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The Potential of Golden Sea Cucumber (Stichopus hermanii) in the Regeneration of Periodontal Tissues: a Literature Review

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ABSTRACT

Periodontitis is a disease in the oral cavity most commonly experienced by humans, namely inflammation characterized by damage to the supporting tissues of the teeth (gingiva, alveolar bone, periodontal ligament, and cementum). Periodontitis, if left untreated, will get worse and can lead to tooth loss. Periodontal disease can be treated with both surgical and non-surgical methods, both of which cause injury to the periodontal tissue. It is a challenge for practitioners to develop methods and materials that can accelerate periodontal tissues' regeneration, both soft and hard tissues. One of the marine biotas used as an additive in periodontal therapy is a sea cucumber. Golden sea cucumber (Stichopus hermanii) contains various bioactive components which are very beneficial for human health. The protein content in dried sea cucumbers is 82 g per 100 g, and about 80% is in the form of collagen. Collagen has function as a tissue binder in regenerating bones and skin

Keywords:stichopus hermanii, golden sea cucumber.

Introduction

Periodontitis is a widespread oral disease characterized by permanent damage to the teethsupporting tissues, which include the alveolar bone, periodontal ligament (PDL), and cementum. This ultimately resulted in the loss of teeth with severe functional and aesthetic problems for the patient, for whom bone destruction was a significant feature of periodontitis. Pathogenic microorganisms in biofilms, genetic factors, and environmental problems such as tobacco use can all contribute to periodontitis and bone loss. Loss of the supporting bone around the tooth causes movement and dislocation of the tooth, resulting in tooth loss. Various techniques have been developed to enhance the osteogenesis process, including bone grafts, scaffolds, stem cells, and growth factors. Bone can regenerate as part of the injury repair process. Bone regeneration consists of a well-regulated series of biologic induction and conduction events involving cell types and intracellular and extracellular molecular signaling pathways to optimize repair and restore function.[1,2]

Golden sea cucumber contains active ingredients and potential therapeutic properties such as triterpene glycosides, carotenoids, bioactive peptides, fatty acids, collagen, gelatin, chondroitin sulfate, vitamins, minerals, amino acids, 86.8% protein, essential fatty acids, doco hexanoic acid, a natural antiseptic, cell growth factors, chondroitin, glucosaminoglycan (GAGs), glucosamine, keratin glycosides, lectins, minerals, mucopolysaccharides, omega 3, 6, and collagen 80.0%. The active ingredient has the potential to be used for nutritional consumption or as medicine.[3,4,5,6]

This literature review discusses the benefits and effectiveness of golden sea cucumbers as a natural ingredient that can help develop periodontal tissues.

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METHODS

Data Source

Data is collected through google, and PubMed searches published from 2016-2021. Data search was performed using keywords; stichopus hermanii and golden sea cucumber

Research Criteria

A. Inclusion criteria

- Published articles from 2016-2021
- Articles are available online and published
- Articles related to the golden sea cucumber

B. Exclusion criteria

- Articles included in systematic reviews, literature reviews, and case reports.
- Inaccessible article

Data Collection

The data used in this review literature are secondary. The data was obtained from articles that are then reviewed based on the criteria made by the author.

