



Omics-based insights into skin ulcerative disease in sea cucumbers: a systematic review

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Abstract

Skin ulcerative disease (SUD) in sea cucumbers poses a significant threat to marine biodiversity, aquaculture sustainability, and ecosystem health. Characterized by localized lesions that can progress to extensive tissue necrosis, SUD arises from complex interactions involving microbial infections, environmental stressors, and impaired host immunity. Advances in omics technologies have greatly advanced our understanding of SUD pathogenesis. Genomics has revealed genetic determinants of susceptibility, resistance, and host pathogen interactions, while transcriptomics has provided insights into dynamic gene expression changes in immune signaling and stress response pathways. Proteomics has identified protein networks involved in inflammation, tissue remodeling, and antioxidant defenses, whereas metabolomics has uncovered metabolic shifts linked to oxidative stress, lipid remodeling, and energy imbalance. The integration of these approaches has highlighted potential biomarkers, predictive signatures, and therapeutic targets, with promising interventions such as bacteriophage therapy and IgY-based treatments. This review synthesizes current omics-driven insights and underscores the importance of multi-omics integration for advancing effective disease management strategies and enhancing aquaculture resilience.

Keywords Omics · Skin ulcerative disease (SUD) · Sea cucumbers · Biomarkers

Introduction

Marine invertebrates, including corals, molluscs, echinoderms, and sponges, play essential roles in maintaining marine ecosystem function. However, skin ulcerative disease (SUD) in sea cucumbers has emerged as a growing concern in marine biology and ecology due to its detrimental effects on both individual organisms and entire ecosystems [1]. SUD typically manifests as skin lesions or ulcers that can progress to tissue necrosis, with multiple

environmental, biological, and biochemical factors contributing to disease onset and progression. These factors often increase susceptibility to secondary infections and, in severe cases, lead to mortality. Since marine ecosystems rely on invertebrates such as corals, molluscs, crustaceans, and echinoderms for nutrient cycling, habitat structure, and biodiversity, the increasing prevalence of SUD poses a significant ecological and conservation challenge [3].

Multiple factors, including complex interactions among infections, environmental stressors, and host immune responses, contribute to the development of cutaneous ulcerative disorders in sea cucumbers. Anthropogenic influences such as pollution, habitat degradation, and climate change further exacerbate these conditions by increasing the susceptibility of marine organisms to damage and infection [4]. Additionally, the role of microbial communities including bacteria, fungi, and viruses in disease onset and progression has become an emerging area of interest [5]. Together, these factors underscore the urgent need to elucidate the molecular and cellular mechanisms underlying SUD to inform the development of effective mitigation strategies.

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Recent advances in omics technologies including genomics, transcriptomics, proteomics, and metabolomics have transformed the study of disease mechanisms in sea cucumbers. By examining genomic, proteomic, and metabolic responses, these high-throughput approaches provide deeper insights into the molecular basis of disease in marine invertebrates [6]. RNA sequencing has revealed dynamic changes in gene expression during the progression of SUD in *Apostichopus japonicus* [7]. Differential expression patterns linked to immune responses, oxidative stress, and apoptosis offer critical insights into how sea cucumbers cope with or succumb to ulcerative conditions when challenged by pathogens such as *Vibrio splendidus* [8]. Proteomic analysis further uncovered significant molecular responses to oxidative stress in sea cucumber-derived polydeoxyribonucleotide (AJS-PDRN), extracted from the sperm of *A. japonicus*. AJS-PDRN demonstrated strong antioxidant activity, effectively scavenging DPPH, ABTS, and hydroxyl radicals, and provided cytoprotective effects in H₂O₂-induced oxidative injury models using RAW264.7 cells. iTRAQ-based proteomic profiling, supported by GO and KEGG pathway analyses, showed that AJS-PDRN mediates its protective effects by regulating immune and inflammatory responses, modulating extracellular matrix organization and signal transduction, promoting membrane repair, and enhancing cellular antioxidant defenses. Protein-protein interaction (PPI) network analysis further revealed that upregulation of intracellular selenoprotein family members plays a central role in reducing oxidative damage. Collectively, these findings highlight the multifaceted antioxidant mechanisms of AJS-PDRN and underscore its therapeutic potential in managing oxidative stress-related disorders [9].

Despite these advancements, several knowledge gaps remain. While many studies focus on specific aspects of the disease such as pathogen identification or immune response pathways the application of omics data to unravel the complex, multifactorial nature of SUD is still in its early stages. Developing targeted treatment strategies will require a clearer understanding of the dynamic interactions among pathogens, host organisms, and environmental stressors. Furthermore, although omics holds great potential for improving disease management and early detection, its application to sea cucumber conservation strategies remains underexplored [11].

This systematic review provides an in-depth examination of SUD in marine invertebrates, with a particular focus on the role of omics technologies in uncovering the molecular and biological mechanisms underlying these conditions. Covering studies published between January 2015 and February 2025, it synthesizes current findings from genomics, transcriptomics, proteomics, and metabolomics, highlighting key discoveries related to the progression of SUD in

sea cucumbers. The review explores how these organisms respond to pathogens, environmental stressors, and immune challenges, emphasizing the contributions of omics data to the identification of biomarkers, pathways, and potential therapeutic targets. It also identifies critical research gaps and proposes future directions for advancing knowledge and management strategies. Ultimately, this review seeks to support efforts to mitigate the impact of SUD on marine ecosystems and biodiversity, offering valuable insights for researchers, conservationists, and stakeholders engaged in addressing these challenges.

Materials and methods

Data sources and search strategy

This systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [12]. Primary articles were retrieved from established scientific databases, including ScienceDirect, Scopus, PubMed, and Web of Science, covering the period from January 2015 to February 2025. The search strategy employed the following keywords: “skin ulcerative diseases,” “sea cucumbers,” “omics data,” “genomics,” “transcriptomics,” “proteomics,” and “metabolomics.” Search results were restricted to articles published in English, and studies published prior to 2015 were excluded. Titles and abstracts of the retrieved articles were exported into Microsoft Excel (Version 2410, Build 16.0.18129.20100) for initial screening. Duplicate records were removed, and full-text articles were subsequently retrieved for detailed evaluation based on availability.

Study selection and data extraction

Article entries were initially screened based on their titles and abstracts. Only those containing keywords such as “skin ulcerative disease,” “sea cucumbers,” and “omics data” were retained. Studies focusing on non-marine species or not addressing SUD in sea cucumbers were excluded. The remaining entries were further filtered to ensure they specifically examined sea cucumber species. Before full-text assessment, these entries were individually reviewed for eligibility using predetermined selection criteria. Any disputes or inconsistencies during the screening process were resolved through consensus. Additional exclusions were applied to entries for which full texts were unavailable, as well as to review articles and non-English publications [13].

