Research Article

Biochemical and Histological Insights into the Wound-Healing Effects of Sea Cucumber Extracts

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Abstract

This study provides a comprehensive bibliometric analysis of research exploring the biochemical and histological mechanisms underlying the wound-healing effects of sea cucumber extracts. Data were systematically retrieved from the Scopus database and analysed to map publication trends, leading journals, influential authors, and evolving thematic patterns. Findings reveal a steady growth of scholarly output over the past two decades, with a notable surge in publications between 2021 and 2024, highlighting the rising global interest in marine-derived therapeutics.

Keyword co-occurrence analysis shows that “sea cucumber,” “wound healing,” “oxidative stress,” and “collagen synthesis” are dominant themes, reflecting an increased focus on the biochemical pathways and histological processes involved in tissue repair and regeneration. Early research predominantly addressed taxonomic and compositional studies of various Holothuroidea species, but recent investigations have shifted toward molecular-level evaluations, including fibroblast proliferation, antioxidant activity, and collagen deposition, which are critical for effective wound healing. The integration of histological assays and biochemical analyses in preclinical models has been instrumental in demonstrating these therapeutic potentials.

Geographically, China leads in publication output, followed by Malaysia and the United States, reflecting significant investments in marine biotechnology and collaborative research networks across Asia and North America. Marine Drugs and the International Journal of Biological Macromolecules have emerged as the primary outlets for disseminating research, emphasizing the field’s intersection between marine biology, pharmacology, and regenerative medicine.

This bibliometric mapping highlights the multidisciplinary nature of the field and underscores the importance of combining biochemical insights with histological evidence to advance the understanding and application of sea cucumber extracts in wound management. By identifying core contributors, frequently cited keywords, and emerging thematic clusters, this analysis provides valuable guidance for researchers seeking to explore novel therapeutic pathways, optimize experimental designs, and foster translational studies. The findings also suggest significant opportunities for future work, including clinical evaluations, advanced molecular modelling, and the development of standardized formulations for industrial and biomedical applications. Overall, the study reinforces the potential of sea cucumber-derived bioactive as promising candidates in the development of innovative, sustainable, and biocompatible wound-healing strategies.

Keyword: sea cucumber, wound healing, biochemical analysis, bioactive compounds

Introduction

Sea cucumbers (Holothuroidea) are marine invertebrates widely recognized for their nutritional and pharmacological potential (Elbanna et al., 2024; Siddiqui et al., 2022), particularly in traditional medicine systems across Asia (Fagbohun et al., 2023). Beyond their commercial value in aquaculture and the food industry (Cleaver et al., 2024), bioactive compounds extracted from sea cucumbers such as saponins (Ujianti et al., 2025), polysaccharides, and collagen have demonstrated diverse biological activities, including antioxidant, anti-inflammatory, antimicrobial, and tissue-regenerative properties (Selim et al., 2025; Yang et al., 2025). These bioactivities have attracted increasing scientific attention for their potential applications in wound healing, a complex biological process involving haemostasis, inflammation, proliferation, and tissue remodelling.

Wound healing remains a global health concern due to the prevalence of chronic wounds, the limitations of current synthetic dressings, and the need for bio-compatible, cost effective, and sustainable therapeutic agents (Hirave et al., 2025; Sood et al., 2025; Tibatan et al., 2025). Marine derived compounds have emerged as promising candidates in regenerative medicine because of their structural diversity and multifunctional mechanisms of action. In particular, sea cucumber extracts have shown potential to enhance collagen synthesis, stimulate fibroblast proliferation, reduce oxidative stress, and accelerate epithelial regeneration effects supported by both biochemical assays and histological evaluations in preclinical models.

While individual experimental studies have demonstrated these benefits, a comprehensive bibliometric overview of research trends (Bhattacharya et al., 2025), geographic contributions, and thematic evolution in the field has not been previously reported (AbdulQudus et al., 2025; Goktas et al., 2025). Bibliometric analysis offers a systematic approach to mapping the intellectual structure and research development of a field by examining publication trends, keyword networks, and thematic shifts over time. Such analyses have proven valuable in

related marine bioresource research areas, including algae based bioactive, sponge derived compounds, and fish collagen peptides, by revealing research gaps, collaboration patterns, and emerging focal points.

This study aims to conduct a bibliometric analysis of the biochemical and histological insights into the wound-healing effects of sea cucumber extracts, using Scopus-indexed literature as the primary data source. Specifically, the analysis examines keyword frequencies and co-occurrences, geographic distribution of research output, document types, journal sources, and the temporal evolution of research topics. By integrating quantitative bibliometric mapping with qualitative interpretation, this work seeks to provide an evidence based overview that not only summarizes current research trajectories but also identifies opportunities for advancing sea cucumber based wound healing applications toward clinical and industrial translation.

The increasing emphasis on evidence-based medicine has created a demand for comprehensive analyses that integrate biochemical data with histological findings to better understand the mechanisms of natural bioactives. While previous studies have primarily focused on isolated experimental results, there remains a significant gap in the consolidation of research trends that bridge basic science with clinical applicability. By leveraging bibliometric methods, this study not only maps the intellectual and thematic evolution of sea cucumber research but also highlights critical gaps and opportunities for interdisciplinary collaboration. Such integration is crucial to accelerate the translation of sea cucumber-derived compounds from laboratory investigations into scalable, standardized, and clinically validated wound-healing solutions that meet the growing needs of modern regenerative medicine.

