing a protective layer over the wound,and the healing process occurs naturally just below this layer, and this reduces the pain associated with stomatitis.[18] This condition speeds up the healing process because it reduces exposure to disturbing substances from food and drink in the wound area.[19]Flavonoids on the other hand, inhibit biofilm formation and suppress virulence factors in the wound healing process.[20]

The mean percentage inflammation recovery was significantly different among the groups (HPMC, HA, 2%, 4% and 8% *C. odorata* gel). The highest mean percentage inflammation recovery (100%) was recorded in the 8% *C. odorata* gel group (Table 3). Aphthous stomatitis is an inflammatory process, so that in aphthous stomatitis, signs of

inflammation in the form of redness, swelling, heat, pain and loss of tissue function are found. Inflammation itself is a local response of mammalian body tissue to trauma and is the body's defence mechanism to prevent the spread of traumatic agents and eliminate cell and tissue necrosis. Inflammation indicates tissue remodelling and repair. Flavonoids a major constituent of *C. odorata* leaves have been shown to exhibit anti-inflammatory activity through inhibition of cyclooxygenase and lipoxygenase, causing a limitation in the number of inflammatory cells that migrate to the wound tissue, which eventually arrest the inflammatory reaction.[14] Tannins also present in *C. odorata* leaves play an important role in the treatment of erythema and mucosal inflammation. Saponins, a component of *C. odorata* leaves also have anti-inflammatory and antioxidant properties which are important in the aphthous stomatitis wound healing process. Flavonoids are useful in dentistry as prophylaxis against bacterial infections and as additional therapy to improve post-operative healing of traumatized tissue in the oral cavity due to their antibacterial/antibiofilm properties.[17] Factors that facilitate resolution of inflammation and initiate proliferation may be more beneficial for wound therapy.

For the histopathological examination of the tongue tissue, the following parameters; thickness of the epidermis, number of fibroblasts, and the number of neovasculature were used to assess the healing process. On the seventh day, it was observed that the group administered 8% *C. odorata* gel had the highest epidermal thickness (Table 4).

Table 3: Percentage inflammation recovery

	HPMC	HA	*C.odorata* 2%	*C.odorata* 4%	*C.odorata* 8%	Sig
ISS	68.75 ± 12.50	70.00 ± 11.18	70.00 ± 11.18	85.00 ± 13.69	100.00 ± 0.00	0.000

Table 4: Mean Epidermal Thickness, Number of Fibroblasts and Number of Neovasculature among the Treatment Groups

	HPMC	Hyaluronic acid	*C. Odorata* 2%	*C. Odorata* 4%	*C. Odorata* 8%	Sig
Epidermal thickness	77.79 ± 5.02	114.29 ± 24.51	134.09 ± 31.1	113.27 ± 32,21	134.22±32.40	0.047
Fibroblast	20.25 ±2.87	24.40 ± 3.91	21.80 ± 9.26	20.80 ± 9.04	27.60 ± 4.88	0.437
Neovasculature	7.00 ± 4.24	9.40 ± 5.90	6.20 ± 2.86	6.00 ± 2.55	11.20 ± 3.83	0.229

Furthermore, the histopathological examination of the tongue tissue after 7 days of treatment showed no significant difference in the number of fibroblasts ($p = 0.437$) and neurovasculature ($p = 0.229$) among the treatment groups, although, the highest number of fibroblasts and neurovasculature was found in the 8% *C. odorata* gel group (Table 4, Figure 3). In the group treated with 8% *C. odorata* gel, the healing process had reached 100%, so that the number of fibroblasts decreased, whereas, in the other groups, the healing process was still in progress, although the number of fibroblasts was sufficient for collagen formation. From day 5 to day 7, fibroblasts begin to form new collagen and glycosaminoglycans, which will form the wound core and help stabilize the wound. Then reepithelialization occurs with the migration of cells from the wound edge and adjacent edges. Initially only a thin layer of superficial epithelial cells is formed, then thicker and more durable layers of cells will bridge the wound over time.