Study characteristic

Studies included in this review were selected based on pre-defined criteria to ensure relevance and quality. Eligible studies were those that involved sea cucumber samples experimentally challenged with *Vibrio* species for omics analyses, or samples of DNA, RNA, or protein obtained from diseased individuals. To qualify, studies had to include clear methods for disease characterization and quantification, as well as the application of Next-Generation Sequencing (NGS) targeting the V3, V4, or combined V3-V4 regions of the 16 S rRNA gene. In addition, only studies that employed omics approaches providing meaningful insights into immune responses, stress-related mechanisms, or metabolic alterations were considered, as these contribute to a deeper understanding of disease pathophysiology. Finally, sea cucumbers included in the studies were required to have been either experimentally challenged with *Vibrio* or collected from aquaculture farms experiencing disease outbreaks.

Studies that focused on host pathogen interactions and explored potential therapeutic strategies, such as phage therapy and IgY antibodies, were also considered relevant. In contrast, studies that did not directly address the pathogenesis or molecular mechanisms of SUD in marine invertebrates such as those examining environmental contaminants, region-specific outbreak reports, or unrelated topics were excluded from this review.

Quality assessment

The Mixed Methods Assessment Tool (MMAT) was applied to evaluate the quality of the included studies [14]. Each study was assessed against the MMAT criteria, which covered: (1) the appropriateness of the research question, (2) the adequacy of data collection methods, (3) the relevance of the sampling strategy, (4) the validity of the measurements or instruments used, and (5) the appropriateness of data analysis techniques. The final appraisal score for each study was determined by the lowest score assigned to any of the assessed components. The quality assessment outcomes were summarized and presented in narrative form within Tables 1 and 2.

Results

Literature search for skin ulcerative diseases in marine invertebrates using omics data

A total of 496 articles were identified through the combined database search. Following the removal of duplicates

($n=334$), non-aquatic-based studies ($n=74$) were excluded. The remaining 88 articles focusing on sea cucumbers were further screened based on their titles and abstracts, resulting in 23 full-text articles being assessed for eligibility. Ultimately, 23 studies met the inclusion criteria and were incorporated into this systematic review (Fig. 1).

Overall, the 23 non-randomized studies included in this review were rated as high quality, with appraisal scores ranging from 66% to 96%. However, certain methodological criteria related to interventions or exposures were not applicable to the objectives of this review and were therefore designated as not applicable (NA).

Omics approaches in understanding skin ulcerative disease (SUD)

Omics insights into SUD: bridging the gap to multi-omics integration

The rising prevalence of SUD across different sea cucumber species poses a serious threat to marine biodiversity and ecosystem health [1]. SUDs are typically characterized by localized lesions or ulcerations that progress to tissue necrosis, with mortality often resulting from a combination of microbial infections, environmental stressors, and impaired immune function [15]. The complexity of SUD, arising from interactions among pathogens, host immune responses, and environmental factors, necessitates a comprehensive approach to fully elucidate its pathogenesis.

In this context, omics approaches such as genomics, transcriptomics, proteomics, and metabolomics provide critical insights into the molecular mechanisms underlying disease progression and host-pathogen interactions. By enabling a holistic examination of molecular alterations in marine invertebrates affected by SUD, these multi-omics strategies offer promising avenues for advancing disease management and supporting conservation efforts.

Genomics as a tool for investigating SUD

Genomics, the comprehensive analysis of an organism's complete DNA sequence, has greatly advanced our understanding of the genetic determinants underlying disease development in marine invertebrates [16]. Although genomic research on marine invertebrates affected by SUD remains relatively limited, pioneering studies have yielded valuable insights into the genetic mechanisms underlying susceptibility, resistance, and adaptive responses [17]. To unravel the genetic basis of these diseases, genomics has emerged as a powerful tool. Genomic approaches enable the identification of genetic factors underlying disease

Table 1 Summary data on SUD research studies, categorized by species, sample type, omics techniques, sequencing methods, environmental conditions, and key findings

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Cao et al. [21]	China	Sea cucumber (<i>A.japonicus</i>)	Coelomic fluid	To investigate the protective effect of Vibrio phage vB_VneM_NB-1 against <i>V. nereis</i> -mediated coelomocyte apoptosis in <i>A. japonicus</i> .	Genome Sequencing	Genomics	<i>V. nereis</i> challenge	The study demonstrated that bacteriophage vB_VneM_NB-1 inhibits <i>V. nereis</i> -induced coelomocyte apoptosis in <i>A. japonicus</i> .
Shu et al. [9]	China	Sea cucumber (<i>A.japonicus</i>)	Sperm (Viscera)	To evaluate the antioxidant activity of PDRN and investigate its protective mechanism against oxidative damage in cells	Antioxidant Assays	Proteomics (iTRAQ)	In vitro oxidative stress model	The study demonstrated that AJS-PDRN mitigates H ₂ O ₂ -induced oxidative damage and enhances oxidative capacity in RAW264.7 cells.
Song et al. [10]	China	Sea cucumber (<i>A. japonicus</i>)	Intestinal tissue	To investigate the therapeutic effect of <i>Bacillus coagulans</i> on pathogen-induced intestinal dysfunction in <i>A. japonicus</i> .	RNA sequencing LC-MS/MS	Transcriptomics & Metabolomics	Pathogen induced	The study demonstrated that <i>B. coagulans</i> restores intestinal dysfunction by modulating the acetate–FFAR2–NF-κB–MLCK–MLC signalling pathway.
Liu et al. [31]	China	Sea cucumber (<i>H.leucospilota</i>)	Bodywall tissue	To investigate molecular mechanisms of body wall regeneration	RNA sequencing	Transcriptomics	Regeneration	The study demonstrated that early body wall regeneration in <i>H.leucospilota</i> involves ECM remodeling, regulation of pluripotency factors, suppression of proliferative signaling, and activation of stress, apoptosis, and cytoskeleton-related genes.

Table 1 (continued)

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Zeng et al. [32]	China	Sea Cucumber (<i>A.japonicus</i>)	Coelomocyte, RT Intestine, Muscle, Tentacle	To explore the role of circRNA254 in regulating coelomocyte apoptosis in <i>A. japonicus</i> under <i>V. splendidus</i> bacterial infection, focusing on the miR-375/BAG2 pathway.	RNA sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The study found that circRNA254 sponges miR-375, regulates AjBAG2 expression, and inhibits coelomocyte apoptosis in <i>A. japonicus</i> during pathogen infection,
Fu et al. [33]	China	Sea Cucumber (<i>A.japonicus</i>)	Coelomic fluid	To investigate the role of circRNA432 in enhancing coelomocyte phagocytosis and its regulation of the miR-2008-ELMO1 axis during <i>V. splendidus</i> infection.	Sanger Sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The Study found that circ432 enhances coelomocyte phagocytosis by regulating the miR-2008-AjELMO1 axis, improving immune responses during <i>V. splendidus</i> infection.
Yu et al. [34]	Japan	Sea Cucumber (<i>A.japonicus</i>)	Intestinal tissue	To identify microbial factors associated with intestinal atrophic disease in <i>A. japonicus</i> and understand their role in disease pathogenesis.	16 s rRNA gene sequencing	Metagenomics	Disease outbreak	Identified potential pathogenic microorganisms associated with intestinal atrophic disease in sea cucumbers. Key species contributing to disease were highlighted.

