Potential of *Stichopus hermanni* as a scaffold material in dental tissue engineering

Potensi *Stichopus hermanni* sebagai bahan penyangga dalam rekayasa jaringan gigi

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ABSTRACT
This article evaluates *Stichopus hermanni* as a scaffold for dental tissue engineering, focusing on biocompatibility, osteogenesis, angiogenesis, and immunomodulation. A systematic literature was conducted through *PubMed/MEDLINE, Scopus, ScienceDirect, Google Scholar*, and national databases. Studies were selected using the PICOS framework, covering both in vitro and in vivo research. The results showed that *S.hermanni*-based scaffolds, either alone or in combination with hydroxyapatite or chitosan, exhibited high biocompatibility, non-toxicity, increased osteogenic markers (CD44, IL-10, osteocalcin, bFGF), angiogenesis, and woven bone formation. This scaffold also reduced osteoclast activity through immunomodulatory effects. It was concluded that *S.hermanni* has strong potential as a biomaterial scaffold in dental tissue engineering, supporting the safe and effective regeneration of hard and soft tissues.
Keywords: *Stichopus hermanni*, scaffold, dental tissue engineering, bone regeneration.

ABSTRAK
Artikel ini mengevaluasi *Stichopus hermanni* sebagai *scaffold* untuk rekayasa jaringan gigi, dengan fokus pada biokompatibilitas, osteogenesis, angiogenesis, dan imunomodulasi. Dilakukan pencarian pustaka secara sistematis dilakukan melalui *PubMed/MEDLINE, Scopus, ScienceDirect, Google Scholar*, dan basis data nasional. Studi dipilih menggunakan kerangka PICOS, mencakup penelitian *in vitro* dan *in vivo*. Hasilnya *scaffold* berbasis *S.hermanni*, baik sendiri maupun dikombinasi dengan hidroksiapatit atau kitosan, menunjukkan biokompatibilitas tinggi, non toksik, peningkatan *marker* osteogenik (CD44, IL-10, osteokalsin, bFGF), angiogenesis, dan pembentukan tulang anyaman. *Scaffold* ini juga menurunkan aktivitas osteoklas melalui efek imunomodulasi. Disimpulkan bahwa *S.hermanni* berpotensi kuat sebagai biomaterial *scaffold* dalam rekayasa jaringan gigi, mendukung regenerasi jaringan keras dan lunak dengan aman dan efektif.
Kata kunci: *Stichopus hermanni*, *scaffold,* rekayasa jaringan gigi, regenerasi tulang
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INTRODUCTION

Damage to dental tissues from caries, trauma, or periodontal disease remains a challenge, with current treatments relying mainly on synthetic materials. Tissue engineering offers scaffolds as temporary frameworks for cell attachment, nutrient supply, and tissue formation. For dental use, scaffolds must be biocompatible, biodegradable, porous, and support bone and soft tissue repair.[1] Natural materials, like the golden sea cucumber (*Stichopus hermanni*), are promising due to their collagen, glycosaminoglycans, and bioactive compounds that promote healing, collagen synthesis, and tissue repair. Marine collagen is highly biocompatible, water retentive, and less allergenic than terrestrial collagen.[2-4]

Figure 1 *S.hermanni* (Mohsen M, Yang Hongsheng. Stichopus. In: Agricultural and Biological Sciences, ScienceDirect Topics. Elsevier. 2021)[5]

Recent studies highlight *S.hermanni* for oral tissue repair. In animal models, scaffolds combining *Anadara granosa* shell and *S.hermanni* enhanced post extraction bone healing by increasing healing markers and reducing osteoclast activity.[6,7] *S.hermanni* nanoparticle gel also promoted oral mucosal repair by increasing fibroblasts, neovascularization, and early collagen deposition. These results suggest that *S.hermanni* functions both as a structural scaffold and a bioactive agent, supporting healing in dental applications involving hard tissues (bone, dentin) and soft tissues (periodontium, mucosa).[7] Although *S.hermanni* shows promise as a dental scaffold, variations in collagen extraction and limited animal-based studies leave human data scarce. Comparisons with other materials like bovine collagen, chitosan, or synthetic polymers are rare.[1] A systematic review is needed to evaluate its full potential, clarify safety and efficacy, and guide future research for clinical applications in dental tissue engineering.