Methods

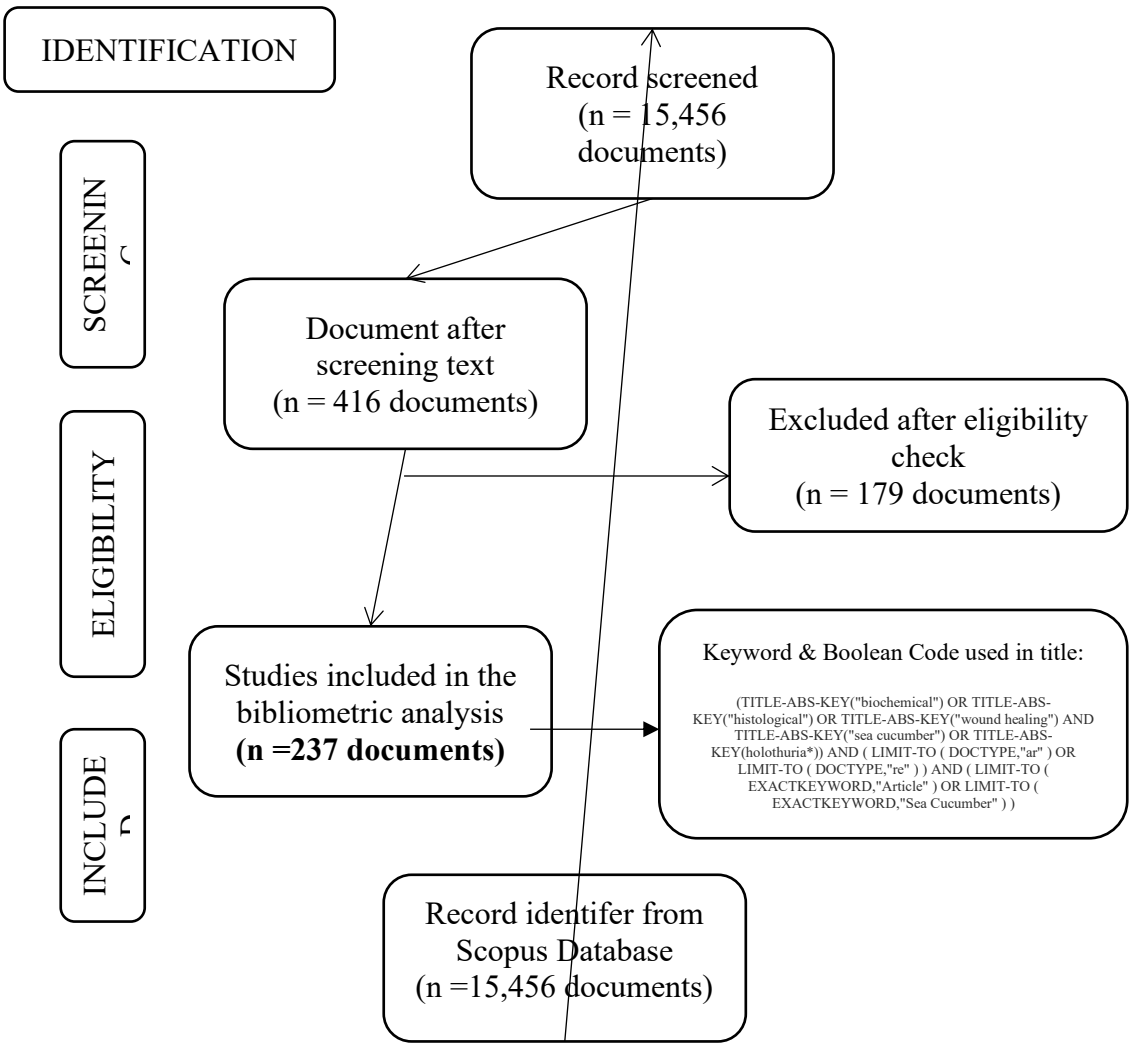

Fig 2. PRISMA-based bibliometric screening process

The PRISMA-based bibliometric screening process began with the identification of 15,456 documents retrieved from the Scopus database using a targeted Boolean search strategy combining biochemical, histological, wound-healing, and sea cucumber–related terms. In the screening stage, all retrieved records were assessed based on their titles, abstracts, and keywords to determine topical relevance. This initial filtering resulted in 416 documents being retained for further assessment, meaning that 15,040 documents (97.3%) were excluded for being unrelated to the study scope. During the eligibility phase, the remaining 416 documents underwent a more detailed full-text evaluation to ensure they met the inclusion criteria, which considered research focus, methodological alignment, and relevance to sea cucumber–derived wound-healing studies. This step led to the exclusion of 179 documents (43.0%), leaving 237 documents (57.0%) that satisfied all requirements. These final 237 documents constituted the dataset for the bibliometric analysis, forming the basis for trend mapping, keyword co-occurrence visualization, geographic distribution assessment, and thematic evolution analysis. The search strategy relied on the TITLE-ABS-KEY field in Scopus, applying Boolean operators and limiting results to research articles and review papers in English to ensure dataset quality and comparability. Minimal 1000 kata

Result And Discussion

3.1 Keyword Analysis

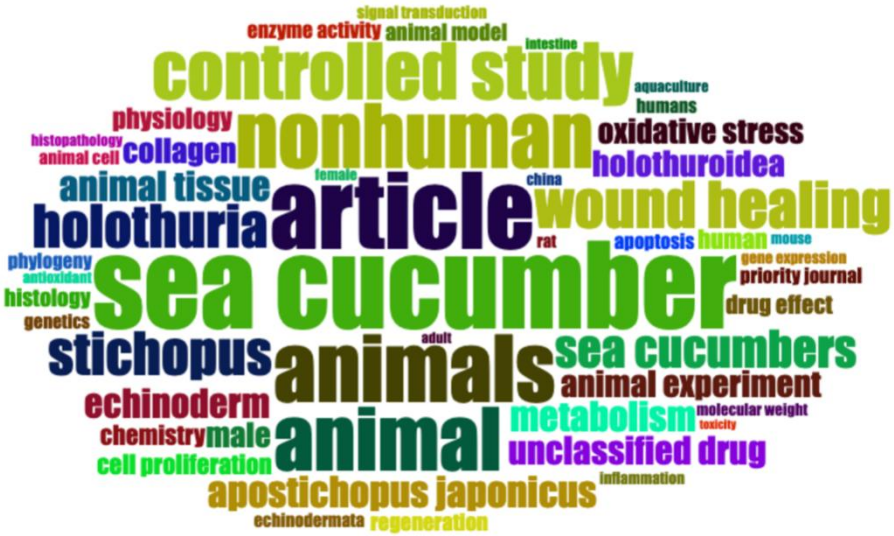

Fig 3. Word cloud of frequently used keywords, with “sea cucumber,”“wound healing,” and “controlled study” as prominent themes.