Table 1 (continued)

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Zhang et al. [24]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	To investigate the role of METTL3 in regulating m6A modification of lncRNAs during bacterial disease development in echinoderms, with a focus on understanding how m6A modifications affect the immune response and disease progression.	RNA sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The study identified that METTL3 modulates the dynamic m6A modification of lncRNAs during bacterial disease development in echinoderms.
Shao et al. [28]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	To analyze the relationship between m6A RNA methylation modifications and mRNA abundance during disease progression in <i>A. japonicus</i> . The goal is to understand the role of m6A methylation in gene regulation during disease development.	RNA sequencing	epiTranscriptomics	<i>V. splendidus</i> challenge	The study found a positive correlation between m6A modification and mRNA abundance during disease development in <i>A. japonicus</i> . m6A methylation plays a role in regulating gene expression related to immune responses and disease progression.
Liu et al. [31]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	To investigate the adverse effects of dietary virgin (nano) microplastics on growth immune responses, and resistance to stress and pathogens in juvenile <i>A. japonicus</i> .	RNA sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The study identified that dietary exposure to virgin (nano) microplastics adversely affected growth performance, immune responses, and resistance to ammonia stress and pathogen challenges in juvenile <i>A. japonicus</i> .

Table 1 (continued)

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Lv. Han and Li. [35]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	To investigate the role of TIMP-1 in ROS-mediated inflammation and its regulation of MMP-1 expression in <i>A. japonicus</i> .	RNA sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The study identified that Tissue Inhibitor of Metalloproteinases 1 (TIMP-1) was found to regulate the expression of Matrix Metalloproteinase 1 (MMP-1) in the presence of reactive oxygen species (ROS), contributing to inflammation in sea cucumbers.
Duan et al. [36]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	To identify m6A modified circRNAs and explore their roles in the development of SUD in <i>A. japonicus</i>	RNA sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The study identified m6A-modified circRNAs in <i>A. japonicus</i> and their significant roles in the progression of SUD, influencing immune response and disease development.
Zhang et al. [27]	China	Sea Cucumber (<i>A. japonicus</i>)	Intestinal tissue	To investigate the role of gut microbiota in mediating skin ulceration syndrome by modulating lipid metabolism in <i>A. japonicus</i> .	16srRNA sequencing, RNA sequencing, LC-MS	Transcriptomics & Metabolomics	<i>V. splendidus</i> challenge	The study identified that Gut microbiota was found to mediate the outbreak of skin ulceration syndrome by influencing lipid metabolism in sea cucumbers.

Table 1 (continued)

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Zhao et al. [46]	China	Sea cucumber (<i>A. japonicus</i>)	Intestine	To investigate metabolic adaptations of sea cucumbers during estivation-arousal cycle	LC- MS analysis	Metabolomics	Estivation	The study demonstrated that estivation in <i>A. japonicus</i> reprograms intestinal metabolism by suppressing glycolysis and TCA cycle while enhancing lipid, amino acid catabolism, and antioxidant defenses.
Zhang et al. [24]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	To identify metabolic changes associated with skin ulceration syndrome in <i>A. japonicus</i> using metabolomics	UPLC/Q-TOF MS	Metabolomics	<i>V. splendidus</i> challenge	The study identified Increased MDA, reduced SOD/CAT, altered metabolites, and pathway enrichment in SUS-affected <i>A. japonicus</i> .
Sun et al. [23]	China	Sea Cucumber (<i>A. japonicus</i>)	Body wall	To investigate the DNA methylation changes in <i>A. japonicus</i> in response to skin ulceration syndrome infection. This research aims to uncover potential epigenetic mechanisms involved in the disease response and to identify biomarkers for disease diagnosis or treatment.	Whole-genome bisulfite sequencing	Genomics	<i>V. splendidus</i> challenge	The study identified significant DNA methylation changes in NLK and mTOR genes, linking them to immune regulation. Integration of methylome and transcriptome analysis

Table 1 (continued)

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Del- roisse et al. [1]	East Africa Madagascar	Sea Cucumber (<i>H. scabra</i>)	Skin	To investigate the epidemiology of skin ulceration disease (SKUD) in <i>H. scabra</i> and review SKUDs in the Holothuroidea class.	Shotgun metagenomics	Metagenomics	Disease outbreak	The study identified increased <i>Vibrionaceae</i> in ulcers, no pathogen induction, potential cold temperature-related SKUD cause in <i>H. scabra</i> .
Zhang et al. [2]	China	Sea Cucumber (<i>A. japonicus</i>)	Hindgut	To explore how environmental factors influence the hindgut microbiome of <i>A. japonicus</i> and contribute to the outbreak of SUD.	RNA sequencing	Metagenomics	<i>V. splendidus</i> challenge	The study identified environmental factors (such as temperature and salinity) were found to alter the hindgut microbiome of <i>A. japonicus</i> , promoting skin ulceration syndrome outbreaks by affecting immune responses and pathogen dynamics.
Dong et al. [40]	China	Sea cucumber (<i>A. japonicus</i>)	Bodywall	To investigate the mechanism of tenderization and the role of protease enhancers	LC-ESI-MS/MS Analysis	Proteomics (iTRAQ)	Tenderization process	The study demonstrated that protease inhibitors modulate AJBW tenderization by suppressing proteolysis, while proteomics revealed upregulation of proteases, stress response, immune and ECM remodeling proteins as key biomarkers

Table 1 (continued)

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Li et al. [41]	China	Sea Cucumber (<i>A.japonicus</i>)	Coelomic fluid	To assess the efficiency of bacteriophage treatment in controlling <i>Vibrio</i> infection in juvenile <i>A. japonicus</i> .	Genome sequencing	Genomics	<i>V. cyclitrophicus</i> challenge	The study demonstrated that bacteriophage treatment effectively reduced <i>Vibrio</i> infection in juvenile sea cucumbers, improving survival rates and reducing pathogen load compared to untreated controls.
Li et al. [42]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	To investigate the protective effects of chicken egg yolk antibody (IgY) against <i>V. splendidus</i> infection in <i>A. japonicus</i> .	Mass spectrometry	Proteomics	<i>V. splendidus</i> challenge	The study demonstrated that chicken egg yolk antibody (IgY) treatment significantly enhanced immune responses and pathogen clearance in <i>A. japonicus</i> during <i>V. splendidus</i> infection. IgY treatment was shown to protect against infection and reduce mortality.

