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The Effect of Golden Sea Cucumber (StichopusHermanii) Extract on the Healing Process of the White Rat (Rattus Norvegicus) Indicated by Oral Ulcer– A Literature Review

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Abstract

Background Indonesia is a maritime country that is rich in marine resources. There are many marine resources that can be used as herbal medicine. One of them is the golden sea cucumber which is thought to be used as an alternative medicine to speed up the healing process of oral ulcers. The purpose of this study was to determine the effect of golden sea cucumber extract *(Stichopushermanii)* on the wound healing process in rats with oral ulcers.

Method This research is a descriptive study with a literature review design. The articles used are articles published in international and national journals in the 2015-2020 period and are indexed by Scopus, Thomson Reuters, Web Science, Scimago and Sinta.

Result The results of the scoping article show that there are active compounds in golden sea cucumbers, namely glycosaminoglycans that consist of hyaluronic acid, heparin / heparan sulfate (HP / HS), chondroitin sulfate / dermatan sulfate (CS / DS) and keratin sulfate (KS) which can form proinflammatory cytokines to trigger the emergence of immune defense cells and can bind to growth factors such as FGF2, VEGF, TGF-b, which will provide stimulation to accelerate the angiogenesis process, fibroblast ploriferation, endothelial differentiation, epithelial differentiation so as to accelerate the wound healing process.

ConclutionThe conclusion of this study is the golden sea cucumber has the potency to accelerate the wound healing process by increasing fibroblast formation, collagen synthesis, endothelial differentiation and epithelial differentiation.

Keywords*: Golden sea cucumber, (Stichopushermanii), Glycosaminoglycans, hyaluronic acid, heparan sulfate, chondroitin sulfate, keratin sulfate, fibroblasts, Oral ulcers*

Introduction

Oral ulcers are painful ulcers that are located on the mucous membrane.oral ulcers attack the mouth[1]. thrush varies and usually affects women more than men.The etiology of oral ulcers is not known with certainty, but there are several predisposing factors, namely genetics, trauma, food allergies, hormones (during the menstrual cycle), stress and anxiety, smoking habits, chemical products, microbial infections, and nutritional deficiencies[2,3]. The treatment given includes the administration of corticosteroids as anti-inflammatory, which in long-term use can have systemic side effects that can reduce life expectancy and increase health care costs.[4]. So far, the use of golden sea cucumbers is only intended for food consumption, even though the golden sea cucumber has many supporting components for health.Development

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of anti-inflammatory provision from natural ingredients such as golden sea cucumber (Stichopushermanii), with complete Glycosaminoglycans (GAGs) content, namely Hyaluronic Acid, Chondroitin Sulfate, Dermatan Sulfate, Heparin, Heparan Sulfate, and Dermatan sulfate which is the component with the highest concentration of ulcers as an alternative therapystill very promising[5,6]. Glycosaminoglycans are one of the main parts of glycocalyx which are often associated with many essential biological cell processes and play a role in the healing process of various diseases[7].

Methodology

Articles were collected using Pubmed and Science Direct database. The search words include Golden sea cucumber, (Stichopushermanii), Glycosaminoglycans, hyaluronic acid, heparan sulfate, chondroitin sulfate, keratin sulfate, fibroblasts, Oral ulcers. Articles were collected from the year 2015-2020 and indexed in Scimago and Scopus.