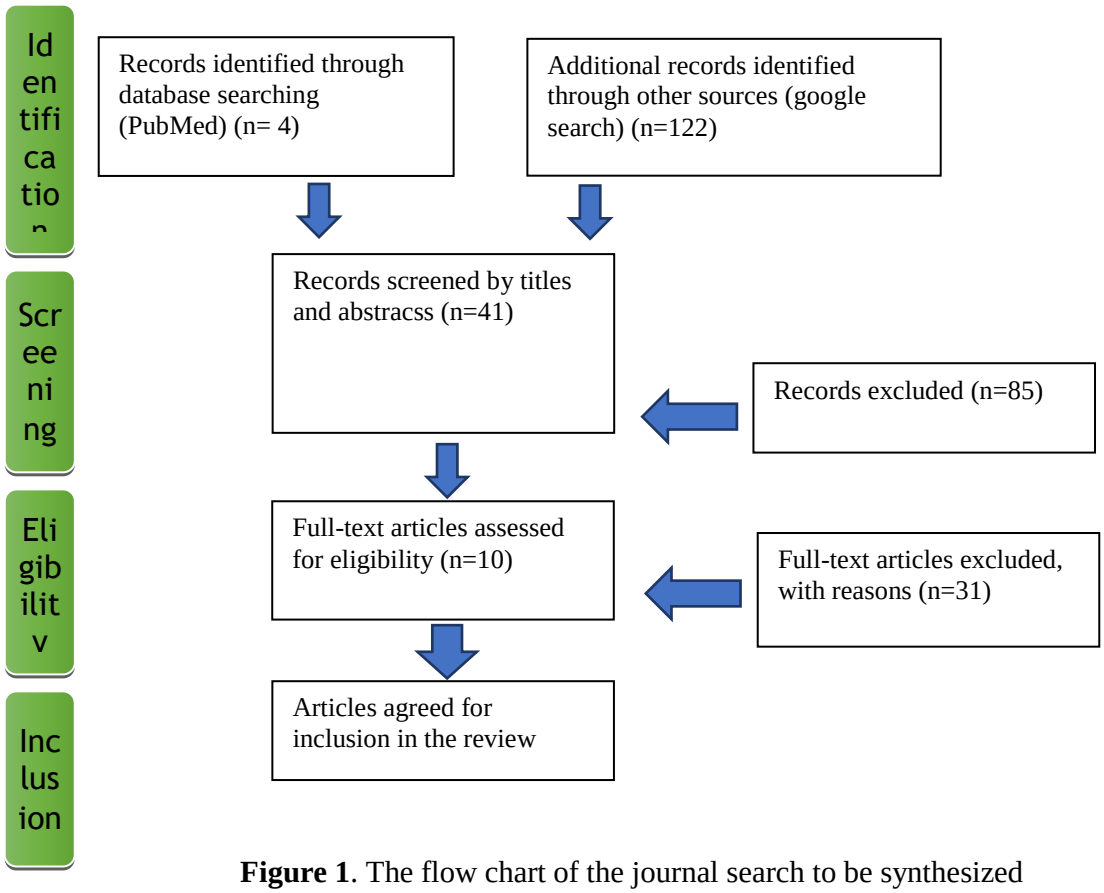

Figure 1. The flow chart of the journal search to be synthesized

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Result

After getting 126 articles on google scholar and PubMed search, 85 articles were excluded because they did not meet the criteria for the publication year that the author wanted. So, 41 articles were read in the title and abstract, after which 31 articles were excluded because they did not meet the inclusion criteria. There are ten articles that will be reviewed and entered into the synthesis table.

NO	AUTHOR	YEAR	TITLE	METHOD	CONCLUSION
1	W. Prananingrum, et al.[7]	2017	The effects of blood cockle's shell and golden sea cucumber on osteoblast-osteoclast in vivo	25 male wistar rats were divided into 5 grups. The graft material were implanted into rat femur for 14 days. Thereafter, histological analysis were performed and the number of osteoclast and osteoblast were evaluated	It was revealed from our study that the combination graft material that contain with blood cockle's shell and sea cucumber 1,6% has a good effect on the number of osteoblast and osteoc;ast in vivo
2	Wahyuningtyas and Erwan Sugianto[8]	2018	Sticopus hermanii collagen with local Hydroxiapatite as bone substitute material toward osteoclast number and toxicity	75 male of Rattus Sprague dawley, divided into 3 groups. Group I, Stichopus hermanii collagen + local HA, group II was S.hermanii collagen, Group III was collagen. Each of the subject was decapitated after 3, 7,14,28,56 days after treatment	Stichopus hermannii collagen with local hydroxyapatite as bone substitute material increase osteoclast compared with Stichopus hermanni collagen, and collagen. Stichopus hermanni collagen with local hydroxyapatite does not cause systemic toxicity
3	Dirmadana, et al.[9]	2017	Inovasi Stichopus hermanii dan TOHB dalam meningkatkan jumlah fibroblast pada ligament periodontal	30 male adult guinea pigs divided into 5 groups, negative group, positive group, S.hermanii treatment group, HBOT group and combination group. Maxillary incisor of guinea pigs was placed a helical spring in order to move the teeth to distal	Inovation of Stichopus hermanii and HBOT increased the number of fibroblast in periodontal ligament during orthodontic tooth movement
4	Rima, hansen[10]	2019	Effectiveness of anadara granosa shell-Stichopus hermanii granules at accelerating woven bone formation fourteen days after tooth	Thirty male rats were divided into five groups. Gelatin was applied as a control. Scaffold from anadara granosa shell applied to the AG group. AGSH 1-3 groups received scaffold from the combination of AG and SH shell at a concentration of 0.4%,	Bone mat formation in the control group occurred on day 14. Application of bone graft from AG showed an increase in the formation of bone webbing. The combined application of the AG-SH bone graft promotes the formation of a wider bony web. The bone graft application of the AG shell