Table 1 (continued)

Study (Author, Year)	Origin	Species	Sample type	Purpose	Methodology	Omics technique	Environmental condition	Key findings
Yang et al. [8]	China	Sea Cucumber (<i>A. japonicus</i>)	BW, Intestine RT, Coelomytes	To capture the transcriptomic landscape and identify key genes involved in the progression of SUD in <i>A. japonicus</i> .	RNA sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The study identified dynamic changes in gene expression during SUD progression, revealing key immune-related and stress-response genes that are activated or repressed as the disease advances.
Gao et al. [7]	China	Sea Cucumber (<i>A. japonicus</i>)	Coelomic fluid	Investigated the role of immune-related genes in the immune response of <i>A. japonicus</i> after <i>V. splendidus</i> challenge.	RNA sequencing	Transcriptomics	<i>V. splendidus</i> challenge	The study identified DEGs (immune-related genes) in coelomocytes, highlighting pathways activated during bacterial infection.

*Bw- Body wall, RT-Respiratory Tree

susceptibility, immune responses, stress tolerance, and resistance mechanisms, thereby providing critical insights into the molecular foundations of SUD and paving the way for effective disease management strategies [16].

Genomics provides a comprehensive perspective on the genetic architecture of marine invertebrates, facilitating the identification of genes associated with disease resistance, immune regulation, and pathogen recognition [17]. It also enables the discovery of genetic markers that can be used to monitor disease progression or predict potential outbreaks. Advances in high-throughput sequencing technologies, particularly Next-Generation Sequencing (NGS), have facilitated the sequencing of genomes from various marine invertebrate species, offering deeper insights into their genetic architecture and elucidating how they respond to diseases and environmental stressors [18].

Key insights revealed by genomics in several important areas

Host immune response

Marine invertebrates such as *A. japonicus* rely on innate immunity, with genomic studies identifying key immune-related genes, including pattern recognition receptors, antimicrobial peptides, and complement like molecules. Two experimental studies [19, 20] provided detailed insights into the role of genomics in understanding host immune responses. These studies highlight critical aspects such as immune mechanisms, host-pathogen interactions, and the genetic factors that influence susceptibility or resistance to infection.

In an experimental study, infection with *V. nereis* activated immune-related genes in *A. japonicus*, triggering inflammation, immune cell infiltration, and epidermal damage hallmarks of an active innate response [19]. However, genomic analyses also indicated that this response may be insufficient against highly virulent pathogens such as *V. cyclitrophicus*. Study [20] demonstrated that phage vB_VcyS_Vc1, which lacks virulence genes, effectively lyses

Table 2 Quality assessment using the mixed method appraisal tool (MMAT) for quantitative non-randomized studies

Authors (Year)	Type of study	Screening questions			Methodology quality criteria					Overall quality Score (%)
		Are there clear research questions?	Do the collected data allow to address the research questions?	Are the participants representative of the target population?	Are measurements appropriate regarding both the outcome and intervention (or exposure)?	Are there complete outcome data?	Are the confounders accounted for in the design and analysis?	During the study period is the intervention administered (or exposure occurred) as intended?		
Cao et al. [21]	Experimental	100%	100%	80%	100%	90%	50%	Yes	86%	
Song et al. [10]	Experimental	100%	100%	75%	100%	50%	50%	Yes	79%	
Shu et al. [9]	Experimental	100%	100%	N/A	100%	100%	80%	Yes	96%	
Zeng et al. [32]	Experimental	100%	100%	50%	100%	50%	0%	Yes	66%	
Fu et al. [33]	Experimental	100%	90%	70%	90%	80%	60%	Yes	81%	
Yu et al. [34]	Observational	100%	95%	70%	95%	80%	60%	Yes	83%	
Liu et al. [31]	Experimental	100%	100%	90%	100%	100%	85%	Yes	95%	
Zhang et al. [24]	Experimental	100%	90%	75%	95%	85%	60%	Yes	84%	
Zhao et al. [46]	Experimental	100%	100%	90%	100%	100%	85%	Yes	95%	
Shao et al. [28]	Experimental	100%	95%	80%	95%	90%	65%	Yes	87%	
Liu et al. [31]	Experimental	100%	100%	75%	100%	75%	50%	Yes	83%	
Lv, Han and Li. [35]	Experimental	100%	100%	75%	100%	100%	100%	Yes	95%	
Duan et al. [36]	Experimental	100%	100%	70%	100%	80%	40%	Yes	81%	
Zhang et al. [2]	Experimental	100%	90%	70%	90%	60%	40%	Yes	75%	
Zhang et al. [27]	Experimental	100%	95%	70%	95%	60%	40%	Yes	76%	
Sun et al. [23]	Experimental	100%	100%	70%	100%	90%	50%	Yes	85%	
Delroisse et al. [1]	Observational	100%	90%	75%	90%	80%	60%	Yes	82%	
Dong et al. [40]	Experimental	100%	100%	90%	100%	100%	85%	Yes	95%	
Zhang et al. [2]	Experimental	80%	90%	60%	95%	75%	50%	Yes	75%	
Li et al. [41]	Experimental	100%	100%	90%	100%	85%	100%	Yes	96%	
Li et al. [42]	Experimental	100%	100%	75%	100%	90%	70%	Yes	89%	
Yang et al. [8]	Experimental	100%	100%	60%	100%	80%	40%	Yes	80%	
Gao et al. [7]	Experimental	100%	90%	50%	100%	80%	30%	Yes	75%	

