Trop J Nat Prod Res, November 2025; 9(11): 5597 - 5601

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Anti-Inflammatory Effect of *Stichopus hermanii* Extract on Oral Ulcers in *Rattus norvegicus*: Modulation of IL-6 and IL-10 Expression

Asmawati Amin[1]*, Bahruddin Thalib[2], Nurlindah Hamrun[1], Laras Panca Sakti[1], Ogilvin Maria Wulandari[1], Alqarama Mahardhika Thalib[3], Yulia Yusrini Jabir[4], Delvi Sintia Reni[2], Rafikah Hasyim[1]

[1]*Department of Oral Biology, Faculty of Dentistry, Universitas Hasanuddin, Makassar, Indonesia*
[2]*Department of Prosthodontic, Faculty of Dentistry, Universitas Hasanuddin, Makassar, Indonesia*
[3]*Department of Dental Material, Faculty of Dentistry, Universitas Hasanuddin, Makassar, Indonesia*
[4]*Faculty of Pharmacy, Universitas Hasanuddin, Makassar, Indonesia*

ARTICLE INFO

Article history:
Received 12 October 2024
Revised 13 November 2025
Accepted 17 November 2025
Published online 01 December 2025

ABSTRACT

Glycosaminoglycans and collagen in *Stichopus hermanii* have been shown to support the wound-healing process, and Indonesia is the largest producer of this species. This study aimed to investigate the anti-inflammatory effect of *Stichopus hermanii* extract gel as a novel natural, cost-effective, and potentially more effective wound healing agent. This study employed a laboratory experimental design with a post-test-only control group to evaluate the effects of *Stichopus hermanii* extract on IL-6 and IL-10 expression in oral ulcers of *Rattus norvegicus*. The experimental groups included a positive control group (Kenalog in Orabase), negative control group (carboxymethyl cellulose, or CMC), and treatment groups which were administered *Stichopus hermanii* extract gel at concentrations of 80%, 40%, and 20%. Treatments were applied twice daily for 10 days following ulcer would incision in rats. Interleukin-6 (IL-6) and Interleukin-10 (IL-10) levels were determined by enzyme-linked immunosorbent assay (ELISA) following the manufacturer's instruction. The results demonstrated that *Stichopus hermanii* extract at 80% concentration produced the greatest reduction in IL-6 and the highest increase in IL-10 expression levels, suggesting its efficacy in enhancing the wound healing process of oral ulcers. This findings therefore revealed the potential of *Stichopus hermanii* extract as an alternative therapy for oral inflammation.

Keywords: Inflammation; Interleukin 6; Interleukin 10; Oral ulcer; *Stichopus hermanii*

Introduction

An ulcer is a destructive epithelial lesion extending beyond the basal membrane, with well-defined borders, often resulting in wounds. Oral ulcers usually present as oval, painful lesions. Ulcers typically present as oval, painful lesions. They may appear as white to yellowish necrotic patches surrounded by extensive erythematous areas.[1,2] Oral ulcers are inflammatory reactions of the oral mucosa, triggered by various factors such as irritants, allergens, infections, or poor oral hygiene. The recovery of oral ulcers follows the fundamental principles of wound healing observed in other areas of the body. This process generally occurs in several phases, including hemostasis (cessation of bleeding), inflammation (clearing the wound and fighting infection), cell proliferation (reconstructing tissue), and remodeling (enhancing and refining newly developed tissue).[3,4] Inflammation is the natural response of the body to combat antigens, eliminate microorganisms, and repair damaged tissues. This process involves the participation of vascular and inflammatory cells such as leukocytes and macrophages, which play a crucial role in destroying invading microorganisms (antigens) during inflammation. Lymphocytes contribute to wound healing by producing lymphokines, which influence the behavior of other cells involved in the inflammatory process.[5,6]

*Corresponding author. Email: asmawati@unhas.ac.id
Tel.: +62 82189018000

Citation: Amin A, Talib B, Hamrun N, Sakti LP, Wulandari OM, Thalib AM, Jabir YY, Reni DS, Hasyim R. Anti-Inflammatory Effect of *Stichopus hermanii* Extract on Oral Ulcers in *Rattus norvegicus*: Modulation of IL-6 and IL-10 Expression. Trop J Nat Prod Res. 2025; 9(11): 5597 – 5601 https://doi.org/10.26538/tjnpr/v9i11.46

