Potential *Stichopus hermanii* as a gingivitis inhibitor

Potensi *Stichopus hermanii* sebagai penghambat gingivitis

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ABSTRACT

Gingivitis is a response to the buildup of bacterial plaque, characterized by symptoms such as bleeding, swelling, redness, and exudate. One of the marine biotas widely found in Indonesia is the golden sea cucumber (*Stichopus hermanii*), which contains various bioactive components such as proteins, hyaluronic acid, chondroitin sulfate, EPA, DHA, and flavonoids. This systematic review aims to reveal the potential of *Stichopus hermanii* as a gingivitis inhibitor. The method used follows a systematic review approach, adhering to the guidelines of the *preferred reporting items for systematic reviews and meta-analyses* (PRISMA). A total of 8 studies met the eligibility criteria to be included in this systematic review. It is concluded that the use of *Stichopus hermanii* has the potential to effectively reduce gingivitis.

Keywords: *Stichopus hermanii*, anti-inflammatory, and gingivitis

ABSTRAK

Gingivitis merupakan respon dari penumpukan plak bakteri yang ditandai dengan gejala-gejala seperti perdarahan, pembengkakan, kemerahan, dan eksudat. Salah satu biota laut yang banyak ditemukan di Indonesia adalah teripang emas (*Stichopus hermanii*), yang mengandung berbagai komponen bioaktif seperti protein, asam hialuronat, kondroitin sulfat, EPA, DHA, dan flavonoid. Tinjauan sistematis ini bertujuan untuk mengungkap potensi *Stichopus hermanii* sebagai penghambat gingivitis. Metode yang digunakan mengikuti pendekatan tinjauan sistematis, sesuai pedoman dari *preferred reporting items for systematic reviews and meta-analysis* (PRISMA). Sebanyak 8 penelitian memenuhi kriteria kelayakan untuk dimasukkan dalam tinjauan sistematis ini. Disimpulkan bahwa penggunaan *Stichopus hermanii* memiliki potensi secara efektif mengurangi gingivitis.

Kata kunci: *Stichopus hermanii*, anti-inflamasi, dan gingivitis
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INTRODUCTION

Dental and oral health issues are often neglected and have yet to become a primary focus for the public in addressing health problems in Indonesia. The national prevalence of dental and oral health problems in 2018 was 57.6% of the Indonesian population. Lack of dental health knowledge causes individuals to ignore these issues, leading to frequent dental and oral health problems.[1]

One commonly neglected dental and oral health issue is inflammation of the gum or gingivitis. The 2018 Basic Health Research report found that 57.6% of Indonesians had dental and oral health issues, with 14.0% experiencing swollen gums and 13.9% having bleeding gums. The causes of gingivitis are categorized into two factors: the primary factor is irritation by bacteria due to the accumulation of dental plaque, and secondary factors consist of local and systemic factors.[3] Gingivitis presents clinical symptoms such as red, swollen, and easily bleeding gums without alveolar bone damage.[2] Gingivitis is reversible but can persist and become periodontitis if untreated.[4,5]

The main bacteria causing gingivitis are gram-negative bacteria, including *Porphyromonas gingivalis*, *Tannerella forsythia*, *Treponema denticola*, *Actinomyces viscosus*, *Selemonas noxia*, *Aggregatibacter actinomycetemtemcomitans*, and gram-positive bacteria like *Streptococcus sanguinis* and *Actinomyces viscosus*.[2] Given these dental and oral health issues, preventive or therapeutic measures are necessary.

Since 2002, the Ministry of Marine Affairs and Fisheries has promoted marine biotechnology as a flagship program. Rapid advancements in marine biotechnology aim to utilize marine biota by extracting bioactive compounds for medicinal purposes. One Indonesian marine organism with significant potential for development is *Stichopus hermanii* (golden sea cucumber).[6]

S.hermanii, commonly known as the golden sea cucumber, is an echinoderm found throughout Indonesian waters, from west to east. It inhabits almost all coastal areas, from shallow waters to depths of 40 m. *S.hermanii* contains active compounds with antibacterial, anti-inflammatory, and antioxidant properties, including proteins, hyaluronic acid, chondroitin sulfate, EPA, DHA, and flavonoids. These compounds make it a potential antibacterial agent against pathogenic bacteria.[7]

Research by Susanto et al reported that *S.hermanii* exhibit anti-inflammatory and antibacterial effects against *S.mutan, S.faecalis, S.viridans, S.pneumoniae, and S.aureus.*[8]

Based on the above, this study aims to explore the potential of *S.hermanii* as a gingivitis inhibitor in the field of dental medicine.