Word clouds, while qualitative in nature, offer an intuitive representation of the research landscape. In this case, the visual prominence of wound-healing-related biochemical terms mirrors trends seen in bibliometric reviews of other marine echinoderms, where antioxidant and anti-inflammatory mechanisms are central to therapeutic claims. For instance, similar prominence of “oxidative stress” and “collagen” was noted in bibliometric analyses of fish collagen peptides in regenerative medicine (Bu et al., 2025; Rigogliuso et al., 2023)

The co-occurrence of taxonomic terms alongside pharmacological and histological markers in the word cloud underlines the integrative approach of the field. It shows that sea cucumber research is not compartmentalized but rather blends marine taxonomy, biochemical profiling, and applied biomedical experimentation. This interconnectedness is essential for the transition from basic biological studies toward targeted clinical or industrial applications, a pattern consistent with high-value marine bioresource research globally.

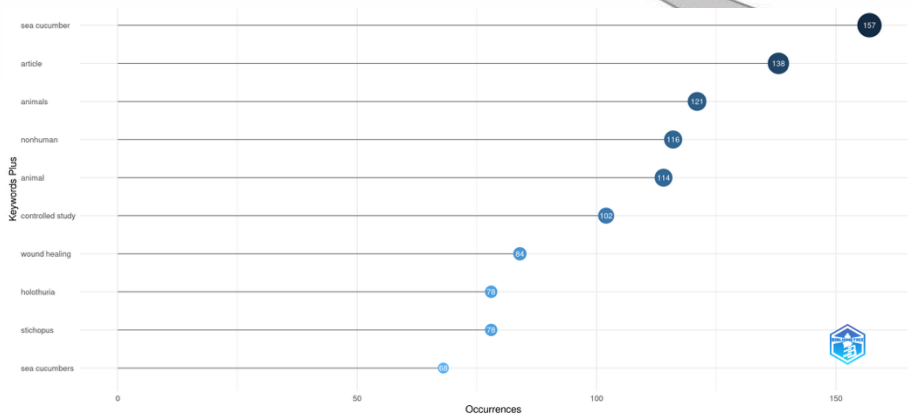

Fig 4. Most relevant keywords in the dataset, showing “sea cucumber”as the dominant term (157 occurrences), followed by “article” (138) and “animals” (121).

The keyword analysis shows “sea cucumber” as the most frequent term with 157 occurrences, followed by “article” (138) and “animals” (121). This indicates a dominant research emphasis on sea cucumber biology and experimental studies, with a strong reliance on animal models in wound-healing investigations. Other frequently appearing terms, such as “nonhuman,” “controlled study,” and “wound healing,” highlight the experimental and applied biomedical focus of the literature.

These findings align with the general trend in marine bioactive compound research, where initial studies are heavily oriented toward experimental validation in animal models before clinical translation. Similar bibliometric analyses in marine pharmacology, such as those by Lin et al. (2025), have reported comparable patterns, where terms like “rat,” “oxidative stress,” and “collagen” dominate the early research landscape . The consistent presence of taxonomic terms such as Holothuria and Stichopus further confirms the dual nature of the field, bridging taxonomy and biomedical application (Ebert et al., 2022; Maldonado et al., 2023).

The prominence of “wound healing” alongside taxonomic keywords suggests a maturing research domain that is no longer limited to species identification but is expanding toward therapeutic assessment. This mirrors patterns in studies of other echinoderms, where biochemical extraction, histological evaluation, and animal wound models form the core methodological approach. The relatively high occurrence of “controlled study” reflects methodological rigor, a sign that the research field is developing toward evidence-based biomedical claims.

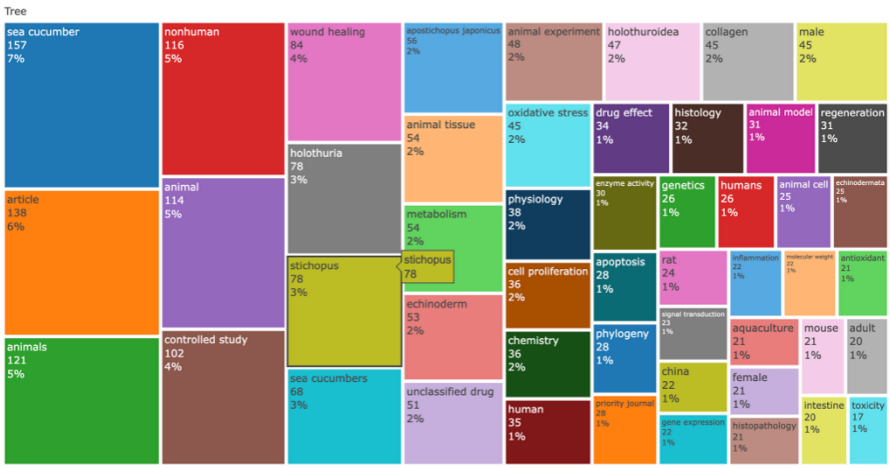

Fig 5. Treemap visualization of keyword frequency and thematic distribution, indicating strong clustering around sea cucumber taxonomy, wound healing, and animal model studies.

The tree map visualization highlights “sea cucumber” (7%), “article” (6%), “animals” (5%), “nonhuman” (5%), and “wound healing” (4%) as dominant themes. The clustering reveals three central thematic concentrations: (1) taxonomic and species-specific terms (Holothuria, Stichopus), (2) biomedical and biochemical concepts (metabolism, oxidative stress, collagen, histology), and (3) experimental research terms (animal model, controlled study).