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

Interleukin-6 (IL-6) is a type of lymphokine that regulates the quantity and activity of various inflammatory cells involved in the inflammation process. IL-6 is a pleiotropic cytokine with diverse effects. It acts as both a pro-inflammatory and anti-inflammatory cytokine. As an anti-inflammatory agent, IL-6 stimulates the production of tissue-degrading matrix metalloproteinases and inhibits the synthesis of pro-inflammatory cytokines, such as IL-1β and tumour necrosis factor (TNF). IL-6 also functions as a pro-inflammatory cytokine, inducing reparative responses during inflammation. However, excessive activation of pro-inflammatory signalling pathways can interfere with wound healing and increase the risk of infection.[7,8]

Interleukin-10, a widely recognized anti-inflammatory cytokine, plays a pivotal role in minimizing scar formation. IL-10 is synthesized and secreted by nearly all components of the immune systems, including granulocytes (neutrophils), mast cells, keratinocytes, and endothelial cells.[9] As an anti-inflammatory mediator, IL-10 inhibits the production of several cytokines, such as TNF, IL-1, chemokines, and IL-12, while also suppressing macrophage activity that supports T-cell activation during the wound healing process. IL-10 activity results in the suppression of both non-specific and specific anti-inflammatory responses mediated by T-cells. This dual action has earned IL-10 the designation of "cytokine synthesis inhibitory factor" as well as "anti-inflammatory cytokines."[10] Indonesia is a vast archipelago comprising over 17,000 islands, boasts a rich abundance of marine resources, with more than 75% of its territory covered by water. Among these resources is *Stichopus hermanii*, a marine species found particularly around Selayar Island that is valued as a human food source. *Stichopus hermanii* is a sea cucumber species that was originally described by the taxonomist Jean-Baptiste Lamarck in 1816. The species is part of the family Stichopodidae.[11-13] *Stichopus hermanii* is recognized as a food rich in polyanions, particularly glycosaminoglycans (GAGs) which have been shown to aid wound healing. As the largest producer of *Stichopus hermanii*, Indonesia holds significant potential for

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

harnessing this marine resource to advance natural and effective wound healing solutions.[14]

Rattus norvegicus is a well-established rodent model for studying oral ulcers and wound healing processes because its oral anatomy and healing responses closely resemble those observed in humans. In this study, the effects of the extract on key inflammatory mediators, such as IL-6 and IL-10, which are critical in regulating the wound healing cascade was investigated in *Rattus norvegicus*. Additionally, this model provides a consistent and controlled experimental framework for systematically evaluating the anti-inflammatory properties of varying concentrations of *Stichopus hermanii* extract, offering valuable insights to guide future clinical research. This study is a novel investigation into the potential of *Stichopus hermanii* from Selayar Island, Indonesia.

This study explored the wound healing properties of *Stichopus hermanii*, a species commonly found in Indonesia. It focused on the roles of IL-6 as a pro-inflammatory cytokine and IL-10 as an anti-inflammatory cytokine in the context of oral wound healing. Targeting these specific pathways represents an innovative therapeutic approach, particularly considering the anti-inflammatory properties of *Stichopus hermanii*. This highlights a promising opportunity to develop natural, cost-effective, and potentially more effective wound-healing therapies, leveraging the abundant availability of *Stichopus hermanii* in Indonesia.

Materials and Methods

Collection and identification of Stichopus hermanii

The sea cucumber *Stichopus hermanii* was colleed in in January 2024 from a local market in the Bontoharu District, Selayar Island, Indonesia (GPS: coordinate: -6.133830, 120.457656). The species was identified based on morphological characteristics and confirmed by Asmawati Amin, Laras Panca Sakti dan Ogilvin Maria Wulandari, in accordance with the guidelines described by the local fishermen.

Preparation of Stichopus hermanii extract

Fresh sea cucumbers (*Stichopus hermanii)* were cleaned, cut into small pieces, and separated from unwanted parts before weighing to determine their net weight. The sea cucumbers were then oven-dried at 100ºC for 24 h. After drying, the sample was macerated with 500 mL of methanol in a maceration vessel for 48 h, The maceration solution was filtered through a filter paper to separate the filtrate from the residue. The methanol extract was concentrated using a rotary evaporator at 40ºC and then dissolved in carboxymethyl cellulose (CMC) to form a gel, which could be applied topically to test animals.