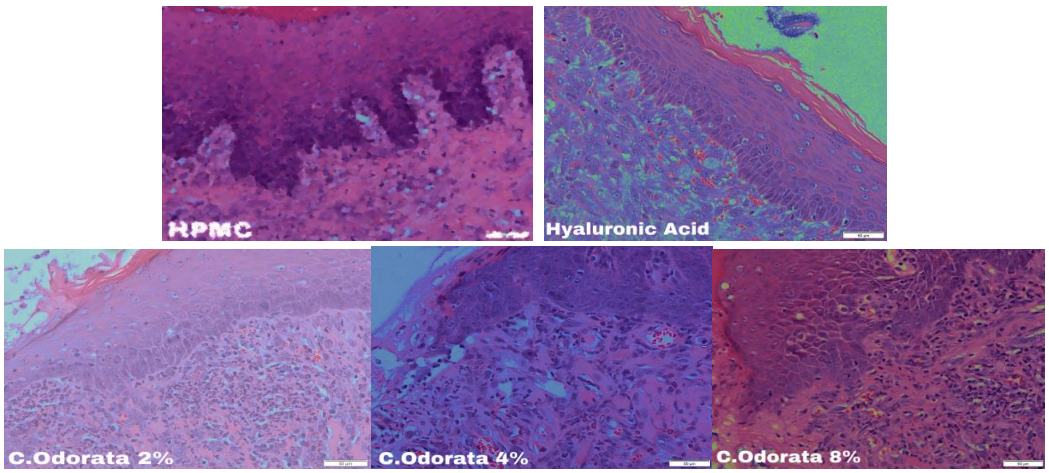

Figure 3: Photomicrograph of the Tongue Tissues Following Histopathological Analysis of Stomatitis Wound

These effects may be attributed to the tannins, saponins, and flavonoids contained in the ethanol extract of *C. odorata* leaves. Tannins help stimulate epidermal growth because they play a role in the transcription and translation of vascular endothelial growth factor (VEGF). VEGF acts in a paracrine manner not only in the vascular endothelium of the skin, but increases re-epithelialization so that the epidermal layer thickens.[10] Saponins has been reported to enhanced the proliferation of epidermal cells by upregulating Bcl-2 (B-cell lymphoma 2) expression in keratinocytes.[21] Saponins also stimulate fibronectin synthesis by fibroblasts. Fibronectin is found in the early phase of wound healing and induces fibroblast migration. By stimulating fibronectin synthesis, fibroblast migration will also be faster. These fibroblasts is used in the

next phase of wound healing to produce collagen. As more and more fibroblasts migrate into the wound area, more and more collagen is synthesized by the fibroblasts and this new collagen builds up with the old collagen in the extracellular matrix, so that the collagen becomes thicker and the wound becomes smaller and heals faster.[22] Malery *et al*. stated that mucoadhesive gel containing flavonoids can efficiently penetrate the human oral mucosa, and subsequently, accelerate wound healing by stimulating fibroblast replication.[23]

Conclusion

This research highlights the promising ameliorative effects of *C. odorata* against aphthous stomatitis wounds, with the extract exhibiting higher wound healing effect than hyaluronic acid, and no toxic effects was observed at the doses tested. These findings suggest *C. odorata* as a viable alternative therapy for aphthous stomatitis, thus warranting further investigation for clinical use. The observed effects may pave the way for future research aimed at optimizing the therapeutic application of *C. odorata* extract in the treatment of aphthous stomatitis wounds.

Conflict of Interest

The authors declare no conflict of interest

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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References