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			extraction	0.8%, I, 6%. Fourteen days later, the subjects were sacrificed, and the RB specimen was taken and then placed in a 10% buffered formalin solution. Specimens stained with eosin hemotoxin.	did not sufficiently expand the area of bony matting. Extensive bone matting was increased through the application of the bone graft in the AGSH 1, AGSH2, AGSH 3 groups, while the most significant expansion was in the AGSH3 group (1.6%)
5	Safina, et al.[11]	2016	The effectiveness of the combination of hyperbaric oxygen therapy and golden sea cucumber gel (S.hermanii) on increasing the number of osteoblasts in DM rats induced by PG	20 Wistar rats were divided into five groups, namely K (untreated), K1 (induced by Streptozotocin + PG bacteria), K2 (induced by streptozotocin + PG bacteria + golden sea cucumber gel), K3 induced by Streptozotocin + PG + hyperbaric oxygen therapy and K4 (Streptozotocin + PG + hyperbaric oxygen therapy + golden sea cucumber gel therapy) .. on day 53 the rats were euthanized. The cervical dislocation was performed and then decapitated to be taken. Decalcification was carried out using EDTA 10%. Furthermore, HE staining was carried out and then observed using a microscope, and the number of osteoblast cells was counted, which was seen at 400 times the ratio	There was a significant difference in the number of osteoblasts in groups K with K2, K3, K4, and groups K1 with K2, K3, K4.
6	Noengki Prameswari, Arya Brahmanta, Syamsulina refianti [12]	2020	The effect of stichopus hermanii to TLR-4 in mediating periodontal ligament remodeling during orthodontic relapse	Thirty-two male guinea pigs were 2,5 months old. They were divided into four groups, namely positive control group, negative control, administration of stichopus hermanii with a concentration of 3%, and administration of stichopus hermanii with a concentration of 3.5%, the preparation in the form of a gel. Immunohistochemical	The highest decrease occurs after administration of 3,5% stichopus hermanii gel wich induces a decreased remodeling reflected in the FGF-2 and collagen site 1 exspression

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				examinations were performed to see a decrease in osteoclasts and TLR-4.	
7	Rima parwati sari et al.[13]	2017	The effect of anadara granosa shell-stichopus hermanni on bFGF exspressions and blood vessel counts in the bone defect healing process of wistar rats	Thirty-two male guinea pigs were 2,5 months old. They were divided into four groups, namely positive control group, negative control, administration of stichopus hermanii with a concentration of 3%, and administration of stichopus hermanii with a concentration of 3.5%, the preparation in the form of a gel. Immunohistochemical examinations were performed to see a decrease in osteoclasts and TLR-4. Thirty-two male guinea pigs were 2,5 months old. They were divided into four groups, namely positive control group, negative control, administration of stichopus hermanii with a concentration of 3%, and administration of stichopus hermanii with a concentration of 3.5%, the preparation in the form of a gel. Immunohistochemical examinations were performed to see a decrease in osteoclasts and TLR-4.	The combination of anadara graanosa and stichopus hermanni can increase bFGF and the number of new blood vessels on the seventh day during the bone healing process in Wistar rats.
8	Noengky[14]	2016	Osteogenesis in the area of the plant after giving golden sea cucumber nanopowder as an effort to protect orthodontic tooth relapse	This research was conducted on 24 male Cavia cobaya aged 2-3 months. Cavia cobaya was divided into three groups. (K-) without relapse and treatment), (K +) was a positive control group that was given orthodontic relapse, and group P was given orthodontic relapse and 3% gold sea cucumber nanopowder. an	The golden sea cucumber nanopowder can reduce relapse by as much as 30% in the osteogenesis process.