METHODS

Data sources

A systematic literature search was performed in *PubMed/MEDLINE, Scopus, ScienceDirect, Google Scholar*, and Indonesian databases (Garuda, Neliti). Keywords included *Stichopus hermanni*, sea cucumber, teripang emas, scaffold, bone graft, tissue engineering, dental, alveolar, collagen, glycosaminoglycan, and bioactive compounds, with additional terms like bone regeneration, osteogenesis, biocompatibility, and wound healing. Boolean operators were applied as appropriate to capture all relevant studies.

Inclusion followed the PICOS framework. Studies involved cells, tissues, or animal models in dental or bone tissue engineering. Interventions used *S.hermanni* extracts or bioactive compounds, alone or with other bio-

materials, as scaffolds or grafts. Comparators were scaffolds without *S.hermanni*. Outcomes included Biocompatibility, cell proliferation, osteogenic markers, osteoconconductivity, bone formation, tissue healing, and scaffold properties. Only full text English or Indonesian articles were included.

Excluded studies were those not involving *S.hermanni* or focused on other sea cucumber species, as well as research unrelated to biocompatibility, osteogenesis, osteoconductivity, or bone regeneration. Reviews, editorials, commentaries, case reports, conference abstracts without full data, and articles not in English or Indonesian or unavailable in full text were also omitted.

Study quality assessment

Methodological quality and risk of bias were assessed using established tools. In vitro studies used the Modified JBI Checklist, evaluating clarity, methodology, controls, replicability, and reporting. In vivo studies applied SYRCLE's Risk of Bias Tool, examining randomization, allocation concealment, blinding, data completeness, selective reporting, and outcome validity.

RESULTS

The search retrieved 194 articles, with 140 remaining after duplicate removal. Screening titles and abstracts excluded 103 studies, and 37 full text articles were assessed for eligibility. Thirty-one were excluded due to limited access, review type, or incomplete data, leaving 6 studies that met all inclusion criteria for this systematic review.

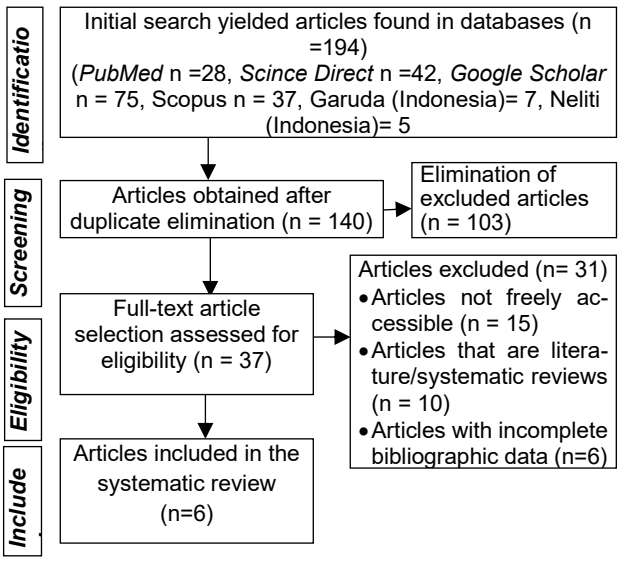

Figure 2 Flowchart of article selection

Study characteristics

Six studies using in vivo animal models, some with in vitro fibroblast assays, evaluated *S.hermanni* based scaffolds collagen, glycosaminoglycans, or combined with hydroxyapatite (HA) or HA chitosan. Applied to tooth extraction sockets or long bone defects, they assessed osteogenic markers (CD44, IL-10, osteocalcin, bFGF), osteoblast/osteoclast activity, angiogenesis, new bone formation, and scaffold properties including biocompatibility, toxicity, and osteoconductivity.

Before data synthesis, all studies were assessed for methodological quality to ensure validity and reliability. In vitro studies used the Modified JBI Checklist, while in vivo studies were evaluated with SYRCLE's Risk of Bias Tool according to their design.