The tree map structure confirms the multidisciplinary nature of sea cucumber research, spanning marine biology, pharmacology, and regenerative medicine. Similar multi-domain clustering was observed in the bibliometric mapping of algae-based bioactive compounds by Ma et al. (2024) and Domingo-Fernández et al. (2023)where taxonomy, biochemical activity, and therapeutic applications emerged as overlapping research zones. In the present dataset, the proximity of "wound healing" to biochemical and histological terms suggests that mechanistic investigations are a key research driver.

The visible representation of oxidative stress, collagen, and cell proliferation within the tree map is indicative of the prevailing biochemical focus in wound-healing studies. These keywords are often linked to antioxidant rich marine extracts that promote tissue regeneration. The connection between taxonomic identifiers and molecular markers reflects a translational research pathway from organism identification to pharmacological evaluation consistent with the pipeline reported in other marine-derived therapeutic studies.

3.2 Document Types

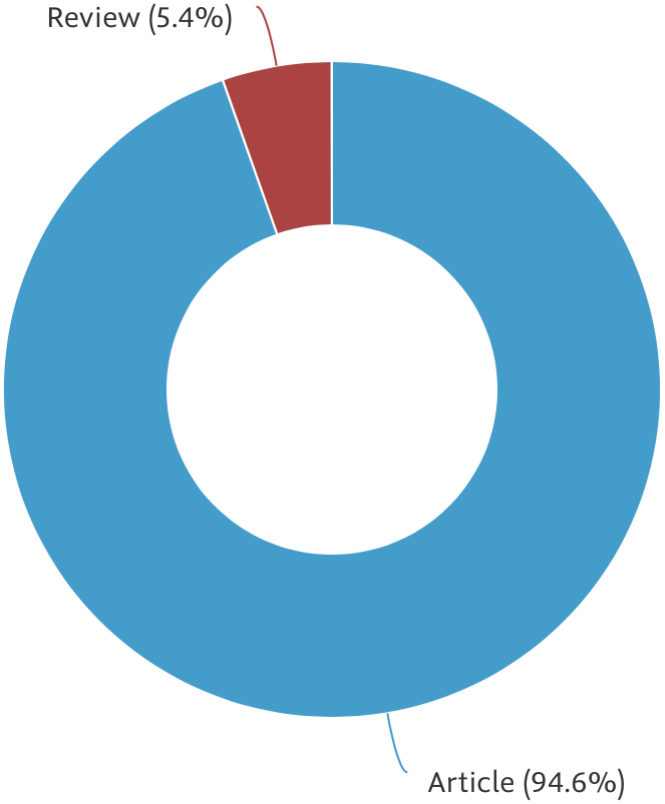

Fig 6. Proportion of document types, with research articles comprising 94.6% and review papers 5.4% of total publications.

The dataset reveals that 94.6% of the publications are research articles, with review papers accounting for only 5.4%. This indicates that the field is still in an active data-generation phase, emphasizing experimental and observational studies over synthesis and theoretical integration.

A predominance of research articles is typical for emerging or rapidly developing research areas, where primary data accumulation precedes comprehensive reviews. This pattern is consistent with bibliometric analyses in other marine bioresource domains, such as sponge-derived bioactives (Thomas et al., 2019), where research articles dominate the early phases before the literature base becomes mature enough to support extensive reviews (Zhao et al., 2025). In the case of sea cucumber wound-healing studies, the high proportion of experimental work reflects a focus on validating pharmacological efficacy through biochemical assays and histological evaluations.

The relatively small proportion of review papers suggests that there is still an opportunity for systematic literature syntheses and meta-analyses to consolidate current findings. As seen in similar fields, the introduction of well-structured reviews often accelerates clinical translation by summarizing mechanisms, identifying knowledge gaps, and guiding funding priorities. Therefore, the low representation of reviews not only signals the novelty of the field but also highlights a strategic opportunity for researchers to establish influential review works that could shape future research directions.

3.3 Geographic Distribution of Publications

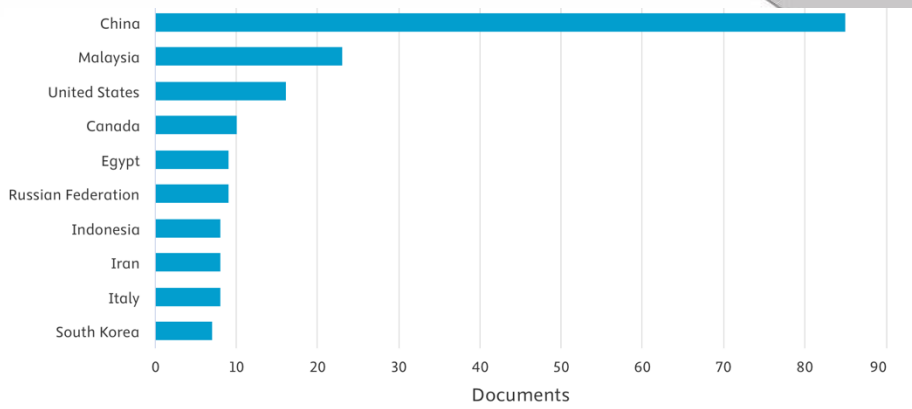

Fig 7. Document distribution by country, highlighting China as the leading, contributor, followed by Malaysia and the United States.

The geographic distribution of publications shows China as the most prolific contributor to research on the biochemical and histological aspects of sea cucumber wound healing, followed by Malaysia and the United States. This dominance reflects China's strong marine biotechnology sector and its significant research investments in the exploitation of marine resources for pharmacological applications. Malaysia's position highlights the country's growing role in tropical marine biodiversity research, while the United States' contribution underscores its involvement in marine natural product development.