METHODS

This systematic review employs the guidelines *preferred report-ing items for systematic reviews and meta-analyses* (PRISMA) guidelines. It is a descriptive study that utilizes a systematic review or synthesis of literature studies that are both systematic and comprehensive. The approach involves identifying, analyzing, and evaluating available data using explicit search methods that incor-

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porate critical analysis in the selection of literature (Fig.1).

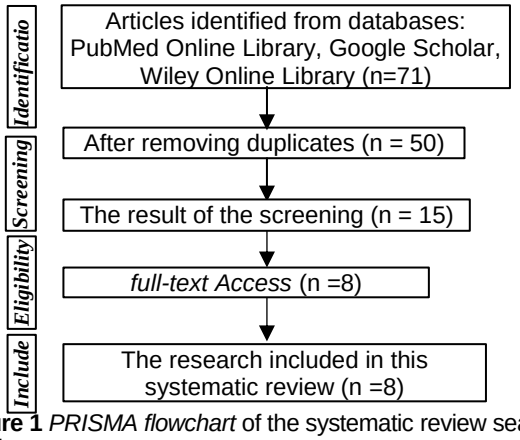

Figure 1 *PRISMA flowchart* of the systematic review search results

The literature search for this systematic review utilized three databases/search engines: Wiley Online Library, PubMed Online Library, and Google Scholar. Articles were searched using keywords and Boolean logic/operators (AND, OR, NOT) to expand or refine the search, facilitating the determination of relevant articles. The keywords for this systematic review were aligned with *medical subject headings* (MeSH). The keywords and Boolean operators used in this systematic review were: "*Stichopus hermanii*" OR "anti-inflammatory" OR "antibacterial" OR "gingivitis" OR "dentistry". Our search included all published studies without any restriction on the year of publication.

The inclusion criteria for this study are as follows: 1) scientific journals in the form of research studies, 2) journal sources from PubMed, Google Scholar, and Wiley Online Library, 3) open access scientific journals, 4) articles must be accessible in full text, 5) scientific journals in English or Indonesian, 6) the publication of the journals is 2014-2024, 7) the journal discussion must include topics on *S.hermanii* and its anti-inflammatory or antibacterial properties.

The exclusion criteria for this study are 1) articles in the form of systematic reviews, literature reviews, and case reports, and 2) inaccessible articles.

Data extraction was begun, the articles identified were independently assessed by two reviewers. All identified article titles were screened to determine the number of abstracts to be examined. In the next stage, the abstracts were screened to assess whether the content of the studies potentially aligned with the objectives of this review. A consensus was reached between the reviewers on the articles that qualified for further review. The full texts of all qualifying articles were then read, and those that did not meet the eligibility criteria were eliminated.

The analytical method applied in this systematic review is a descriptive method based on the topics specified in this study. Descriptive analysis is performed to describe the findings of the selected articles through narrative synthesis. A narrative assessment is conducted to gather data related to the potential of *S.hermanii* as a gingivitis inhibitor in of dentistry. Textual narratives will be developed regarding the potential of *S.hermanii* as a gingivitis inhibitor within a single study or across studies for the articles selected to obtain data for this systematic review.

LITERATURE REVIEW

Sea cucumbers, found in intertidal zones, encompass over a thousand species globally. They play significant ecological, health, economic, and social roles. Ecologically, sea cucumbers function as deposit feeders, aiding in the reorganization of organic matter and increasing oxygen content in sediments. They are crucial in coral reefs and related ecosystems across various trophic levels. Indonesian dried sea cucumbers are nutritionally rich, containing 62.7% protein, 1.83% lipid, 11.9% ash, 5.21% carbohydrates, 18.4% moisture, and are high in magnesium, calcium, potassium, and sodium. Additionally, they have bioactive compounds like vitamins, minerals, collagen, mucopolysaccharides, saponins, and glycosaminoglycans, which provide antioxidant, antitumor, antimicrobial, and anticoagulant benefits. The harvesting and trade of sea cucumbers significantly impact the socioeconomic lives of coastal fishermen.[9]

S.hermanii, also known as curryfish or golden sea cucumber, belongs to the genus Stichopus and was formerly known as *S.variegatus*. In Indonesia and Malaysia, *S.hermanii* has long been used in traditional medicine to produce products like gamat oil and water. This species is acknowledged by some consumers, as well as medical and biomedical researchers, for its potential health benefits. *S.hermanii* is rich in protein (47.00% ± 0.36%) and has a low lipid content (0.80% ± 0.02%).[9]