Animals

Twenty-five (25) male *Rattus norvegicus* with average weight of 250 g were obtained from a local farm. The rats were housed in cages with wood shavings for bedding and placed in a temperature-controlled room at 22 ± 2°C with a 12-hour light/dark cycle. They were provided a standard rodent diet and had access to water *ad libitum*. Food and water were replaced daily and the cages were cleaned three times a week to ensure a clean and hygienic environment. Prior to the start of the experiment, the rats were acclimatized to the laboratory conditions for seven days to allow them to adjust to their environment and minimize stress or other confounding factors. The housing and husbandry conditions were carefully designed to provide a comfortable and enriched environment, supporting the animals' health and well-being throughout the study period.

Ethical approval

The ethical approval with reference number 157/UN4.6.4.5.31/PP36/2023 was obtained from the ethics committee of Hasanuddin University Dr. Wahidin Sudirohusodo Hospital.

Study design

Twenty-five male rats were divided into five groups of 5 animals each. The groups are as follows:

Group 1 (Positive control): Rats with oral ulcer treated with Kenalog gel.

Group 2 (Negative control): Rats with oral ulcer treated with CMC base.

Group 3: Rats with oral ulcer treated with 20% *Stichopus hermanii* extract gel.

Group 4: Rats with oral ulcer treated with 40% *Stichopus hermanii* extract gel.

Group 5: Rats with oral ulcer treated with 80% *Stichopus hermanii* extract gel.

Initial blood sample collection

The animals were anesthetized using ether anaesthesia. Blood samples were collected using capillary tubes and transferred into tubes containing EDTA as an anticoagulant.

Induction of incision wounds

A 1 cm long, 1 mm deep incision was made on the gingival area of the rat using a sterile, disposable scalpel under ether anesthesia. Any blood that emerged was gently washed with distilled water.

Application of Stichopus hermanii extract to animals

The wounds were treated according to the predetermined groups, with *Stichopus hermanii* extract gel applied twice a day to the incision area for 8-9 hours over a period of ten days. The gel was applied at graded concentrations: 80%, 40%, and 20% as indicated in the grouping above. Kenalog in Orabase served as the positive control, while CMC gel base was used as the negative control.

Following the experimental procedures, animals were anesthetized to minimize pain and distress. They were closely monitored for any signs of discomfort or complications and received appropriate analgesics and veterinary care to ensure their well-being and promote optimal recovery. Housing conditions were maintained at the highest animal welfare standards, with access to food and water *ad libitum* and environmental enrichment to support the animals' physiological and behavioral needs during the postoperative period.

Blood sample collection

Blood samples were collected one hour after incision and 24 h after applying the extract gel to each group to assess the IL-6 expression levels. IL-10 levels were measured on the first, third, and fifth day following the application of the extract gel in each group. Blood was drawn from the eyes of the rats and immediately after collection, it was placed in a tube containing the anticoagulant EDTA. A 0.5 mL EDTA tube was used for this purpose, as EDTA is effective in preserving the stability of most inflammatory biomarkers when blood is stored in a refrigerator.[15] The samples were then centrifuged at 3000 rpm for 15 minutes at 2-8°C. If there was a delay in testing, the separated plasma was stored at -70°C until analysis.

IL-6 and IL-10 expression levels

The levels of Il-6 and Il-10 expressions were determined using the enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instruction.

Statistical analysis

Data were analyzed using a paired sample T-test in SPSS statistics version 27, with a significance level set at $p < 0.05$. Differences between the estimated means and true values were tested at $\alpha = 5\%$.