Result

Effectofglycosaminoglycansinstichopushermanii onwound healing

Damaiyanti and Soesilowati (2019), which is an experimental laboratory study with a post-test only group design, using 20 (twenty) male WistarRattusnorvegicus strains, weighing 200-300 grams, 3 months old, and using golden sea cucumber extract (Stichopushermanii) prepared using the freeze-dried method with a water extract concentration of 80%, 40%, and 20% (m / v) of gold sea cucumber gel, made by diluting the water extract of the golden sea cucumber powder on a PEG 400: 4000 basis. Animal treatment was classified into 4 groups. The treatment was given: groups 1 to 3 were given water with golden sea cucumber extract gel with a concentration of 80%, 40%, and 20%, respectively. Group 4, as negative control, was given nothing. Golden sea cucumber extract gel was applied to the ulcer on the 3rd day. Ulcer diameter was measured by digital calipers and animals were weighed using digital scales. All measurements are made by the same operator. Ulcer diameter and body weight were evaluated on day 3 to day 7. Mucosal specimens were taken, stained with hematoxylin and eosin (HE) and immunohistochemistry with anti-collagen monoclonal antibody type I. Collagen expression type I was calculated with a modification of the Brandacher method. The results above showed that the highest expression of type I collagen was found in group 1, which was smeared with water extract of golden sea cucumber with a concentration of 80% for a total of 5.86 ± 0.91 mg. There was an increase in the expression of collagen type I in the applied groups with 80%, 40%, and 20% golden sea cucumber extract, respectively, when compared to the negative control group. The ANOVA test results proved significant differences in all groups ($p < 0.05$). LSD analysis results showed that the difference between group 1 and 2 and between group 3 and group 4 was not significant ($p > 0.05$), while the other groups showed a significant difference ($p < 0.05$). This study shows that glycosaminoglycans (GAGs) in goldfish play a role in a variety of biological processes including cell matrix interactions as well as activation of chemokines, enzymes and growth factors.[8]

Rima Darwati Sari and EndahWahjuningsih (2017) using the true experimental research method, the post test only control group design. By using the parameter of the number of fibroblasts in the maturation phase. The sample used was 48 Wistar rats, taken by simple random sampling and divided into 6 groups, namely control (X1), hyaluronic acid 0.2% (X2), crude extract of golden sea cucumber 60% (X3) and 80% (X4) and the ethanol extract of the golden sea cucumber 60% (X5) and 80% (X6). The mice used were male, weighing 200-300 g with an age of about 3 months. The statistical test showed that the expression of CD 105 did not show any significant difference ($p > 0.05$) in all groups. All groups were sacrificed for taking the labial mucosa of the mice to observe the number of fibroblasts with HE (Hematoxylin Eosin) staining. Physiologically, wound healing is a complex process involving the coordination of various interventions. Expression (TGF-β) plays a role in regulating many processes involved in tissue repair, including the production of extra cellular matrix (MES), proteases, protease inhibitors, migration, chemotaxis, and proliferation of macrophages, fibroblasts, epithelium and capillary blood vessels. Lots of interactions occur due to endoglin which regulates a number of cell functions such as cell adhesion, migration, permeability, apoptosis and proliferation of various cell types.[10]

Research I Arundina, Y Yuliati and P Soesilowati (2015) is a laboratory experimental study with a

randomized post test only control group design. Performed with two variables after treatment using a random sample, and a negative control group as a comparison. This study used 20 male rats aged 2-4 months and weighing 200-300 grams as a sample (Rattusnorvegicus) with certain criteria, and divided into four treatment groups, namely treatment group I with golden sea cucumber extract 80%, 40%, 20%. and the group with aquadest as the control group. The number of lymphocytes was calculated in the preparation of histometric paraffin blocks under a compound light microscope with a magnification of 400x. (Arundina et al., 2015) The largest number of lymphocytes was found in the treatment group with 40% golden sea cucumber extract, while the lowest was in the control group. Previous studies have shown that 40% golden sea cucumber extract is optimal for increasing the number of fibroblasts in the healing process of traumatic ulcers. Sea cucumber extract can accelerate the wound healing process. The results of histological examination showed that the largest number of lymphocytes was found in the treatment group with 40% golden sea cucumber extract. The 20% golden sea cucumber extract could not affect the lymphocyte count, while the 80% golden sea cucumber extract could reduce the lymphocyte count. This shows that the concentration of golden sea cucumber extract can have a different effect on the number of lymphocytes, so it needs to be dosed correctly and correctly.[9]

Damayanti's (2015) research is a laboratory experimental research. The research design used was a randomized post test only control group design. With a total sample size of 20 Wistar rats which were divided into 4 groups. The materials and tools used were golden sea cucumber extract obtained by freeze dried, PEG 400: 4000. Gold sea cucumber extract gel with a concentration of 80%, 40% and 20% respectively was prepared to be applied to the ulcer as much as 0.1 mg for each treatment group (negative control). After the ulcer was formed, the golden sea cucumber extract was given successively in Group I 0.1 mg with a concentration of 80%; group II 0.1 mg with a concentration of 40%; group III 0.1 mg concentration of 20%, and in the negative control group was not given treatment (negative control). Staining using immunohistochemical techniques with primary monoclonal antibodies, namely murine monoclonal antibodies against HMGB1 molecule and secondary antibodies that have been biotinated. The results showed that the 40% concentration group had the highest expression compared to other groups. (Damaiyanti, 2015) High Mobility Protein Box 1 (HMGB1) usually binds to DNA in the cell nucleus, but monocytes and macrophages can actively secrete HMGB1. HMGB1 acts as a cytokine stimulating inflammatory responses in various cell types including monocytes, macrophages, neutrophils, dendritic cells including inducing cell migration.[12]