S.hermanii has a relatively large, trapezoidal cross-sectional body shape. Integument is thick and smooth, with folds on the dorsal surface that are regularly scattered with papillae on both dorsolateral sides. The dorsal side is brownish-yellow, with papillae or wart-like protrusions that are dark in color. The external body structure of the *S.hermanii* specimen is characterized by a smooth, thick, and segmented dorsal surface, separated by ambulacral lines. The dorsal side features wart-like protrusions or papillae scattered across the entire dorsal surface. On the ventral side, tube feet measuring about 0.5-1 cm are spread throughout. Other anatomical parts of *S.hermanii* include tentacles, a calcareous ring, polian vesicles, a stomach, respiratory trees, brownish-yellow intestines, and an anus. The tentacles of this sea cucumber species are shield-shaped (peltate) and have a white to yellowish color.[10]

S.hermanii is highly valued for its numerous benefits to human health. It is widely used in the cosmetics indus-

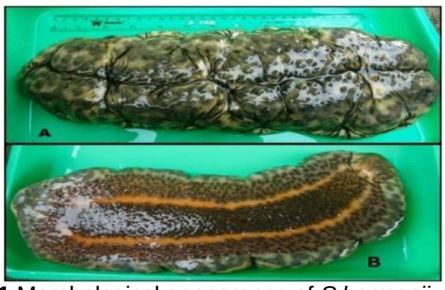

Figure 1 Morphological appearance of *S.hermanii*; **A** dorsal side, **B** ventral side.[10]

Table 1. Characteristics of the studies included in the systematic review

No	Authors/ year/ country	Research subject	Gender/ Av.Age (months)	Av.Weight (g)/ Number of subjects	Research Object	Drug Formulation/ Method	Title	Contents
1	Rosari KG, Et al (2017)[25] Indonesia	*Cavia Cobaya*	M/ 2-3	UK/24	Lebar bigonial pada remodeling ekspansi sutura maksila	Gel *S.hermanii*/ LE	Effect of Stichopus hermanni to bigonial width on maxillary suture expansion using cephalometric analysis	• *S.hermanii* is known to contain flavonoids, chondroitin sulfate, and saponins which function to inhibit inflammation, enhance bone metabolism and mineralization, and play a role in the wound healing process. • *S.hermanii* produces various variants of bioactive elements for therapy, such as anticancer, anti-inflammatory, anti-angiogenic, and antimicrobial properties.
2	Yasin JJ, et al (2019)[26] Indonesia	*Cavia Cobaya*	M/ UK	UK/30	Periodontal ligament	Gel *S.hermanii*/ LE	Innovation of HBOT and *S.hermanii* to the number of macrophages in periodontal ligaments in pressure and tension areas during orthodontic tooth movement	• *S.hermanii* contains Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which can decrease the production of inflammatory cytokines such as IL-6 and TNF-α, thus controlling bone resorption. • *S.hermanii* supports its anti-inflammatory effects by limiting the number of inflammatory cells migrating to the injured tissue.
3	Maulana F, et al (2017)[27] Indonesia	*Wistar*	M/ 3-4	150-200/ 20	DM with periodontitis	Combination of *S.hermanii* gel & HBOT/ LE	Combination administration of *S.hermanii* gel and HBOT the number of fibroblasts in diabetes mellitus rats with periodontitis	The administration of a combination of S.Hermanii gel and HBOT is effective in increasing the number of fibroblast cells.
4	Aziza LS, et al (2016)[28] Indonesia	*Wistar*	M/ 4	150-200/ 20	DM induce by *P.gingivalis*	Combination of *S.hermanii* gel & HBOT/ LE	The effect of golden sea cucumber (*S.hermanii*) and HBOT to the expression of osteoprotegerin in diabetes mellitus induce by *P.gingivalis* bacteria	• *S.hermanii* powder combined with HBOT reduces blood glucose levels in rats. • *.hermanii* powder has the potential for antioxidant and antibacterial properties.
5	Wahyuningtiyas E (2018)[29] Indonesia	*Sprague Dawley*	M/ 3	250-300/ 75	Bone substitute material	*S.hermanni* collagen's extraction/ LE	*S.hermanni* collagen with local hydroxyapatite as bone substitute material toward osteoclast number and toxicity	• After extraction, S.hermanni is found to contain 80% collagen. Collagen is obtained through separation using chloroform and methanol.
6	Reviyanti S, 2016[30] Indonesia	*Wistar*	M/ 3	175/ 30	Oral candidiasis treatment	*S.hermanii* ethanol extract/LE	The potency of *S.hermanii* extract as oral candidiasis treatment on epithelial rat tongue	• *S.hermanii* extract increases the expression of TNF-α, reducing inflammation. • *S.hermanii* extract decreases the expression of *the C.albicans* antibody.
7	Monika R.,et al (2021)[31] Indonesia	*S.mutans*	UK/ UK	UK/ UK	Antibacterial against *S.mutans*	*S.hermanii* methanol extract/LE	Potential of *S.hermanni*, Semper 1868 (Holothuroidea: Stichopodidae) Extract as producer of antibacterial compounds against *S.mutans* Clarke, 1924 (Bacilli: *Streptococcaceae*)	Methanol extract of S.hermanii demonstrates the ability to inhibit *S.mutans* bacteria, producing an inhibition zone of 5.86 mm ± 4.92 at a concentration of 80 g/disc for 24 hours. This indicates that the methanol extract of S.hermanii has antibacterial activity against *S.mutans*.
8	Arundina I et al (2015)[32] Indonesia	*Wistar*	M/ 2-4	200-300/ 20	Traumatic ulcers	*S.hermanii* extract gel/ LE	The effects of golden sea cucumber extract (*S.hermanii*) on the number of lymphocytes during the healing process of traumatic ulcer on Wistar rat's oral mucous	The use of 40% *S.hermanii* extract significantly accelerates ulcer healing by increasing the number of lymphocytes.