Results and Discussion

Effect of Stichopus hermanii extract on IL-6 and IL-10 expression levels

This study evaluated the effect of *Stichopus hermanii* extract on IL-6 and IL-10 expressions in post-incision wound *Rattus norvegicus*. There was a significant difference in IL-6 expression between the control and 80% *Stichopus hermanii* extract treatment groups. IL-6 analysis revealed that all groups, except the negative control, experienced a decrease in serum IL-6 levels. Table 1 illustrates the difference in IL-6 expression before and after treatment in all groups treated with *Stichopus hermanii* and in the control group. The results indicated that *Stichopus hermanii*, particularly at concentrations of 40% and 80%, significantly reduced IL-6 expression after treatment compared to the negative control.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 1: Mean Il-6 levels before and after treatment

Treatment Group	Timing of Observation	n	Mean ± SD	p-value
SH 20%	Before Application	5	8.32 ± 1.29	0.675
	After Application (24h)	5	8.24 ± 1.19	
SH 40%	Before Application	5	7.20 ± 1.29	0.152
	After Application (24h)	5	6.17 ± 0.96	
SH 80%	Before Application	5	8.22 ± 1.91	0.016
	After Application (24h)	5	6.60 ± 1.51	
Control (+)	Before Application	5	8.92 ± 1.26	0.013
	After Application (24h)	5	7.35 ± 1.20	
Control (-)	Before Application	5	8.89 ± 1.22	0.011
	After Application (24h)	5	9.39 ± 1.19	

SH: *Stichopus hermanii*

On the other hand, the anti-inflammatory effect of *Stichopus hermanii* extract was assessed by measuring interleukin 10 (Table 2) level in the plasma samples of *Rattus norvegicus* on the initial day, and on the third and fifth days using the ELISA method. The results showed an increase in IL-10 expression across all groups, with the greatest increase observed in the group treated with the 80% *Stichopus hermanii* extract, although there was no statistically significant difference. The results show that treatment with *Stichopus hermanii*, particularly at higher concentrations (80%), significantly increased IL-10 expression from day 3 to day 5, compared to the control group.

Table 2: Mean IL-10 on the third and fifth days

Treatment Group	Day of Observation	n	Mean ± SD	p-value
SH 20%	Day 3	5	83.81 ± 20.55	0.700
	Day 5	5	90.04 ± 17.08	
SH 40%	Day 3	5	81.55 ± 36.07	0.623
	Day 5	5	94.01 ± 26.24	
SH 80%	Day 3	5	93.51 ± 33.03	0.651
	Day 5	5	104.16 ± 19.01	
Control (+)	Day 3	5	81.38 ± 16.43	0.726
	Day 5	5	88.26 ± 31.65	
Control (-)	Day 3	5	71.64 ± 22.29	0.147
	Day 5	5	87.58 ± 13.03	

SH: *Stichopus hermanii*

These findings highlight the promising anti-inflammatory properties of *Stichopus hermanii* extract in oral ulcer. By examining the modulation of key cytokines IL-6 and IL-10 in a *Rattus norvegicus* model, the results offer valuable insights into the mechanisms by which this natural, marine-derived compound may exert its therapeutic effects. The use of *Rattus norvegicus* as an experimental model was justified, as these animals exhibit wound-healing responses analogous to those observed in humans, making them an ideal model for studying the biological activities of *Stichopus hermanii* extract.

The healing process of an oral ulcer involves several phases including hemostasis, inflammation, proliferation, and remodeling. When an ulcer occurs, the body's response to wound healing, which consists of three stages, enables wound closure to prevent microbial invasion or infection of foreign agents into the tissue and prevent chronic infection formation.[15] Lymphocytes are at the center of the cellular immune system and play an essential role in the inflammatory process by destroying microorganisms that enter the body (antigens) and forms antibody immunity in the form of immunoglobulins. Lymphocytes release lymphokines, which trigger other inflammatory cell populations. Some released lymphokines can stimulate macrophage aggregation during the wound healing process. In addition to macrophages, IL-10 is secreted by lymphocytes.[5]

IL-6 is a versatile pro-inflammatory cytokine strongly associated with both local and systemic inflammatory processes.[15] It is produced by T cells, B cells, and macrophages, and has diverse biological effects. IL-6 plays a crucial role in regulating the activation of B cell immune responses, immunoglobulin production, and T-lymphocyte differentiation. As a confirmed pro-inflammatory cytokine, IL-6 is involved in various inflammatory conditions, including oral ulcers.[16]

Anti-inflammatory interleukins, such as IL-10 and transforming growth factor-beta (TGF-β), are essential for limiting inflammation and preventing tissue damage. They inhibit the production of proinflammatory cytokines and promote the differentiation and activation of regulatory immune cells, which can help control immune responses and promote tissue repair.[17]