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				immunohistochemical examination was performed to see the expression of HSP-70, IL-17, MMP-8, Integrin α2β1, ALP, TRAP-6	
9	Rima parwati sari et al[15]	2021	The Effect of Anadara granosa Shell's-Stichopus hermanni Scaffold on CD44 and IL-10 Expression to Decrease Osteoclasts in Socket Healing	Thirty male Wistar rats were divided into five groups. We made a bone graft from a combination of AGSH extract using the freeze-dried method. Third and Seventh days post extraction, animals are killed. CD44 and IL-10 expression were examined with immunohistochemistry, as well as osteoclast was examined with hematoxylin-eosin.	Scaffold from a combination of AGSH increased CD44 expression significantly, which enhanced IL-10 expression thereby decreased the number of osteoclasts in socket healing on days 3 and 7.
10	Noengky Prameswari et al.[16]	2020	Effect of Stichopus Hermanni to Remodeling Maxillary Suture Expansionon Craniofacial Structure and Teeth	24 Male Cavia cobaya were divided into 4 groups;K(-) as the negative control group. Helical spring were applied to the other 3 groups for 10 days. K(+) was given NaCMC 2% gel, P1 and P2 were given Stichopus hermanii gel 3%	3% of Stichopus Hermanni's gel with a slow maxillary expansion showed that appliance can increase the cranial width and insisivi distance but can't increase the bizygomatic and bigonial width using cephalometric analyze

Literature Review

Golden sea cucumber (Stichopus hermanii)

Sea cucumber, also known as sea cucumber, is a soft-bodied sea animal that is elongated like a cucumber. Various species of sea cucumbers can be found in Indonesian waters, even inbreeding. Holothuridea or better known as sea cucumber or sea cucumber, is one of the Echinodermata species. Echinoderms have five classes, namely the Asteroide class (sea stars), the Ophiuroidea class (sea stars), the Echinoid class (sea urchins), the Crinoidea class (sea lilies), and the Holothuridea class (sea cucumbers). Holothuridae or sea cucumbers have three families, namely the Holothuridae (genus Actinopyga and Holothuria), Stichopodidae (genus Stichopus), and Synaptidae (genus Synapta).[17,18]

Golden sea cucumber contains various bioactive components that are very

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beneficial to human health, one of which is an antibiotic and anti-inflammatory. The protein content in dried sea cucumbers is 82 g per 100 g, and about 80% is in the form of collagen. Collagen functions as a tissue binder in bone and skin growth. Collagen is the main structural protein in bone and cartilage. Stichopus hermanii, a type of sea cucumber that is known to have many health benefits. Golden sea cucumber (S. hermanii) contains many minerals and ingredients to reduce inflammatory reactions to accelerate the bone remodeling process.[3,19,20,21,22]

Periodontal tissueregeneration

Bone tissue functions to provide support to muscles, allow movement and locomotion, provide protection for organs, accommodate bone marrow, and regulate mineral homeostasis and endocrine functions of the body, such as glucose tolerance, insulin sensitivity, and cognitive behavior. Regeneration refers to the restoration of a lost or injured part, as opposed to repair, which describes the healing of a wound by a tissue that does not fully restore the function of the part.[23,24]

The histological sequence of bone healing events begins with blood clots' formation (platelets) (0 hours), which carry many growth factors. Furthermore, the blood clot is gradually reabsorbed and replaced by immature granulation tissue (7 days), which becomes a temporary extracellular matrix characterized by the appearance of new blood vessels, infiltration of inflammatory cells, and immature connective tissue containing large amounts of fibroblasts and collagen fibers. This granulation tissue will be replaced by mature connective tissue (14 days) characterized by a reduction in inflammatory infiltrates and increased bone formation. The bone healing process is considered complete when the bone matting is visible on the visible defect on radiographs (21 days).[25,26]

Osteoblasts represent 4-6% of the total bone cell population and are mostly known for their function of forming bone, derived from mesenchymal stem cells (MSC). After engaging osteogenic cells, it differentiates into osteoblast progenitors that express the genes Runx2 (Runt-related transcription factor 2) and Col1a1 (Collagen 1a1). Pre-osteoblasts then evolve into mature osteoblasts that undergo morphological changes into large cells and are cuboidal in shape. At this stage, mature osteoblasts can undergo apoptosis or become osteocytes or bone lining cells.[23]

Osteocytes represent the final state of differentiation of osteoblasts that remain embedded in the bone matrix in lacunae. Osteocytes are critical cells for normal skeletal

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function. Play an essential role in maintaining bone homeostasis, act as mechanosensory, regulate phosphate homeostasis through secretion into circulating fibroblast growth factor 23 (FGF23), and regulate bone remodeling processes through direct regulation of osteoblast and osteoclast activity.[23]