Total (n): 219; **Av**.: average, ***M**: Male, ***F**: Female, ***UK**: Unknown, **LE**: Laboratory experiment

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try due to its content of polysaccharides, collagen, saponins, mycosporine-like amino acids, vitamins, and minerals. This sea cucumber exhibits biological activities such as anti-aging, skin whitening, wound healing, and antibacterial properties.[9]

Beyond cosmetics, *S.hermanii* is also extensively utilized in oral health. Several studies and articles have demonstrated its effectiveness. For instance, research by Sandana et al. explored the potential of *S.hermanii* gel combined with hyperbaric oxygen therapy (HBOT) to accelerate tooth movement in orthodontic treatment. Another study by Safina et al. on rats with DM induced by *P. gingivalis* investigated the effectiveness of combining *S. hermanii* gel with HBOT, revealing an increase in osteoblasts in the test group.[9]

RESULT

The electronic search identified 71 articles. After removing duplicates, screening was conducted on 50 studies. From that phase, 15 articles were selected based on their abstracts and titles. Subsequently, further screening was done through full-text examination, resulting in 8 articles meeting the inclusion and exclusion criteria for review in this systematic review. The search results, after being filtered, analyzed, and defined in this systematic review, are briefly presented in the flowchart below.

Table 1 represents the characteristics of the articles eligible for review in this systematic review. The reviewed articles were published 2014-2024. There are 8 articles, each from the years 2019, and 2021. Additionally, there are 3 articles each from 2015, 2016, and 2017. All obtained articles originated from Indonesia and are published research results.

The subjects used in this systematic review comprise 4 studies involving wistar rats *(Rattus norvegicus*) with a total of 90 subjects, 2 studies using *Cavia cobaya* with 54 subjects, 1 study using *Sprague Dawley* rats with 75 subjects, and 1 study involving *S.mutans*.

The table presents the mechanisms of *S.hermanii* as a gingivitis inhibitor that are indicated by the following reasons; 1) anti-inflammatory properties: *S.hermanii* has demonstrated anti-inflammatory properties that can help reduce inflammation in the gingiva affected by gingivitis; 2) antibacterial potential: Compounds in *S.hermanii* may possess antibacterial effects, helping to inhibit the growth of bacteria contributing to the development of gingivitis; 3) Stimulation of healing process: Components in *S.hermanii* can stimulate the healing process of damaged gingival tissue due to gingivitis, aiding in restoring gingival health; 4) protection of gingival tissue: Utilizing *S.hermanii* as a gingivitis inhibitor can help protect gingival tissue from further damage and prevent the progression of more severe conditions; 5) as natural source, *S.hermanii* can be used as an alternative or adjunct in the treatment of gingivitis, with potential effectiveness worth further exploration in research and drug development.