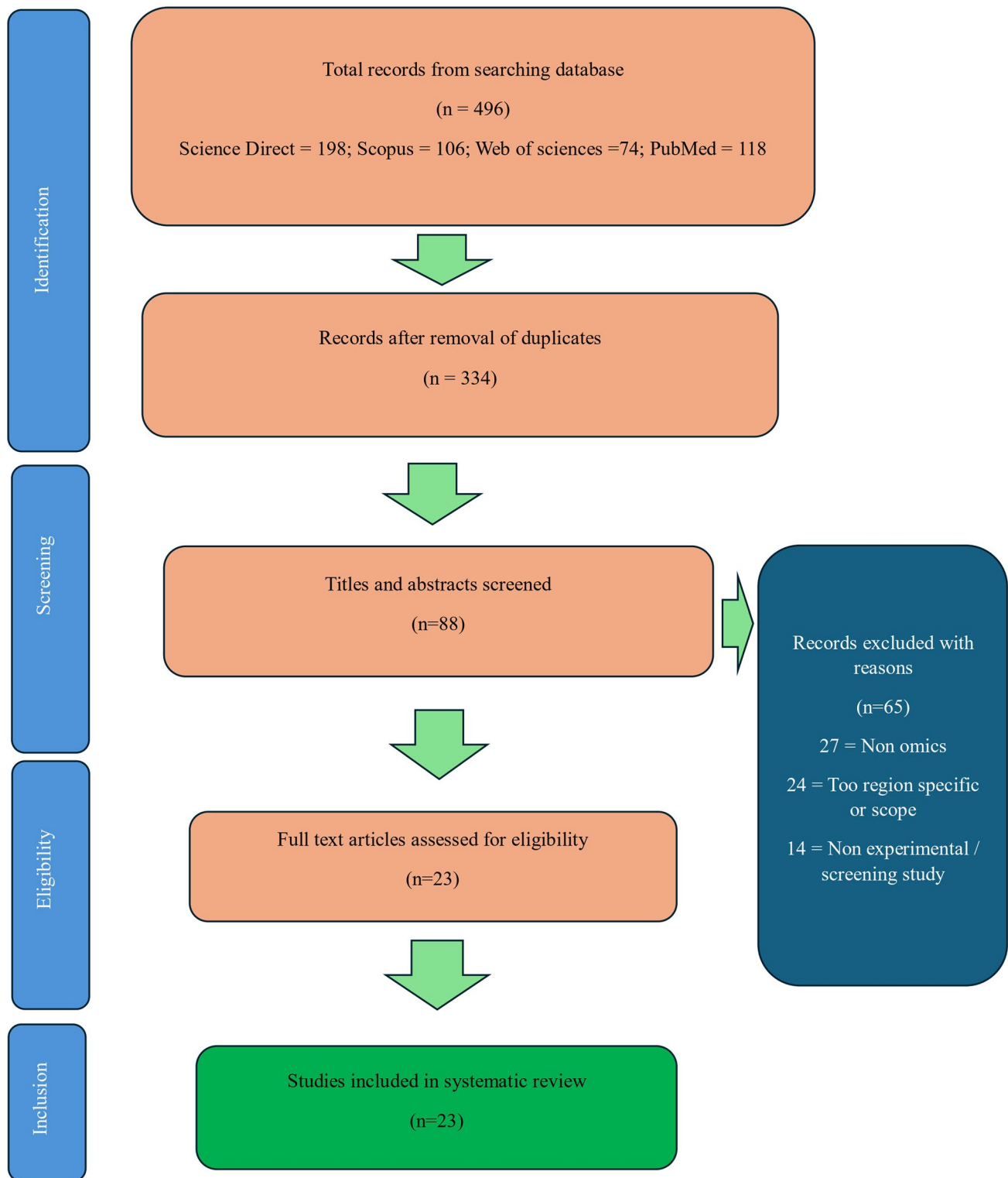


Fig. 1 Flow diagram of the methodology and selection process used in this systematic review. It follows the rules and templates of PRISMA Preferred Reporting Items for Systematic Reviews [12]

V. cyclitrophicus and increases host survival by up to 81% when administered through feed. This finding suggests that phage therapy can complement the host's genetically encoded defenses. Similarly, passive immunization with pathogen-specific IgY antibodies against *V. splendidus* significantly improved survival and enhanced coelomocyte phagocytosis. These immune-supportive strategies, guided by genomic and functional data, not only reduce pathogen load but also strengthen the host's innate capacity to respond. Integrating such approaches with genomic insights offers a promising avenue for sustainable disease management in sea cucumber aquaculture.

Pathogen-host interactions, genetic susceptibility and resistance

Genomic research has been instrumental in elucidating the complex interactions between sea cucumbers and the pathogens responsible for SUD. A recent study identified *V. nereis* as a causative agent of SUD in *A. japonicus*, demonstrating how the pathogen adheres to coelomocytes and contributes to tissue damage. Genomic insights guided the use of bacteriophage vB_VneM_NB-1, which effectively reduces *V. nereis* adhesion to host immune cells, highlighting both the molecular basis of host-pathogen interactions and the therapeutic potential of phage application [19]. Similarly, genomic characterization of bacteriophage vB_VcyS_Vc1, which targets *V. cyclitrophicus*, underscores the promise of phage therapy as a targeted, genomics-informed biological control strategy [20].

Genomic research has advanced our understanding of genetic susceptibility and resistance in *A. japonicus* to *Vibrio* infections. One study investigating *V. nereis* infection demonstrated that survival rates of sea cucumbers declined with increasing bacterial concentrations, highlighting genetic and immune factors identified through genomic analysis. Specifically, genomic characterization of the *V. nereis* NB-6 strain and its interaction with juvenile sea cucumbers revealed dose-dependent mortality, tissue damage, and immune responses, underscoring the pivotal role of genomics in elucidating disease mechanisms and host defense strategies [19].

Environmental stress and disease pathogenesis

Environmental stressors, including temperature fluctuations, ocean acidification, and pollution, can compromise the immune defenses of marine invertebrates, increasing their susceptibility to diseases [21]. Genomic studies have been pivotal in revealing how these organisms genetically respond and adapt to such environmental pressures, and how these adaptations influence their vulnerability to SUD. For

instance, research conducted in breeding ponds in Dalian, China, identified *V. nereis* strains as major contributors to infection outbreaks in *A. japonicus*.

The detection of bacteriophage vB_VneM_NB-1 in pond sediments further suggests that environmental factors influence pathogen ecology and distribution [19]. Additionally, genomic data from another study demonstrate how intensive aquaculture practices and sewage contamination in sea cucumber farms promote the proliferation of *V. cyclitrophicus* [20]. These findings underscore the interplay between environmental stressors and disease outbreaks, highlighting the crucial role of genomics in understanding pathogen dynamics and host susceptibility under changing ecological conditions."

Application of genomics in *Vibrio*-infected juvenile sea cucumber *A. japonicus*

Genomics has been instrumental in developing strategies to control *Vibrio* infections in juvenile *A. japonicus*. In a key study, researchers employed genomic sequencing to isolate and characterize the bacteriophage vB_VcyS_Vc1, which specifically targets *V. cyclitrophicus*. Genomic analysis revealed that the phage genome comprises 44,541 base pairs and lacks genes associated with virulence or toxins, confirming its safety for aquaculture applications. Furthermore, genomics provided detailed insights into the phage's life cycle, identifying an eclipse period of 25 min and a burst size of 215 plaque-forming units per infected cell, demonstrating its high efficiency in lysing the pathogen.

Application of the phage through various delivery methods, including feed supplementation, injection, and immersion, significantly improved survival rates in infected juvenile sea cucumbers [20]. This study illustrates how genomic technologies are essential for developing targeted and sustainable phage therapies, providing a promising alternative to antibiotics for managing *Vibrio* infections in sea cucumber aquaculture (Table 3).

Transcriptomics

Transcriptomics, the comprehensive analysis of RNA transcripts within an organism, provides critical insights into the molecular mechanisms underlying SUD in sea cucumbers. By examining gene expression profiles, transcriptomic approaches reveal how organisms respond at the molecular level to pathogens, environmental stressors, and immune challenges key factors that drive SUD [7].

This approach allows the identification of genes that are differentially expressed during disease progression, providing insights into the host's immune defenses, cellular stress responses, and physiological adaptations. Such

Table 3 Genomic insights into SUD; focus area, key findings, and implications

Focus Area	Key Findings	Implications	References
Host Immune Response	PRRs, AMPs, complement-like molecules identified; phage therapy boosts survival	Supports immune-boosting strategies and phage therapy development	[19, 20]
Pathogen-Host Interactions	Phages reduce <i>Vibrio</i> adhesion; genomic data informs biocontrol	Informs targeted biocontrol approaches	[19, 20]
Genetic Susceptibility & Resistance	Dose-dependent mortality; genomic insights reveal immune factors	Guides selective breeding for disease resistance	[19]
Environmental Stress & Pathogenesis	Aquaculture stress and pollution linked to <i>Vibrio</i> proliferation	Highlights environmental management in aquaculture	[19, 20]
Applications in Juveniles	Phage vB_VcyS_Vc1 improves survival, safe alternative to antibiotics	Provides sustainable alternative to antibiotics	[20]

molecular-level understanding is essential for elucidating the complex biological pathways involved in SUD development and for identifying potential biomarkers to enhance early detection and intervention strategies.