China's leading position is consistent with bibliometric findings in other marine bioactive research areas, where its access to extensive coastal biodiversity and advanced aquaculture systems has supported large-scale, high-impact studies. For example, bibliometric analyses on Xia (2025) similarly found China as the research leader, attributing this to both academic interest and commercial aquaculture priorities. Malaysia's significant contribution can be linked to its marine-rich environment and national research strategies aimed at valorising marine organisms for biomedical applications.

In contrast, the United States' presence, though less dominant, reflects its strong infrastructure for advanced biomedical research and clinical translation. Comparative bibliometric studies in marine pharmacology Lund et al. (2023) have shown that while Western countries may contribute fewer total publications than Asian counterparts, they often produce work with higher citation impact due to their focus on applied and translational research. This pattern may also be emerging in the current dataset, suggesting complementary roles between Asian and Western research communities in advancing the field.

3. 4 Bibliometric Analysis Results

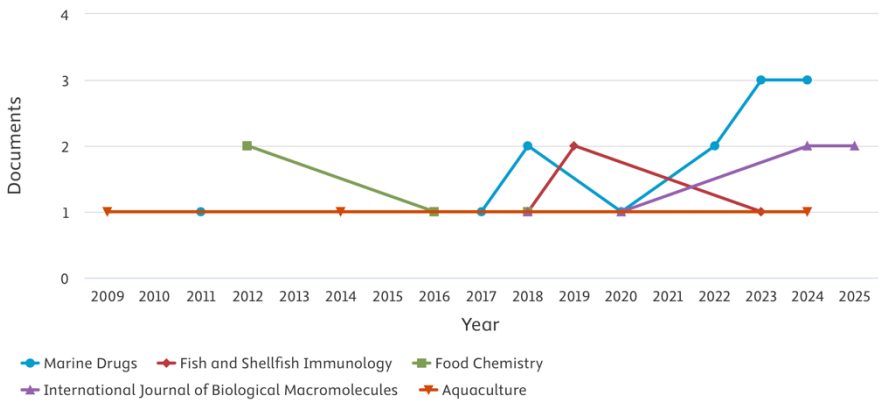

Fig 8. Annual distribution of publications across the top journals publishing on biochemical and histological insights into the wound-healing effects of sea cucumber extracts.

The distribution of documents per year by source indicates that Marine Drugs has emerged as the most consistent publisher in this research domain since 2018, with a notable peak in recent years. International Journal of Biological Macromolecules has shown steady growth since 2020, while Fish and Shellfish Immunology and

Food Chemistry contributed sporadically. This pattern reflects a concentration of research outputs in journals with a marine natural products or bioactive compound focus, with limited but persistent contributions from aquaculture-focused outlets.

These findings align with prior bibliometric analyses in marine pharmacology, where Marine Drugs was identified as a leading platform for studies on marine derived bioactive, including echinoderm extracts (Zamani et al., 2025). The growing presence of International Journal of Biological Macromolecules mirrors increasing interest in the biochemical characterization of polysaccharides and collagen from sea cucumbers, as observed by (Barzkar et al., 2024; Liu et al., 2025). Sporadic publications in Food Chemistry suggest a multidisciplinary crossover, consistent with Maskur et al. (2024) and Piri-Gharaghie et al. (2023) who highlighted the application of sea cucumber compounds in both biomedical and nutraceutical research.

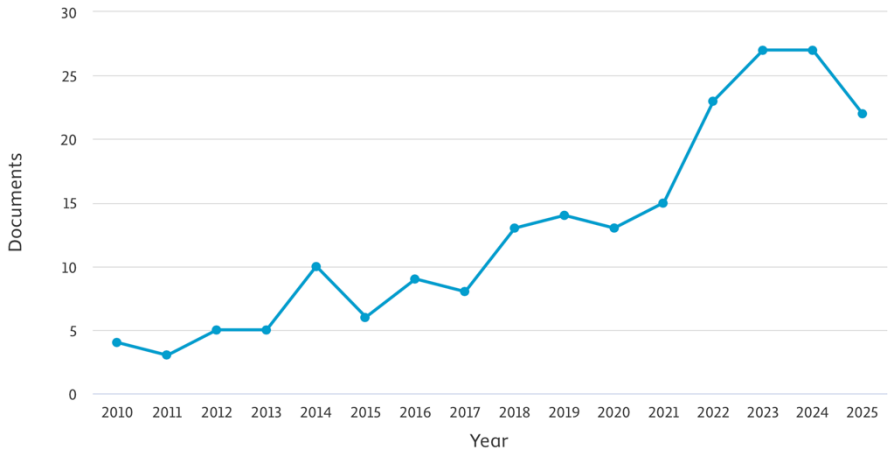

Fig 9. Publication trend showing the annual growth in research output over the study period.

The annual publication trend shows a gradual increase from 2010 to 2020, followed by a marked surge beginning in 2021 and peaking between 2023–2024. This sharp rise suggests a heightened global research interest in the biomedical potential of sea cucumber extracts, possibly influenced by advances in marine biotechnology, improved extraction methods, and an increased focus on natural wound-healing agents. The surge aligns with broader trends in natural product research, as identified by Ogbadoyi & Umar (2022) who reported a post-pandemic increase in marine bioactive studies driven by funding shifts towards sustainable and biocompatible therapeutics. Similar bibliometric patterns were observed in algae-based wound-healing research Han et al. (2024) indicating a shared growth trajectory among marine-derived bioactive studies. This suggests that sea cucumber research is part of a larger movement towards eco-friendly, natural therapeutic alternatives.