The positive control used in this study was Kenalog in Orabase, which contains triamcinolone acetonide, a corticosteroid that helps reduce inflammation and relieves symptoms, such as pain and swelling in the mouth. Kenalog in Orabase is specifically formulated as an emollient dental paste (Orabase), allowing it to adhere well to the gingiva and oral mucosa. This anti-inflammatory treatment effectively alleviates the inflammation associated with oral ulcers and other inflammatory lesions.[18,19]

The results indicated that *Sthicopus hermanii* extract reduced IL-6 levels in the healing of oral ulcers in *Rattus norvegicus*. This is evident from the significant differences observed between the groups. The lowest IL-6 levels were found in the *Stichopus hermanii* 80% group, suggesting that the highest effectiveness was achieved with this concentration. The IL-6 levels in the positive control group, treated with Kenalog in Orabase, further support that the 80% *Stichopus hermanii* extract is the optimal anti-inflammatory dose, based on the reduction of IL-6 expression.

In line with this study, the research by Zohdi *et al*. (2011)[20] also showed that *Stichopus hermanii* extract significantly modulated the wound inflammatory response by reducing pro-inflammatory cytokines, including IL-6.[20] The initial wound-healing action observed in this study can be partly attributed to the early reduction of inflammatory responses. The anti-inflammatory and antioxidant properties of *Stichopus hermanii* can be considered as a primary mechanism regulating inflammatory reactions. A decrease in pro-inflammatory cytokines may lead to fewer neutrophils and macrophages being recruited to the wound and fewer cytokines being released to provide conditions that allow the wound healing process to continue. Excessive production of pro-inflammatory cytokines may lead to the progression of advanced tissue damage. Additionally, this study is in agreement with the findings from the study of Damayanti (2015) which showed that rats treated with 80% *Stichopus hermanii* extract had the most significant reduction in ulcer diameter and the highest expression of type I collagen compared to the 40% and 20% concentrations.[13]

Overall, this study suggests that *Sthicopus hermanii* enhances IL-10 levels during *Rattus norvegicus* gingival wound healing. This was evident from the average increase in IL-10 levels in the treatment group on days 3 and 5, which was higher than that in the control group. Flavonoids in *Stichopus hermanii* extracts are known for their strong anti-inflammatory properties. These flavonoids promote an increase in M2 macrophages, which in turn secrete anti-inflammatory cytokines, such as IL-10. Therefore, the increase in M2 macrophages leads to increased production of the anti-inflammatory cytokine, IL-10.[21]

IL-10 plays a crucial role in the wound healing process by regulating and suppressing pro-inflammatory cytokine expression during the recovery phase of infection, thereby reducing the tissue damage caused by inflammatory cytokines. The group treated with 80% *Stichopus hermanii* extract gel showed the highest level of IL-10 compared to the other groups, indicating that this concentration is the optimal dose for its anti-inflammatory effects. Previous *in vitro* and *in vivo* studies have shown that *Stichopus hermanii* is non-toxic and can stimulate fibroblast growth factor-2 (FGF-2) in rats with traumatic ulcers. This is attributed to the presence of glycosaminoglycans (GAGs) and omega-3 fatty acids

in *Stichopus hermanii*, which play a role in tissue remodeling. GAGs in *Stichopus hermanii* can act as inflammatory modulators, activating macrophages, which are essential for the wound healing process. These include hyaluronic acid, dermatan sulfate, chondroitin sulfate, heparin, and heparan sulfate, all of which are required for the wound healing process. Hyaluronic acid is essential in the early inflammatory process as it can increase inflammatory cell infiltration and pro-inflammatory cytokine products.[6]

About 80% of the protein content of the ethanol extract of *Stichopus hermanii* is composed primarily of collagen. During the hemostasis and inflammation phases, collagen helps in the clotting process, attracts macrophages through chemotaxis, and aids in naturally resolving inflammation. During the proliferation phase, collagen forms a scaffold that unites fibroblasts and attracts them to the wound site. As a part of the matrix structure, it serves as a framework for new tissue growth. In the maturation phase, collagen strengthens new tissues and enhances the organization of specific collagen fibers during the remodeling phase of wound healing.[22-27]

Stichopus hermanii is commonly found in the marine regions of Indonesia. The observed reduction in pro-inflammatory IL-6 levels and increase in anti-inflammatory IL-10 levels after treatment with *Stichopus hermanii* extract suggest that this natural substance has potential as a therapeutic agent for treating oral ulcers and other inflammatory conditions. These findings emphasize the need for further research, including studies on the relationship between dosage and response as well as the effects of the extract on other indicators of inflammation and healing. If these preclinical results can be successfully translated into clinical practice, they could lead to innovative therapies derived from natural sources.