Research conducted by Maulana (2017) is a true experimental laboratory with a factorial research design. The parameter of this study was the number of fibroblasts. With a total sample of 20 male Wistar rats (Rattusnovergicus), 3-4 months old with a body weight of 150-200 grams which were divided into five groups. in P. gingivalis induction and given 3% gold sea cucumber gel therapy and hyperbaric oxygen therapy. The results showed that the golden sea cucumber (Stichopushermanii) contained a lot of GAG, a polysaccharide that is very useful in the wound healing process to modulate FGF2 in activating fibroblast proliferation. Hyaluronic acid is known to increase TGF-β activity which can trigger migration and mitosis of fibroblasts and epithelial cells during the proliferation phase. Dermatan sulfate has the ability to activate growth factors, such as FGF-2 and FGF-7, thereby triggering cell proliferation. In addition, it is strengthened in previous research regarding the effect of the 3% concentration of golden sea cucumber gel extract which is non-toxic and can increase the activity of superoxide dismutase (SOD) in periodontitis caused by mixed periodontopathogenic. The group that was given hyperbaric oxygen therapy 2.4 ATA 3x30 '5' interval for 7 days (49.725 ± 10.088) there was a significant increase in the number of fibroblasts. Giving HBO can increase a number of growth factors such as bFGF (FGF), TGF-β which directly increases the activity of fibroblasts in forming the extracellular matrix of the wound so that granulation tissue is produced faster and more.[11]

Discussion

Effect of AsamHialuronat, KondroitinSulfat, DermatanSulfat, Heparin, HeparanSulfat, dandermatansulfat onwound healing

Chondroitin sulfate plays a role in regulating granulation tissue formation during wound healing.

Chondroitin sulfate has the ability to bind to growth factors such as Fibroblast Growth Factor-2 (FGF-2) so that it can help FGF-2 trigger cell proliferation, especially fibroblast cells[10].

Heparan sulfate is useful in accelerating the wound healing process by helping the process of blood clotting and cell proliferation.Heparan sulfate also functions for angiogenesis, inhibition of vascular endothelial growth factor or decreases the mitogenic activity of FGF[13].

Dermal sulfate is a large component of wound fluid and becomes dissolved.Dermatan sulfate that dissolves has the ability to activate growth factors, such as FGF-2 and FGF-7 as well as keratinocyte growth factor, thereby triggering cell proliferation.If there is a deficiency of dermatan sulfate, it will result in fragility of the wound. The minimal size of sulfate dermatan needed to trigger FGF-2 increase is octacaccharide[10].

Effect of the inflammatory process with wound healing

Inflammation is the body's attempt to respond to an injury or infection, in that timely acute inflammation is essential for restoration of tissue homeostasis. The body's response to acute inflammation can be divided into 2 phases: initiation and resolution. Initiation is characterized by the appearance of tissue edema due to increased blood flow and microvascularization permeability; processes that are mediated, in part, by lipid mediators (eg, cysteine, leukotriene and prostaglandins) and other vasoactive products (eg, histamine and bradykinin). Then polymorphonuclear neutrophils (PMN) move to the injured area to defend the tissue from invading microbes or bacteria. PMN is attracted to the site of injury by chemical signals released including proinflammatory lipid mediators (for example, leukotriene B4 and chemokines, where PMN crosses the blood vessels by interacting with endothelial adhesion receptors and then degrades pathogens in the phagolysosomes. PMN is discontinued at a rate suitable for timely apoptosis[14].