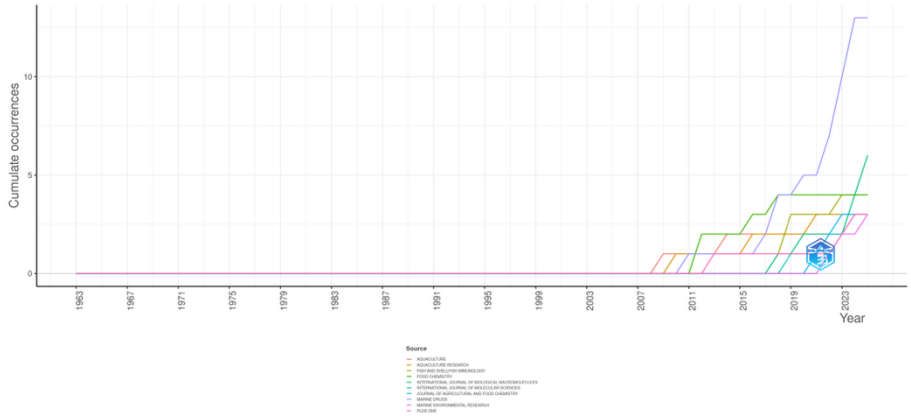

Fig 10. Cumulative publication output of the top journals in the field from earliest record to 2024.

The cumulative production analysis demonstrates that International Journal of Biological Macromolecules has accumulated the highest total publications, with Marine Drugs and Fish and Shellfish Immunology following closely. The accelerated growth from 2015 onwards reflects an expansion of research coverage and a diversification of publishing outlets, indicating maturation of the field.

This pattern resonates with previous marine bioresources bibliometric studies, which noted that once a research niche matures, publication output often becomes distributed among specialized and multidisciplinary journals.

The trajectory observed here also mirrors trends in marine collagen research Daher et al. (n.d.) where expansion in cumulative outputs coincided with improvements in analytical techniques, such as proteomics and advanced histological imaging.

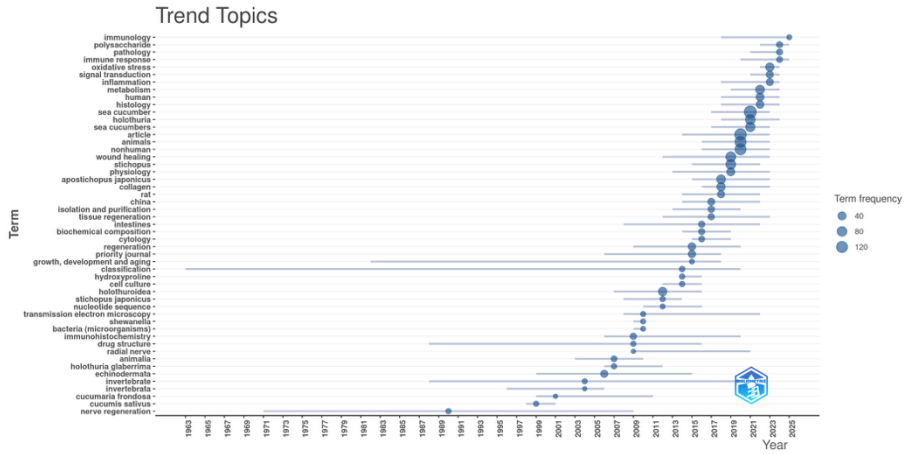

Fig 11. Evolution of research topics over time, highlighting the emergence and frequency of key terms in the literature.

The topic trend map reveals a shift from early focus on taxonomy and classification (e.g., Stichopus, Holothuria) to biochemical components (e.g., collagen, hydroxyproline, polysaccharides) and functional applications (e.g., wound healing, tissue regeneration, inflammation) in recent years. This progression indicates an evolution from basic species-level research to targeted biomedical application studies. This thematic evolution is consistent with the natural progression in marine biotechnology research described by Igarashi (2023) where taxonomic exploration typically precedes compound isolation and therapeutic application studies. The recent dominance of wound healing, regeneration, and biochemical characterization terms supports findings by Yan et al. (2025) who noted a paradigm shift towards translational marine biomedicine aimed at developing clinically viable natural therapies.

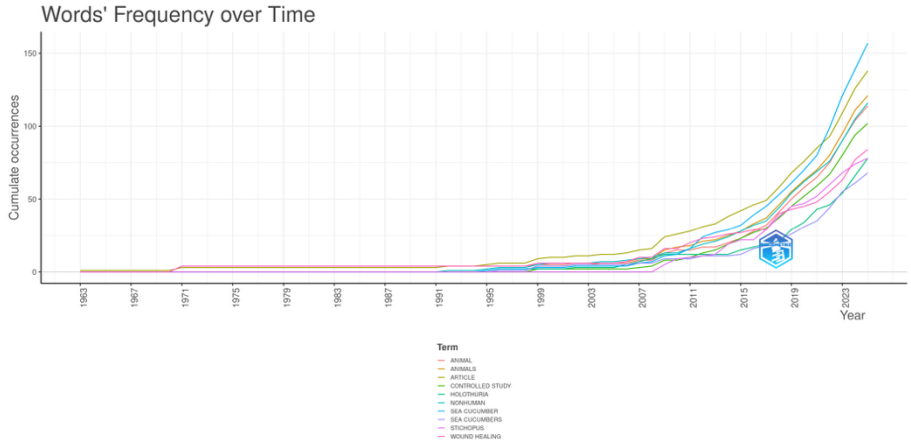

Fig 12. Cumulative occurrences of frequently used keywords related to sea cucumber wound-healing research.