Gene expression in marine invertebrates affected by SUD

Gene expression is the process by which genetic information is used to produce functional products, typically proteins, that carry out biological functions within an organism [22]. In sea cucumbers affected by SUD, the expression of various genes is altered in response to infections or environmental stressors, contributing to the development of ulcerations. Transcriptomic studies detect and quantify RNA molecules, which serve as intermediates in gene expression, providing insights into which genes are upregulated or downregulated in diseased versus healthy individuals. These analyses reveal the molecular pathways involved in disease resistance and susceptibility [24].

In a study conducted in China, the economically important sea cucumber *A. japonicus* was examined due to severe impacts from SUD. Transcriptomic approaches were used to investigate gene expression changes in *A. japonicus* infected with *V. splendidus* at different stages of SUD. A total of 21 cDNA libraries were sequenced, yielding over 542 million high-quality reads, which enabled the construction of a comprehensive reference transcriptome comprising 93,163 unigenes, of which 33,860 were successfully annotated. Transcriptomic analysis revealed that the body wall

exhibited the most pronounced gene expression changes, particularly in pathways related to immune responses, signal transduction, metabolism, and cellular functions. Ninety-two differentially expressed genes (DEGs) were associated with pathogen recognition, inflammation, oxidative stress, and programmed cell death [8]. This study highlights the power of transcriptomics to uncover complex molecular changes during disease progression, providing valuable insights into SUD mechanisms and informing improved disease management strategies for sea cucumbers.

Mechanisms of gene expression in SUD

Immune response genes & stress response genes

Transcriptomics play a crucial role in elucidating how marine invertebrates, which lack adaptive immunity, rely on innate immune responses to combat infections [25]. In a key experimental study, significant differences in immune gene expression were observed between resistant and susceptible sea cucumber biotypes challenged with *V. splendidus*. Transcriptomic analysis enabled comprehensive profiling of gene expression differences between these biotypes following pathogen exposure. From over 319 million high-quality sequencing reads, 186,658 contigs were assembled and clustered into 89,891 representative sequences for differential expression analysis. This approach identified 358 DEGs in resistant sea cucumbers and 102 DEGs in susceptible individuals relative to controls. Functional annotation and pathway analysis revealed that many DEGs were involved in critical immune pathways, including endocytosis, lysosome activity, MAPK, chemokine, and ERBB signaling. Key immune genes, such as those encoding pattern recognition receptors, antimicrobial peptides, and signaling molecules, were differentially regulated. Overall, this transcriptomic study provided a high-resolution framework for uncovering the complex immune networks that contribute to pathogen resistance in sea cucumbers [7].

Environmental stressors, including rising water temperatures, pollution, and ocean acidification, play a critical role in the onset and progression of SUD in marine invertebrates. Transcriptomic profiling has facilitated the investigation of molecular responses to these stressors, particularly the role of heat shock proteins (HSPs), which act as molecular chaperones to protect cells from stress-induced damage [26]. In a study of *A. japonicus* affected by *V. splendidus* in China, RNA sequencing of 21 cDNA libraries from different tissues and disease stages generated over 542 million high-quality reads and assembled 93,163 unigenes, enabling detailed exploration of gene expression changes during disease progression [8]. Transcriptome analysis revealed pronounced gene expression changes, especially in the body wall, with

upregulation of genes related to immune response, oxidative stress, and inflammation. Among 92 key DEGs, functional categories included pathogen recognition, inflammation, oxidative stress response, and apoptosis. Notably, HSPs such as Hsp70 and Hsp90 were highly expressed, reflecting their essential roles in stress adaptation, protein folding, and immune regulation during SUD progression. Transcriptomic analysis thus provided a detailed view of dynamic molecular responses, elucidating pathways involved in signal transduction, immune signaling, and apoptosis that underpin the sea cucumber's defense mechanisms against infection and environmental stress."

Pathogen recognition, immune modulation, regeneration and tissue repair

Transcriptomics is essential for identifying genes involved in pathogen recognition and immune modulation, providing key insights into how marine invertebrates mount immune responses to infections that cause SUD [27]. A recent study examined how *A. japonicus* responds to *V. splendidus* infection by profiling genome-wide N6-methyladenosine (m6A) modifications on circular RNAs (circRNAs), revealing their critical role in SUD development [28]. Transcriptomic analysis using MeRIP-seq showed that m6A-modified circRNAs were present in all groups but were most abundant in SUD resistant sea cucumbers, with the majority of m6A peaks upregulated following infection. Functional enrichment analysis indicated that genes associated with these circRNAs were primarily involved in adhesion pathways, which are essential for pathogen recognition and immune response modulation. Furthermore, construction of a circRNA-miRNA-mRNA regulatory network demonstrated that m6A-modified circRNAs regulate immune processes such as the ubiquitination system and cell adhesion, influencing pathogen clearance and inflammation. This transcriptomic approach was pivotal in identifying dynamic epigenetic modifications and their regulatory roles, highlighting specific m6A-modified circRNAs as potential biomarkers for SUD diagnosis and providing new insights into the molecular mechanisms underlying disease resistance in sea cucumbers."

Sea cucumbers exhibit remarkable regenerative capabilities, enabling the restoration of damaged tissues and organs through processes such as transverse fission, in which anterior and posterior fragments regenerate independently. A recent study on *H. leucospilota* used rubber band induced fission to investigate the early stages of body wall regeneration. Histological analysis revealed initial collagen fiber degradation and loosening by day 3, followed by increased density and a disorganized connective tissue structure by day 7. Transcriptome profiling at 0, 3, and 7

days post-fission uncovered significant molecular changes, including upregulation of genes involved in extracellular matrix remodeling and altered expression of pluripotency factors Sox2 was upregulated, whereas Myc, Klf2, and Oct1 were downregulated. Key signaling pathways, such as Wnt, Hippo, TGF- β , and MAPK, showed progressive transcription factor decline, suggesting reduced cell proliferation during regeneration. Additionally, genes associated with development, stress response, apoptosis, and cytoskeletal organization were differentially expressed. These findings underscore the pivotal role of extracellular matrix remodeling and dynamic gene regulation in early body wall regeneration, providing valuable insights into the cellular and molecular mechanisms underlying whole-body regeneration in echinoderms and their potential relevance for regenerative medicine [29].