Table 2 Results of the Modified Joanna Briggs Institute checklist

No	Title	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
1	Wahyuningtyas et al. (2019)	+	+	+	+	+	+	+	?	+	+

D1 : Were the research objectives clearly stated?
D2 : Was the sample preparation clearly described?
D3 : Was the experimental procedure well-defined and replicable?
D4 : Were the experimental conditions (e.g., media, temperature, time) clearly stated?
D5 : Were appropriate controls used?
D6 : Were outcomes measured in a valid and reliable way?
D7 : Was statistical analysis appropriate?
D8 : Were the results clearly presented?
D9 : Was there any conflict of interest or funding bias disclosed?
D10 : Were conclusions supported by results?

Judgement
Yes = low risk of bias
No = high risk of bias
? = unclear risk of bias

According to the Modified JBI Checklist results (Table 1), the in vitro study by Wahyuningtyas et al. (2019) demonstrated good methodological quality, with nearly all domains fulfilled except for one unclear aspect concerning the blinding procedure of outcome assessors.

SYRCLE's Risk of Bias assessment (Table 2) indicated that most in vivo studies had low risk of bias, with random allocation, group balance, and outcome reporting generally met. Some had one *unclear* domain, mainly involving blinding or subjective assessments, but overall methodological validity was considered adequate. Overall, most included studies showed strong methodological quality, providing a reliable basis for interpretation. High quality studies are key references for assessing *S.hermanni* as a dental scaffold, while others still contribute valuable insights despite certain limitations.

DISCUSSION

Overview of study findings

All six studies evaluated *S.hermanni* bioactive compounds for bone regeneration using scaffolds or grafts in post extraction sockets and femoral defects. Collagen, glycosaminoglycans, and hyaluronic acid alone or with HA/chitosan enhanced osteogenesis, angiogenesis, and bone formation, modulated resorption, and were biocompatible and non-toxic in animal models.[3,8-12]

Biocompatibility of *S.hermanni* based scaffold

S.hermanni based scaffolds are biocompatible and non-toxic, as shown in vitro and in vivo. Studies reported maintained fibroblast viability, enhanced osteoblast proliferation, absence of tissue rejection, and stable systemic biochemical parameters, confirming *S.hermanni* as a safe marine biomaterial for intraoral scaffold applications.[3,8-12]

Osteogenic effects and bone regeneration

S.hermanni scaffolds consistently enhance osteogenesis. Studies reported accelerated woven bone formation, increased osteoblast numbers, and elevated osteogenic markers such as osteocalcin, ALP, calcium, phos-

Table 3. Results of the SYRCLE's risk of bias tool for in vivo animal studies

No	Title	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
1	Sari, et al. (2021)	+	+	+	+	+	+	+	?	+	+
2	Sari & Kurniawan (2019)	+	+	+	+	+	+	?	+	+	+
3	Safira et al. (2023)	+	+	+	+	+	+	?	+	+	+
4	Adam et al. (2022)	+	+	+	+	+	+	+	+	?	+
5	Sari RP et al. (2017)	+	+	+	+	+	+	+	?	+	+

Selection bias: D1 : Sequence generation
D2 : Baseline characteristics balance
D3 : Allocation concealment
Performance bias: D4 : Random housing
D5 : Blinding of caregivers/investigators
Detection bias: D6 : Random outcome assessment
D7 : Blinding of outcome assessor
Attrition bias: D8 : Incomplete outcome data
Reporting bias: D9 : Selective outcome reporting
Other biases: D10 : Other sources of bias

Judgement
Yes = low risk of bias
No = high risk of bias
? = unclear risk of bias

Table 3. Journal synthesis[3,8-12]