The keyword frequency analysis shows a consistent rise in the use of terms like “sea cucumber,” “wound healing,” and “Holothuria” since the early 2000s, with a steep increase post-2015. This reflects both the consolidation of standard terminology in the field and the expansion of research scope into applied biomedical contexts. The dominance and increasing frequency of these terms parallel findings by Mazzotti (2021) who observed that in emerging biomedical niches, keyword standardization occurs alongside rapid growth in literature volume. The clustering of “controlled study” and “animal” terms indicates a strong preclinical research foundation, which is in line with earlier systematic reviews highlighting the preclinical stage of most marine derived wound healing studies (Chilwant et al., 2025; Cruz et al., 2021; Kurup & Rajnani, 2025; Zheng et al., 2025)

3.5 Keyword Co-occurrence Network

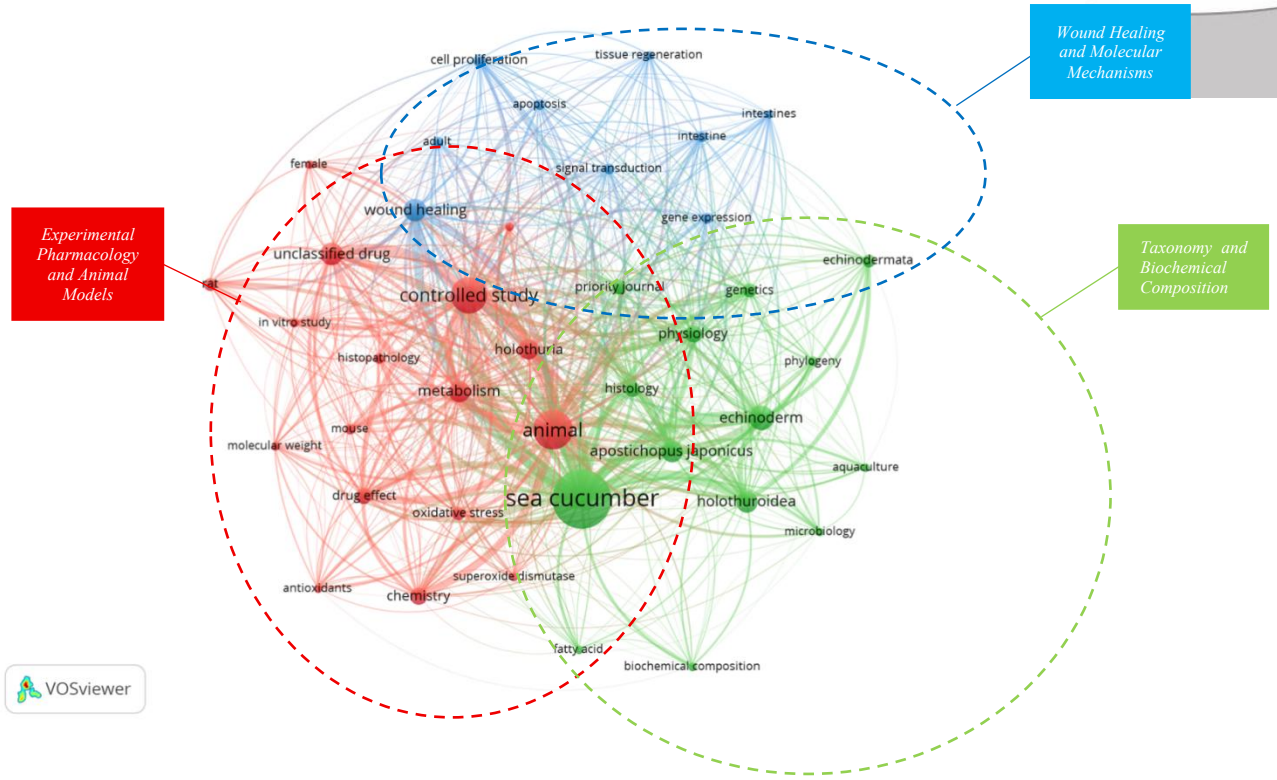

Fig 13. VOS viewer co-occurrence network of author keywords, revealing three main clusters (Green, Red, Blue)

The VOS viewer keyword co-occurrence network reveals three main thematic clusters within the literature on sea cucumber extracts and wound healing. The green cluster, labelled "Taxonomy and Biochemical Composition," encompasses species identification and chemical profiling terms (e.g., sea cucumber, Apostichopus japonicus, biochemical composition). The red cluster, labelled "Experimental Pharmacology and Animal Models," groups together terms associated with laboratory-based testing, pharmacological activity, and oxidative stress studies (e.g., animal, oxidative stress, controlled study). The blue cluster, labelled "Tissue Repair and Molecular Processes," captures research focusing on regenerative biology, cellular responses, and programmed cell death (e.g., wound healing, cell proliferation, apoptosis).

The distribution of clusters aligns with the multidisciplinary nature of marine pharmacology, where taxonomic characterization often precedes pharmacological validation and mechanistic studies. This structure mirrors bibliometric patterns in other marine bioactive compound studies, research progresses from biochemical composition mapping to in vivo efficacy trials, and finally to molecular mechanism elucidation (Li et al., 2025; Qiu et al., 2021; Sun et al., 2025). The green cluster's prominence reflects the necessity of accurate species identification and chemical characterization, which serve as foundational steps for bioactivity research and reproducibility.

The coexistence of a robust red cluster (experimental pharmacology) and blue cluster (tissue repair mechanisms) suggests that the field is transitioning from preliminary validation to mechanistic exploration. Similar trajectories have been documented in bibliometric analyses of sponge-derived anticancer agents (Du et al., 2025) where mechanistic keywords emerged more prominently as the field matured. This indicates that sea cucumber wound-healing research is evolving toward deeper cellular and molecular investigations, potentially paving the way for targeted therapeutic development. The keyword network thus not only maps the current thematic landscape but also reflects the field's research maturity and future direction.