Wound repair consists of three phases: the initial inflammatory phase, the proliferative / repair phase and ends with the remodeling phase, which results in scarring. In response to tissue injury, the inflammatory cells destroy the injured tissue. The acute inflammatory response is followed by proliferation of fibroblasts, which function to synthesize collagen and the extracellular matrix. Fibroblasts can differentiate into myofibroblasts, which are responsible for collagen deposition and wound contraction, resulting in scarring due to extracellular matrix accumulation. The initial stage of inflammation is considered to be a critical period of the wound healing process, essential for cleaning contaminated bacteria and creating an environment conducive to tissue repair and repair events. The injury causes a gap, which is immediately filled with clumps of platelet aggregates. Then, during the inflammatory phase, leukocytes, such as neutrophils, monocytes, and macrophages, go to the tissue, rid of cell breakdown cytokines and damaged cell clots, and release various growth factors and cytokines.[15].

Effect of golden sea cucumber (stichopus hermanii) with fibroblast proliferation and wound healing

There are various growth factors in the extracellular matrix (ECM), including members of Transforming Growth Factor Beta (TGF-β), and Vascular Endothelial Growth Factor (VEGF).This growth factor stimulates cells and repairs wounds.Proteoglycans consist of several glycosaminoglycans that modulate the ability of heparin-binding growth factors, such as (VEGF), and Fibroblast Growth Factor (FGF).Proteoglycans regulate TGF-β activity and preparation of collagen fibrils type I and III.The release of TGF-β causes an increase in collagen synthesis.so that the wound healing process is faster and reduces the wound diameter.Ulcer diameter and expression of type 1 collagen had a strong correlation.Sulfated glycosaminoglycan (GAGs) from Stichopushermanii, has been shown to accelerate wound healing through wound contractions[8].

Giving golden sea cucumber with higher concentrations did not show good results.This is because in the 80% golden sea cucumber group, besides glycosaminoglycans, there are also triterpene glycosides which can inhibit the cycle pathway in TGFβ. In the TGFβ group, TGFβ1 plays an important role in the inflammatory process, angiogenesis, regulation of connective tissue formation, extracellular matrix remodeling and re-epithelialization processes.TGFβ also stimulates fibroblast chemotaxis, inhibits collagen and fibronectin production, inhibits collagen degradation

due to an increase or decrease in protease inhibitors. Fibroblasts and fibrocytes play an important role in the reconstruction of the extracellular matrix, by replacing old collagen type III with type I collagen and binding to collagen molecules[10].

Glycosaminoglycan, (GAG) which is the content of golden sea cucumbers, consists of two types, namely sulfate GAG and non sulfate GAG. Examples of sulfate GAG are chondroitin sulfate, dermatan sulfate, kerat sulfate, heparan sulfate, and heparin. Chondroitin sulfate and heparan sulfate have a positive effect on the wound healing process. Heparan sulfate is involved in various physiological processes, such as proliferation, migration, differentiation, and interactions between cells. Heparan sulfate is known for its substantial role in various cell interactions, and its binding with various types of proteins can place these proteins on the cell surface. Binding of cytokines with heparan sulfate can modulate the bioactivity of the cytokines themselves. Heparan sulfate binds to various types of cytokines and fibroblast growth factors. The T lymphocytes then secrete various types of cytokines, one of which is IL-2 which functions to activate macrophages by stimulating IFNγ synthesis. T lymphocytes also produce TGF-β which functions to proliferate fibroblasts. Some of the cytokinins that can bind to heparan sulfate are IL-2 and IFN-γ. A study shows that the binding of heparan sulfate with IL-2 can trigger the activation and proliferation of T lymphocytes. In addition, IFN-γ is considered the main cytokine stimulant to activate monocytes and macrophages, as a result, activated macrophages will activate lymphocytes and other cells that will cooperate in the inflammatory process until the inflammation is gone[9].

Conclusion

Golden Sea Cucumber (StichopusHermanii) contains glycosaminoglicans which consist of those that can accelerate wound healing by increasing the formation of fibroblasts through several mechanisms such as increasing tgf-b, the process of forming FGF and increasing the VEGF process can increase collagen synthesis, endothelial differentiation and epithelial differentiation, all of which play a role in the healing process of oral ulcer-induced white rats (Rattusnorvegicus).

Ethical Clearance – Not required since it is a literature review

Source of Funding – Nil

Conflict of Interest – Nil

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