DISCUSSION

Gingival inflammation is a response to the accumulation of bacterial plaque (microbial biofilm), considered a primary risk factor for the onset of periodontitis. Plaque buildup on teeth can lead to gingivitis, characterized by inflammation of the gingiva and presenting symptoms such as bleeding, swelling, redness, and exudate.[11]

S.mutans is a crucial oral bacterium that plays a pivotal role in dental plaque formation. It is the primary etiological agent of dental caries, typically residing in biofilm on the tooth surface, known as dental plaque. *S.mutans* produces an enzyme called glucosyl transferase, aiding in converting sucrose into a sticky substance called dextran, which can contribute to plaque and tartar formation on teeth, leading to gum inflammation and infection, ultimately resulting in gingivitis.[12]

Research findings on the antimicrobial properties of *S.hermanii* by Monika, et al report its activity against *S. mutans*, finding that its methanol extract can inhibit these bacteria. Research by Aziza et al, states that *S.hermanii* contains antioxidants and antibacterial properties, reports that gel made from *S.hermanii* combined with HBOT increases the expression of osteoprotegerin in rats infected with *P.gingivalis*.

Another study by Maulana et al. reports that a combination of *S.hermanii* gel and HBOT effectively increases the number of fibroblast cells. Fibroblasts play a crucial role in reducing inflammation in gingivitis by regulating the immune response to oral pathogens attacking gingival tissue. Gingival fibroblasts (GFs) are essential components of the periodontium for maintaining tissue structure and integrity and also act as immune cells producing cytokines, chemokines, and other inflammatory mediators in response to bacteria.[13]

During gingival inflammation, GFs are known to withstand apoptosis in response to oxidative stress induced by lipopolysaccharides (LPS) from periodontal pathogens. Apoptosis enables fibroblasts to continue producing anti-inflammatory factors and maintain tissue homeostasis, thereby reducing inflammation.[14]

Research by Reviyanti et al reports that *S.hermanii* can increase the expression of TNF-α, which can reduce inflammation. The use of *S.hermanIi* extract can lead to increased TNF-α expression in the tongue epithelium. TNF-α is a cytokine playing a central role in the inflammation process, released by various immune cells, including macrophages, dendritic cells, and lymphocytes, in response to infection, injury, or other inflammatory stimuli. TNF-α triggers a cascade of cellular responses leading to inflammation, including proinflammatory cytokine activation.[16,17]

Arundina et al report that *S.hermanii* can accelerate the increase in lymphocyte count, thus enhancing wound healing processes. Lymphocytes, especially T cells, play a crucial role in the inflammatory phase of wound healing and are also involved in pathogen recognition and elimination, helping to reduce inflammation.[18,19]

Rosari et al report that *S.hermanii* contains flavonoid compounds, which act as antioxidants and anti-inflammatory agents, inhibiting the inflammation process during maxillary suture expansion, enhancing bone metabolism and mineralization, and aiding in wound healing.

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Flavonoids are also found to reduce inflammation in the gingiva and periodontal diseases as they inhibit the development of gingivitis and periodontitis. Specifically, flavonoids such as eriositrin and eriodictyol, citrus flavonoids, are reported to inhibit periodontal inflammation in rats by reducing chronic and acute inflammatory cell. Additionally, flavonoids have been found to regulate the expression and activation of cytokines such as interleukin-1ß (IL-1β), a key proinflammatory factor in periodontal disease. These findings make flavonoids useful agents in the prevention and treatment of periodontal diseases.[20,21]

Yasin et al report that *S.hermanii* contains Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), omega-3 fatty acids known for their anti-inflammatory properties. This study also shows that EPA and DHA can reduce inflammatory cytokines in the body. In this research, the combination of HBOT and *S.hermanii* was found to reduce the number of macrophages in pressure and tension areas during orthodontic tooth movement, indicating a reduction in various conditions.

Research by Wahyuningtiyas et al reports that *S.hermanii* contains 80% collagen, obtained by separation using chloroform and methanol. Collagen plays a crucial role in healing gingivitis. The body's natural response to injury involves three stages: inflammation, new tissue formation, and remodeling.[22]

Golden sea cucumber collagen has high hydrophobic amino acids, so it can reduce the activity of the tyrosinase enzyme. Collagen is essential for repairing damaged tissue, as seen in bovine collagen's ability to enhance gingival healing, resulting in thicker margins around the teeth and closure of exposed roots. This collagen matrix acts as a framework for cells to repair damage and form connective tissue grafts. Furthermore, researches has shown that flavonoids reduce macrophages and tissue edema and increase fibroblast production, contributing to gingivitis and periodontitis healing.[23,24]

It is concluded that *S.hermanii* has the potential as a gingivitis inhibitor. *S.hermanii* in treating gingivitis could be an effective alternative with benefits in reducing gingival inflammation and improving overall oral health. However, further research is needed to validate these findings and to understand its mechanisms of action more deeply.

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