Apart from collagen type I (85-90 wt%), osteocalcin (OC) is the next most abundant protein in the organic matrix of adult human bones and plays a significant role as a structure-directing molecule and in the regulation of osteoblast and osteoclast activity. OC is present on the surface of mineralized collagen fibrils. Investigations have revealed an association of osteocalcin with collagen type I where the binding is reversible. Inside the collagen, osteocalcin fibrils have been detected in the part of the fissure area and the adjacent overlap zone. Thus, we assume that OC mediates nucleation and growth of platelet-shaped hydroxyapatite (HAP) crystals. Osteocalcin participates in mineralization regulation because observations in osteocalcin knockout mice suggest that osteocalcin may limit bone formation.[4, 27,28]

Collagen content in sea cucumber protein is about 80% of all the protein found in the body. Including glycoproteins, collagen, glycosaminoglycans (Hyaluronic Acid, Chondroitin Sulfate, Dermatan Sulfate, Heparin, Heparin Sulfate), mucopolysaccharides, proteoglycans. Collagen functions to build bones, teeth, joints, muscles, and skin. The protein is also easily digested by the pepsin enzyme. Collagen is needed for the formation of bones, teeth, and metabolism in the body. Collagen intake will help grow mucosal tissue, gingiva, muscles, and bones, increase body immunity, and heal wounds both in soft tissue and bone tissue. This is in line with Endang Wahyuningtyas's (2018) research, which combines collagen from golden sea cucumbers with HA. Endang stated that the combination of collagen from sea cucumber and HA could increase osteoblasts in bone remodeling.[3,8]

Sea cucumber (S. cucumber) has produced various bioactive therapeutic elements such as anticancer, anti-inflammatory, and antimicrobial, which can be used as a pharmacological complex to treat bone defects. The presence of various bioactive elements such as triterpene glycosides (saponins), chondroitin sulfate, glycosaminoglycans (GAG), sulfated polysaccharides, mucopolysaccharides, glucosamine, vitamins, and minerals, especially calcium are responsible for the biomedical properties of sea cucumbers which have beneficial effects in the treatment of arthritis disorders. Previous research studies have shown that sea cucumbers are beneficial in healing inflammatory defects of muscle bones by maintaining prostaglandins' balance.[29]

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Discussion

Prananingrum, et al.[7], Noengki et al.[3] looked at the effectiveness of glycosaminoglycan (GAG) in golden sea cucumbers through osteoblast-osteoclast expression in the bone remodeling process. Many previous studies have stated that GAG, such as chondroitin sulfate and heparin sulfate, has a positive effect on the wound healing process because it can increase the number of fibroblasts.

Safina et al.[11] conducted a study on diabetes mellitus rats induced by P.gingivalis bacteria to see the effectiveness of a combination of hyperbaric oxygen therapy and golden sea cucumber gel (S.hermanii), and the results showed an increase in osteoblasts in the test group. This is in line with the results of research by Sandana et al.[30], which examined the potential of Stichopus hermanii gel and hyperbaric oxygen therapy (HBOT) in accelerating the process of tooth movement in orthodontic treatment. Chondroitin sulfate has antiosteoclastogenic and flavonoid effects that increase OPG expression, increase osteoblast differentiation, and decrease RANKL expression.

The hyaluronic acid content in sea cucumbers has a bacteriostatic and anti-inflammatory effect that plays an important role in the wound healing process. Hyaluronic acid also plays a role in osteoconductivity; in this case, it can accelerate bone regeneration by means of chemotaxis, proliferation, and differentiation of mesenchymal cells. Hyaluronic acid, together with osteogenic substances in sea cucumbers, can form bone-inducing characteristics. This is in line with research conducted by Rima et al.[10], who examined the combination therapy of golden sea cucumber and anadara granosa. They stated that the combination of HA from anadara granosa and hyaluronic acid from sea cucumbers effectively accelerates the formation of woven bones after 14 days after tooth extraction.[3,30, 31, 32, 33, 34]

Rima et al.[15] again investigated the combination of the AG-Stichopus Hermanii inhibitor through the expression of CD44 and IL-10 in reducing the number of osteoclasts in the tooth socket. Hyaluronic acid in golden sea cucumbers interacts strongly with CD44 receptors. The bond between HA and CD44 has been shown to reduce osteoclast activity after tooth extraction.

Conclusion

Golden sea cucumber is one of the marine microorganisms that have economic value and can be used as food and in the health sector. Its use in tissue engineering is also

undergoing development. Several studies have proven that the golden sea cucumber content can accelerate the regeneration of periodontal tissue, but further research is still needed regarding the potential of golden sea cucumber in combination with other ingredients.

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