Disease-specific gene expression signatures and the potential of transcriptomics in SUD management

Transcriptomics offers valuable insights into disease-specific gene expression signatures, facilitating the identification of biomarkers for early detection and monitoring of SUD. By comparing gene expression profiles between healthy and diseased marine invertebrates, specific genes consistently associated with disease outbreaks can be identified [30]. Transcriptomic studies have also been pivotal in evaluating the molecular impacts of environmental stressors, such as microplastics and nanoplastics, on sea cucumbers. A study on *A. japonicus* examined the effects of dietary polystyrene micro and nanoplastics, revealing significant disruptions in growth, immune response, and pathogen resistance. Exposed sea cucumbers exhibited increased oxidative stress, evidenced by elevated reactive oxygen species production and malondialdehyde levels. Furthermore, immune-related genes, including Hsp90, Hsp70, TLR, and CASP2, were downregulated, and ammonia detoxification processes were significantly impaired, particularly by 100 nm nanoplastics. These findings underscore the toxic effects of plastic pollutants on marine invertebrates and highlight the importance of molecular biomarkers for early detection of environmental stress and assessment of potential risks to marine ecosystems [31].

The application of transcriptomics in the study of SUD provides several key advantages, particularly for developing effective disease management strategies. First, by identifying disease-specific gene expression signatures, molecular diagnostic tools can be developed to detect early disease onset, enabling timely interventions to reduce mortality rates [24]. Second, transcriptomic data can evaluate the efficacy of therapeutic interventions, such as probiotics, antimicrobial peptides, or stress-reducing treatments,

by monitoring changes in gene expression before and after treatment [31]. Third, transcriptomics can inform selective breeding programs for disease-resistant marine invertebrates by identifying genes associated with SUD resistance, thereby enhancing the resilience of aquaculture species to disease outbreaks [30] (Table 4).

Proteomics

Protein expression and functional changes

Protein expression changes refer to variations in the abundance or activity of specific proteins in response to different conditions or environmental stimuli [26]. SUD in sea cucumbers is often characterized by inflammation, immune activation, and tissue damage. Proteomic analyses have identified several key proteins involved in these processes, including inflammatory cytokines, heat shock proteins (HSPs), enzymes associated with tissue remodeling, and other immune-related proteins.”

Proteomics employs techniques such as two-dimensional gel electrophoresis (2-DE), mass spectrometry (MS), and liquid chromatography-mass spectrometry (LC-MS) to identify and quantify proteins. These approaches have been widely applied in marine invertebrates to investigate physiological responses to environmental stressors and disease. Advances in specialized proteomic tools have enabled detailed analysis of protein expression in various tissues, including the skin and immune system, which are directly involved in disease responses [6].

Table 4 Transcriptomic insights into SUD; focus area; key findings, and implications

Focus Area	Key Findings	Implications	References
Gene Expression	92 DEGs in body wall; immune, oxidative stress, apoptosis pathways activated	Identifies biomarkers and molecular pathways for diagnostics	[8]
Immune & Stress Genes	Resistant vs. susceptible strains show distinct DEGs in immune pathways	Supports breeding for resistant strains	[7]
Pathogen Recognition & Modulation	m6A circRNAs regulate immune processes; biomarkers identified	Provides molecular biomarkers for early diagnosis	[28]
Regeneration & Repair	ECM remodeling, pluripotency factors, and signaling pathways in regeneration	Advances understanding of tissue repair mechanisms	[29]
Disease-Specific Signatures	Plastics disrupt immunity (HSPs, TLR, CASP2 downregulated)	Reveals pollution risks to aquaculture health	[31]

Recent studies on bioactive compounds from sea cucumbers have highlighted the therapeutic potential of polydeoxyribonucleotide (PDRN), a biologically active molecule with anti-inflammatory, anti-apoptotic, and tissue-repair properties. Advanced proteomic and biochemical analyses have revealed that PDRN extracted from *A. japonicus* sperm (AJS-PDRN) also exhibits potent antioxidant activity. Using radical scavenging assays (DPPH, ABTS, and hydroxyl radical) and an H₂O₂ induced oxidative stress model in RAW264.7 cells, AJS-PDRN was shown to significantly enhance cellular antioxidant capacity and confer cytoprotection. iTRAQ-based proteomic profiling, supported by GO and KEGG enrichment analyses, demonstrated that AJS-PDRN exerts its protective effects through modulation of immune and inflammatory responses, extracellular matrix remodeling, promotion of membrane repair, and activation of antioxidant pathways. Moreover, protein-protein interaction network analysis revealed upregulation of selenoprotein family members, which play a critical role in mitigating oxidative damage. These findings underscore the multifunctional bioactivity of AJS-PDRN and its potential application in preventing oxidative stress-related disorders [9].

Heat shock proteins (HSPs), stress responses and Immune-Related proteins

Heat shock proteins (HSPs) function as molecular chaperones that protect cells from stress-induced damage. Antioxidant and immune responses in marine invertebrates are crucial for mitigating stress caused by environmental fluctuations. In the sea cucumber *Isostichopus badionotus*, exposure to varying temperatures (16–36 °C) under two pH conditions (7.70 and 8.17) elicited significant physiological adjustments. Heat shock protein 70 (Hsp70) was synthesized at both cold (16 °C) and warm (34 °C) extremes, highlighting its role in thermal stress adaptation. Antioxidant defenses were temperature-dependent, with glutathione peroxidase (GPx) activity peaking at extreme temperatures (16, 20, and 36 °C), while superoxide dismutase (SOD) activity increased within a narrower range (28–30 °C) to counteract oxidative damage. Although pH had no significant effect on Hsp70 expression, antioxidant enzyme activity was stimulated under acidic conditions (pH 7.70). Mucosal immunity, assessed via phenoloxidase (PO) activation, was elevated at pH 7.70 and higher temperatures (28–34 °C), indicating an enhanced defense mechanism under combined thermal and pH stress. These findings demonstrate the coordinated roles of HSPs, antioxidant enzymes, and immune responses in maintaining homeostasis under challenging environmental conditions. Understanding these adaptive mechanisms is

essential for evaluating stress resilience in sea cucumbers and predicting their responses to climate change [37].

The immune response is essential for marine invertebrates to defend against pathogens [38]. Key immune-related proteins, including antimicrobial peptides (AMPs), lectins, and pattern recognition receptors (PRRs), play critical roles in recognizing and combating bacterial, fungal, and viral infections. During infection or tissue damage, inflammatory cytokines such as tumor necrosis factor (TNF) and interleukins are often elevated to coordinate immune defenses [39]. An experimental study evaluated the efficacy of chicken egg yolk antibodies (IgY) against *V. splendidus* infection in sea cucumbers. White Leghorn hens were immunized with whole *V. splendidus* cells, and IgY antibodies were purified from egg yolks using water dilution, salt precipitation, and ultrafiltration, achieving 83% purity. The antibodies exhibited a high titer of 320,000, confirmed by enzyme-linked immunosorbent assay. IgY inhibited *V. splendidus* growth in a dose-dependent manner at concentrations of 1–10 mg/mL. When administered to infected sea cucumbers, specific IgY antibodies improved survival rates up to 75–80% compared to controls, reduced bacterial loads in the respiratory tree, intestine, and coelomic fluid, and enhanced phagocytosis of bacteria by coelomocytes. These results demonstrate that specific IgY provides effective protection against *V. splendidus* infection and highlight the crucial role of immune-related proteins in combating pathogens in sea cucumbers.