Conclusion

Findings from this study has revealed the potential anti-inflammatory effect of *Stichopus hermanii* extract in ulcer wound healing. The 80% concentration of the extract was found to be the most effective in reducing IL-6 levels and increasing IL-10 levels. Therefore, *Stichopus hermanii* extract shows potential as an alternative therapy for oral inflammation. These findings highlight the need for further research, including studies on the relationship between dosage and response, as well as the effects of the extract on additional inflammatory markers and recovery.

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.

References

1. Asmawati, Thalib B, Natsir N, Thalib AM, Hasyim R. The Increase of Fibroblast Cell Number in Rat (*Rattus norvegicus*) Gingival Wound After the Application of Moringa (*Moringa oleifera* Lam) Fruit Oil. J Dentomaxillofac Sci. 2020; 5(3):173-176.
2. Marya CM, Mehlawat J, Nagpal R, Kataria S, Taneja P. Comparative Assessment of Low-Level Laser Therapy (LLLT) vs. Topical Application of Amlexanox + Lidocaine to Treat Recurrent Aphthous Ulcers (RAUs): A Randomized Controlled Trial. J Dent Res Dent Clin Dent Prospects. 2021; 15(1):11-15.
3. Falodun A, Okunrobo LO, Uzoamaka N. Phytochemical Screening and Anti-Inflammatory Evaluation of Methanolic and Aqueous Extracts of *Euphorbia heterophylla* Linn (Euphorbiaceae). Afr J Biotechnol. 2006; 5(6):529-531.
4. Waasdorp M, Krom BP, Bikker FJ, van Zuijlen PPM, Niessen FB, Gibbs S. The Bigger Picture: Why Oral Mucosa Heals Better Than Skin. Biomolecules. 2021; 11(8):4-5.
5. Toma AI, Fuller JM, Willet NJ, Goudy SL. Oral Wound Healing Models and Emerging Regenerative Therapies. Transl Res. 2021; 236:20-23.
6. Mahdani FY, Ernawati DS, Hadi P, Soebadi B. *Citrus limon* L. Gel Stimulates Lymphocytes and Interleukin-10 Expression in Traumatic Diabetic Oral Ulcers. Pharmacogn Res. 2020; 12(3):299-302.
7. Arundina I, Yuliati, Soesilawati P. The Effects of Golden Sea Cucumber Extract (*Stichopus hermanii*) on the Number of Lymphocytes During the Healing Process of Traumatic Ulcer on Wistar Rat's Oral Mucous. Dent J (Majalah Kedokteran Gigi). 2015; 48(2):100-103.
8. Sugiharto S, Ramadany S, Handayani H, Achmad H, Mutmainnah N, Inayah NH, Sesioria A, Thamrin AZ. Assessment of the Anti-Inflammatory Activities of the Moringa Leaf Extract in Periodontitis Cases Through IL-6 Cytokine Analysis in Wistar (*Rattus norvegicus*). Maced J Med Sci. 2022; 10(D):124-130.
9. Johnson BZ, Stevenson AW, Prêle CM, Fear MW, Wood FM. The Role of IL-6 in Skin Fibrosis and Cutaneous Wound Healing. Biomedicines. 2020; 8(5):101.
10. Singampalli KL, Balaji S, Wang X, Parikh UM, Kaul A, Gilley J, Birla RK, Bollyky PL, Keswani SG. The Role of an IL-10/Hyaluronan Axis in Dermal Wound Healing. Front Cell Dev Biol. 2020; 8:1-5.
11. Sandiah JH, Hardianto A, Tasman Yuza A, Hadikrishna I, Mulut DB, Maxillofasial D, Sakit R, Sadikin H. Differences in Oral Function and Interleukin-10 Expression After Odontectomy Using Micromotor and Piezosurgery. Padjadjaran J Dent Res Student. 2020; 4(1):75-80.