1. Neville BW, Damm DD, Allen CM, Chi AC. Oral and Maxillofacial Pathology. Philadelphia: Elsevier Health Sciences; 2016. 303-310 p
2. Hariyani N, Bramantoro T, Nair R, Singh A, Sengupta K. Depression symptoms and recurrent aphthous stomatitis - evidence from a population-based study in Indonesia. Oral Dis. 2020; 26(5):948–954.
3. Sánchez-Bernal J, Conejero C, Conejero R. Recurrent Aphthous Stomatitis. Acta Dermosifiliogr (Engl Ed). 2020; 111(6):471-480.
4. Fourie J and Boy SC. Oral mucosal ulceration – a clinician's guide to diagnosis and treatment. South Afr Dent J. 2016; 71(10):500-508.
5. Zhang Z, Zhangh Q, Gao S, Xu H, Guo J, Yan F. Antibacterial, anti-inflammatory and wet-adhesive poly(ionic liquid)-based oral patch for the treatment of oral ulcers with bacterial infection. Acta Biomater. 2023; 166:254–265.
6. Chiang CP, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A. Recurrent aphthous stomatitis - Etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. J Formos Med Assoc. 2019; 118(9):1279-1289.
7. Bakhshi M, Gholami S, Mahboubi, A, Jaafari MR, Namdari M. Combination Therapy with 1% Nanocurcumin Gel and 0.1% Triamcinolone Acetonide Mouth Rinse for Oral Lichen Planus: A Randomized Double-Blind Placebo Controlled Clinical Trial. Dermatol Res Pract. 2020; 2020:4298193.
8. Tedjasulaksana R, Ratmini NK. Studi Kualitatif dan Kuantitatif Ekstrak Air dan Ekstrak Etanol Daun Kirinyuh (*Chromolaena Odorata L*.) yang Tumbuh di Provinsi Bali. Intisari Sains Medis. 2022; 13(1):70-74.
9. Sirinthipaporn A, Jiraungkooskul W. Wound Healing Property Review of Siam Weed, *Chromolaena odorata*. Pharmacogn Rev. 2017; 11(21):35–38.
10. Orlowski P, Zmigrodzka M, Tomaszewska E, Ranoszek-Soliwoda K, Czupryn M, Antos-Bielska M, Szemraj J, Celichowski G, Grobelny J, Krzyzowska M. Tannic acid-modified silver nanoparticles for wound healing: the importance of size. Int J Nanomed. 2018; 13:991-1007.
11. Panche AN, Diwan AD, ChandraSR. Flavonoids: An Overview. J Nutr Sci. 2016; 5:e47
12. Radahmadi M, Izadi MS, Rayatpour A, Ghasemi M. Comparative Study of CRH Micro injections Into PVN and CeA Nuclei on Food Intake, Ghrelin, Leptin, and Glucose Levels in Acute Stressed Rats. Basic Clin Neurosci. 2021; 12(1):133-148.
13. Klazkin RR, Baldassaro A, Rashid S. Physiological responses to acute stress and the drive to eat: The impact of perceived life stress. Appet. 2019; 133:393-399.
14. Schamer S, Stengel A. Animal models for anorexia nervosa-a systematic review. Front Hum Neurosci. 2021; 14:596381.
15. Cheng H, Huang H, Guo Z, Chang Y, Li Z. Role of prostaglandin E2 in tissue repair and regeneration. Theranostics. 2021; 11(18):8836-8854.
16. Papanstasopoulou F. Reccurentapthous stomatitis: a case presentation with 915 nm diode laser therapy. Laser. 2016; 2:10–13.
17. Landén NX, Li D, Ståhle M. Transition from inflammation to proliferation: a critical step during wound healing. Cell Mol Life Sci. 2016; 73(20):3861-3885.
18. Hakim RF, Idroes R, Hanafiah, O A, Ginting, B, Fakhrurrazi, F. Potential Effect of Red Algae Content on Fibroblasts and Collagen Type 3 in Oral Mucosa Wound Healing Diabetes-Induced *Rattus norvegicus*. Trop J Nat Prod Res. 7(8):3683–3690.
19. Kováč J, Slobodníková L, Trajčíková E, Rendeková K, Mučaji P, Sychrová A, Bittner Fialová S. Therapeutic Potential of Flavonoids and Tannins in Management of Oral Infectious Diseases-A Review. Molecules. 2022; 28(1):158.
20. Fernández-Rojas B, Gutiérrez-Venegas G. Flavonoids Exert Multiple Periodontic Benefits Including Anti-Inflammatory, Periodontal Ligament-Supporting, and Alveolar Bone-Preserving Effects. Life Sci. 2018; 209:435–454.
21. Park KS, Park DH. The effect of Korean Red Ginseng on full-thickness skin wound healing in rats. J Ginseng Res. 2019; 43(2):226-235.
22. Cialdai F, Risaliti C, Monici M. Role of fibroblasts in wound healing and tissue remodeling on Earth and in space. Front Bioeng Biotechnol. 2022; 10:958381.
23. Zulkefli N, CheZahari CNM, Sayuti NH, Kamarudin AA, Saad N, Hamezah HS, Bunawan H, Baharum SN, Mediani A, Ahmed QU, Ismail AFH, Sarian MN. Flavonoids as Potential Wound-Healing Molecules: Emphasis on Pathways Perspective. Int J Mol Sci. 2023; 24(5):4607.