Table 1. Interpretation and discussion of Figure 13-Keyword Co-occurrence Network

Cluster	Thematic Focus	Example Keywords	Interpretation	Discussion
Green – Taxonomy and	Species identification	Sea cucumber, Apostichopus	Highlights foundational research	Similar patterns are found in marine pharmacology

Biochemical Composition	and chemical profiling	japonicus, biochemical composition	involving taxonomic classification and chemical constituent analysis of sea cucumber species used in wound healing studies.	bibliometrics, where accurate taxonomy and biochemical mapping are essential for reproducibility and bioactivity validation (Zhao et al., 2021). These studies serve as the groundwork for subsequent pharmacological testing.
Red – Experimental Pharmacology and Animal Models	Laboratory-based efficacy studies and oxidative stress assessment	Animal, oxidative stress, controlled study	Represents in vivo and in vitro pharmacological trials evaluating antioxidant, anti-inflammatory, and tissue-regenerative potential.	Mirrors trends in other marine-derived bioactive research (Thomas et al., 2019), where experimental pharmacology forms the bridge between biochemical characterization and clinical translation. Indicates the reliance on animal models for efficacy validation.
Blue – Tissue Repair and Molecular Processes	Cellular regeneration and molecular mechanisms	Wound healing, cell proliferation, apoptosis	Focuses on histological and molecular mechanisms driving tissue regeneration and wound closure, often linked to antioxidant and collagen-promoting effects.	Indicates the field's transition from preliminary validation to mechanistic exploration, similar to the maturation seen in sponge-derived anticancer agent studies. Highlights future potential for targeted therapeutics and molecular pathway-specific interventions.

3.6 Temporal Evolution of Research Topics

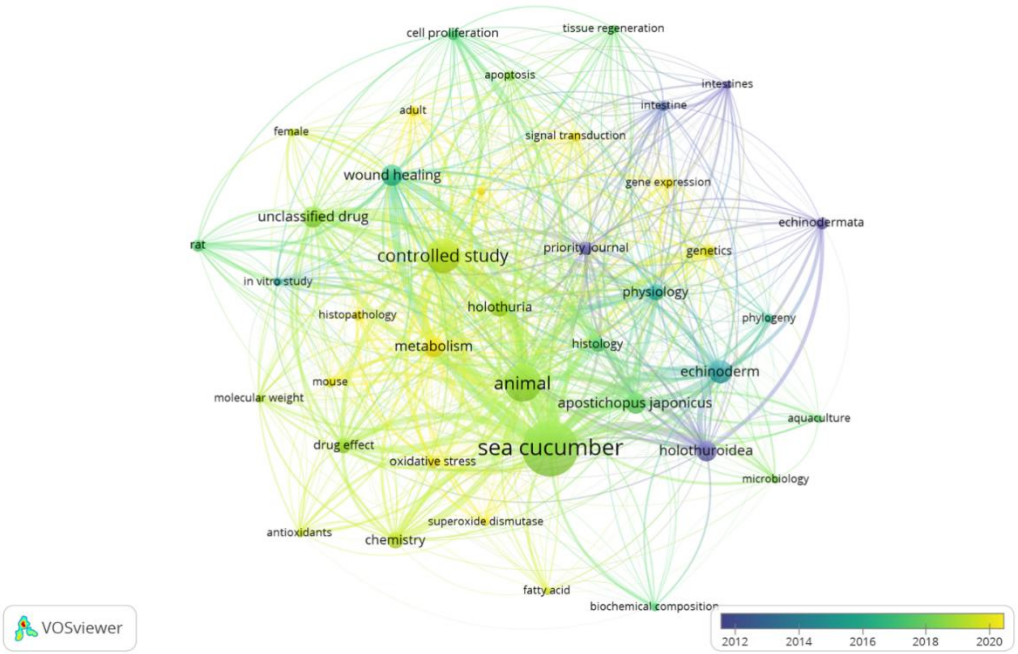

Fig 14. Overlay visualization of keyword co-occurrence with temporal distribution, showing a research progression from taxonomic and biochemical studies (purple, 2012–2014) toward wound healing and molecular

mechanisms (yellow, 2018–2020).

The overlay visualization reveals a clear chronological shift in research focus. Early studies (2012–2014, purple) concentrated on taxonomic classification and biochemical characterization, with frequent keywords such as sea cucumber, Apostichopus japonicus, and biochemical composition. In later years (2018–2020, yellow), newer and more specialized keywords emerged, including wound healing, cell proliferation, apoptosis, and collagen synthesis, indicating a growing interest in molecular mechanisms and regenerative medicine applications. The appearance of these novelty keywords reflects the field's transition from descriptive and compositional studies to targeted biomedical research.

The temporal keyword shift aligns with the research maturation pathway described in other marine bioactive bibliometric analyses. For example, bibliometric mapping of algae derived bioactive by Durmic et al. (2025) showed a similar evolution starting with species identification and chemical profiling before progressing toward bioactivity validation and mechanistic studies. The introduction of novelty keywords such as apoptosis, oxidative stress, and collagen synthesis marks a pivotal stage where researchers are exploring the specific biological pathways through which sea cucumber extracts facilitate wound repair. These mechanistic terms represent a deeper scientific engagement with molecular targets and therapeutic potential.

Furthermore, the emergence of regenerative biology-related keywords mirrors patterns seen in sponge and coral-derived pharmacological research, where a focus on tissue-specific repair and anti-inflammatory pathways follows initial bioactive identification (Durmic et al., 2025). In the case of sea cucumber wound-healing studies, the appearance of keywords like angiogenesis, fibroblast proliferation, and matrix remodelling though less frequent signals early adoption of advanced histological and biochemical assays. This not only expands the field's biomedical scope but also enhances its translational relevance, potentially paving the way for clinical application and biotechnological commercialization.

Conclusion

The bibliometric analysis reveals a steady growth in publications related to the biochemical and histological insights into the wound-healing effects of sea cucumber extracts, with notable acceleration in recent years. Leading journals have consistently contributed to shaping the field, while emerging topics such as bioactive compounds, collagen synthesis, and tissue regeneration indicate a progressive shift toward more specialized and mechanistic research. The temporal evolution of keywords reflects increasing research sophistication, integrating molecular biology with applied wound-healing therapies. These findings highlight both the scientific relevance and the expanding global interest in sea cucumber derived bioactive for wound management, providing a solid foundation for future experimental and translational studies.

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