12. Setiyowati D, Ayub AF, Zulkifli M. Central Bureau of Statistics 2016. Marine and Coastal Resources Statistics. Statistics of Marine and Coastal Resources. 2016.
13. Damaiyanti DW. Characterization of Aqueous Extracts of Golden Sea Cucumber (*Stichopus hermanii*). Dent J (Majalah Kedokteran Gigi). 2015; 9(1):75-79.
14. Bordbar S, Anwar F, Saari N. High-Value Components and Bioactives From Sea Cucumbers for Functional Foods—A Review. Mar Drugs. 2011; 9(10):1761-1805.
15. Aziz N, Detels R, Quint JJ, Li Q, Gjertson D, Butch AW. Stability of Cytokines, Chemokines and Soluble Activation Markers in Unprocessed Blood Stored Under Different Conditions. Cytokine. 2016; 84:17-24.
16. Chairunas, Abdat M. Effectiveness of Cocoa Beans (*Theobroma cacao* L.) Extract Gel 8% and 16% in the Healing of Wistar Rats (*Rattus norvegicus*) Gingiva Incision Wound. J Dentomaxillofac Sci. 2022; 7(2):114-120.
17. Shen C, Ye W, Gong L, Lv K, Gao B, Yao H. Serum Interleukin-6, Interleukin-17A, and Tumor Necrosis Factor-Alpha in Patients with Recurrent Aphthous Stomatitis. J Oral Pathol Med. 2021; 50(4):418-423.
18. Mochol MM, Bonsmann T, Mochol M, Baran AP, Pawlik A. The Role of Interleukin 6 in Periodontitis and Its Complications. Int J Mol Sci. 2024; 25:2146.
19. Al-Qahtani AA, Alhamlan FS, Al-Qahtani AA. Pro-Inflammatory and Anti-Inflammatory Interleukins in Infectious Diseases: A Comprehensive Review. Trop Med Infect Dis. 2024; 9:13.
20. Zohdi RM, Zakaria ZA, Yusof N, Mustapha NM, Abdullah MN. Sea cucumber (*Stichopus hermanii*) based hydrogel to treat burn wounds in rats. J Biomed Mater Res B Appl Biomater. 2011; 98(1):30-37.
21. Thantawi A, Khairiati, Nova MM, Marlisa S, Bakar A. Stomatitis Aphthosa Rekuren (SAR) Minor Multiple Premenstrual Syndrome (Case Report). ODONTO Dent J. 2014; 1(2):61.
22. Ibrahim S, Elkot RA, Hend ES. Lactic Acid 5% Mouthwash vs. Kenalog in Orabase 0.1% for Treatment and Prophylaxis of Recurrent Aphthous Ulcer. J Cosmet Dermatol. 2014; 19(4):964-969.
23. Mujayanto R, Shafia A, Feranisa A. Bay Leaf (*Syzygum polyanthum*) Extract Effect on IL-10 Expression in Oral Ulcer. ODONTO Dent J. 2020; 7(1):53-58.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

24. Sari RP. Characterization and Potency of *Stichopus hermanii* Ethanol Extract on Oral Wound Healing. ODONTO Dent J. 2020; 7(1):15-16.
25. Steen EH, Wang X, Balaji S, Butte MJ, Bollyky PL, Keswani SG. The Role of the Anti-Inflammatory Cytokine Interleukin 10 in Tissue Fibrosis. Adv Wound Care. 2020; 9(4):184-198.
26. Suryono, Sari R, Wulandari FR, Andini H, Widjaja J, Nugraheni TD. Effect of 10% Kapok Banana Peel Extract Gel (*Musa paradisiaca* Linn. Kapok) on Periodontal Regeneration Process of Wistar Rat. J Dentomaxillofac Sci. 2023; 8(2):81-85.
27. Saqib U, Sarkar S, Suk K, Mohammad O, Baig MS, Savai R. Phytochemicals as Modulators of M1-M2 Macrophages in Inflammation. Oncotarget. 2018; 9(25):17937-17950.