Author (Year)	Study Title	Study Design/Subjects	Intervention/ Bioactive Compound	Outcome Measures	Main Results
Sari RP et al. (2021)	The effect of anadara granosa shell's–*S.hermanni* scaffold on CD44 and IL-10 expression to decrease osteoclasts in socket healing	In vivo Male Wistar rats	Scaffold combination of Anadara granosa HA+ collagen & GAG from *S. hermanni*	CD44, IL-10 expression, osteoclast count	Increased CD44 and IL-10 expression, decreased osteoclast number, accelerated socket healing
Sari & Kurniawan (2019)	Effectiveness of Anadara granosa shell–*S.hermanni* granules at accelerating woven bone formation fourteen days after tooth extraction	In vivo Male Wistar rats	Granules of Anadara granosa + *S. hermanni* (0.4%, 0.8%, 1.6%)	Woven bone area (histology)	Granules accelerated woven bone formation; 0.8% concentration most effective on day 14 post extraction
Wahyuningtyas et al. (2019)	Application of a promising bone graft substitute in bone tissue regeneration: characterization, biocompatibility, and in vivo animal study	In vitro (fibroblast MTT assay) & In vivo (rat femur defect) Sprague-Dawley rats	Biocomposite of local HA + *S.hermanni* collagen (65:35)	Fibroblast viability, osteoblast count, histology	Non toxic, biocompatible biocomposite, enhanced osteoblast numbers and supported bone regeneration better than control
Safira et al. (2023)	HA–chitosan composites derived from sea cucumbers and shrimp shells ameliorate femoral bone defects in an albino rat model	In vivo Male albino rats	HA from sea cucumber + chitosan from shrimp shell	Cytokines (IL-4, IL-6, IL-10, TNF-α),PMN, liver enzymes(ALP,AST, ALT, GGT), Ca, phosphate,PINP	HA–Ch decreased IL-6 & PMN, increased ALP, Ca, phosphate, and PINP; accelerated femoral bone defect healing
Adam M, et al. (2022)	Stimulation of Osteoblast and Osteocalcin in the Bone Regeneration by Giving Bonegraft Golden Sea Cucumber	In vivo Male guinea pigs	Collagen + GAG *S. hermanni* based bone graft	Osteoblast count (histology),osteoteocalcin expression immunohistochemistry)	*S.hermanni* based bone graft increased osteoblast and osteocalcin compared to controls
Sari RP et al (2017)	The effects of Anadara gra-nosa shell–S.hermanni on bFGF expressions and blood vessel counts in the bone defect healing pro-cess of Wistar rats	In vivo Male Wistar rats	Scaffold of Anadara granosa shell + *S. hermanni*	bFGF expression (immunohistochemistry), blood vessel count (HE histology)	Combination significantly increased bFGF expression and blood vessel count, enhancing angiogenesis and bone healing

phate, and PINP. These findings confirm that *S.hermanni* bioactive compounds effectively stimulate bone formation and support dental tissue regeneration.[3,8-12]

Role of angiogenesis in bone healing

S.hermanni scaffolds promote angiogenesis, a key process for bone healing. Studies showed increased bFGF expression and blood vessel formation in animal models, accelerating tissue regeneration. These findings indicate that *S.hermanni* not only enhances osteogenesis but also provides the vascular support necessary for effective dental tissue engineering.[3,8-12]

Immunomodulation and bone remodeling

S.hermanni scaffolds modulate the immune response to support bone regeneration. Studies showed increased CD44 and IL-10, reduced osteoclast activity, and decreased IL-6 levels, creating a microenvironment favorable for new bone formation. This immunomodulatory effect accelerates alveolar healing by promoting the shift from inflammation to tissue regeneration.[3,8-12]

Quality and limitations of evidence

The included studies were mostly high-quality in vivo experiments with some in vitro support. While randodomization and outcome reporting were adequate, blinding was often unclear. Limitations include small sample sizes, short follow up (≤42 days), and lack of human clinical trials, restricting conclusions on long term safety and efficacy of *S.hermanni* scaffolds.[3,8-12]

Clinical implications and future research

S.hermanni is a promising scaffold for dental tissue engineering, enhancing alveolar bone regeneration, especially when combined with HA or chitosan. Future research should standardize dose and composition, compare directly with conventional scaffolds, and advance to human clinical trials to confirm safety, efficacy, and clinical applicability in regenerative dentistry.[3,8-12]

It is concluded that *S.hermanni* shows significant potential as a scaffold for dental tissue engineering, supporting alveolar bone regeneration through osteogenesis, angiogenesis, and immunomodulation. Its bioactive compounds are biocompatible and safe in animal models. However, evidence remains preclinical, highlighting the need for larger, long term studies and human trials before clinical use.

Future studies should prioritize standardized preclinical testing, comprehensive physicochemical scaffold characterization, and head to head comparisons with benchmark scaffolds. Human clinical trials are essential to establish the scaffold's efficacy, safety, and potential clinical use in regenerative dentistry.

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