Table 5 Proteomic insights into SUD: focus areas, key findings and implications

Focus area	Key findings	Implications	References
Protein Expression Changes	HSPs, cytokines, enzymes involved in tissue remodeling	Highlights proteins as potential therapeutic targets	[26]
Heat Shock Proteins	Hsp70 modulated by temperature; antioxidant enzymes vary with stress	Indicates role of HSPs in climate resilience	[37]
Immune Proteins	AMPs, lectins, PRRs; IgY improved survival and reduced bacterial loads	Supports immunotherapy and antibody-based strategies	[39]
Chronic Inflammation	MMPs, cathepsins, caspases upregulated; impaired immune regulation	Reveals molecular basis of chronic ulceration	[40, 43], [40]

Chronic inflammation, enzymes involved in tissue remodelling and immune dysregulation

SUD in sea cucumbers results in severe tissue degradation, necessitating activation of proteolytic enzymes responsible for extracellular matrix (ECM) remodeling. Proteomic studies in *A. japonicus* have reported significant upregulation of matrix metalloproteinases (MMPs), cathepsins, calpains, caspases, and proteasomes during tissue breakdown and repair [40]. These enzymes facilitate ECM degradation and remodeling, which are essential for wound healing; however, their uncontrolled activity can exacerbate tissue destruction and delay recovery, contributing to the chronicity of ulcerative lesions. Similar to other invertebrates, MMPs in sea cucumbers are regulated by conserved signaling pathways, highlighting the evolutionary conservation of these molecular mechanisms [43].

In addition to enzymatic activity, immune dysregulation plays a central role in the progression of SUD. Persistent infections by opportunistic pathogens and environmental stressors can overwhelm the innate immune system, resulting in either excessive or insufficient immune activation. High-throughput proteomic and transcriptomic studies in *A. japonicus* under stress and infection conditions have revealed differential expression of immune-related proteins involved in oxidative stress response, apoptosis, cytoskeletal organization, and NF- κ B-mediated inflammatory pathways. For instance, an iTRAQ-based proteomic analysis under experimentally induced stress conditions identified large-scale changes in protein abundance, including those associated with antioxidant defense and immune signaling [40]. These findings suggest that chronic immune activation, combined with impaired regulatory mechanisms, hampers effective tissue regeneration and contributes to the persistence of ulcerative lesions in sea cucumbers” (Table 5).

Metabolomics

Metabolomics focuses on the study of small molecules (metabolites) involved in cellular metabolic processes, providing critical insights into biochemical changes that occur during disease progression and healing, and offering a snapshot of an organism’s physiological state [44]. In the context of SUD in marine invertebrates, metabolomics provides a unique opportunity to understand how metabolic pathways are altered in response to disease and environmental stress. These metabolic shifts can illuminate disease mechanisms, stress responses, and potential biomarkers for early diagnosis and therapeutic intervention [3].

Metabolomic analyses employ high-throughput technologies such as nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) to identify, quantify, and

profile metabolites in biological samples. These techniques enable comprehensive characterization of small molecules, including amino acids, lipids, carbohydrates, and other metabolites that reflect an organism's metabolic processes [45]. In marine invertebrates, metabolomics has been used to investigate metabolic alterations induced by environmental stressors, diseases, and injuries. Recent studies have highlighted changes in pathways related to inflammation, immune responses, and tissue repair [44].

Altered energy metabolism, altered lipid metabolism and membrane remodelling

One of the most notable findings from metabolomic studies of SUD in sea cucumbers is the disruption of energy metabolism. In response to skin ulcerations, energy demanding processes such as immune activation and tissue repair become critical. Several studies have reported alterations in metabolites associated with energy production, including changes in glucose, fatty acids, and amino acids [3]. A recent metabolomic study on *A. japonicus* revealed extensive metabolic reprogramming associated with the estivation arousal cycle. Using UPLC-ESI-Q-TOF/MS, researchers identified 424 metabolites, with significant shifts observed across non-estivation (NA), deep-estivation (DA), and arousal (AA) phases. During estivation, metabolites linked to glycolysis and the tricarboxylic acid (TCA) cycle were markedly reduced, whereas levels of long-chain fatty acids, phospholipids, and free amino acids increased, indicating a strategic shift from carbohydrate utilization to lipid and amino acid catabolism for ATP production. Additionally, enhanced carbon flux into the pentose phosphate pathway and the accumulation of antioxidant compounds such as tocotrienols, folic acid, catechin, genistein, and resveratrol suggest an adaptive mechanism to mitigate oxidative stress while conserving energy. These findings indicate that metabolic depression, coupled with reinforced antioxidant defenses, underpins the survival strategy of *A. japonicus* during estivation, ensuring long-term viability under harsh environmental conditions [46].

SUD in marine invertebrates causes epidermal and tissue damage, necessitating extensive tissue repair and remodeling. Lipid metabolism plays a central role in these processes, and metabolomic studies have revealed significant alterations in lipid profiles in affected organisms. Specifically, fluctuations in phospholipids, ceramides, and fatty acids indicate both membrane damage and the need for repair [27]. A recent study on *A. japonicus* with SUD reported notable lipid metabolic changes, including increased levels of palmitic acid and taurine, alongside decreased levels of cholesterol-3-sulfate and thioether amide-PC. These lipid alterations reflect both membrane damage and reparative

processes during healing, highlighting the critical role of lipid metabolism in the pathogenesis and tissue remodeling associated with SUD [3].

Inflammatory metabolites, immune activation, oxidative stress and antioxidant defense

The immune system of marine invertebrates responds to SUD through inflammation, which is essential for combating infection but can also contribute to tissue damage. Metabolomic analyses have identified significant changes in metabolites associated with inflammation, including upregulation of prostaglandins, leukotrienes, and other eicosanoids. These lipid mediators play key roles in modulating the immune response and are commonly involved in inflammatory pathways activated during SUD [3]. In sea cucumbers infected with *V. splendidus*, a pronounced immune response was observed, characterized by upregulated transcription of inflammatory factor genes in intestinal tissue. Metabolomic analyses further revealed alterations in lipid metabolites, particularly long-chain fatty acids such as triglycerides (TG), phosphatidylethanolamines (PE), and phosphatidylglycerols (PG), which were modulated by infection [27]. These inflammatory metabolites are critical for orchestrating the immune response and contribute to SUD progression, providing valuable insights into the underlying disease mechanisms.

The progression of SUD is often accompanied by oxidative stress, resulting from an imbalance between reactive oxygen species (ROS) production and the organism's antioxidant defenses. Metabolomic profiling of marine invertebrates with SUD has revealed elevated levels of ROS-related metabolites, such as malondialdehyde (MDA), a marker of lipid peroxidation, alongside altered levels of antioxidants, including glutathione (GSH) and ascorbate (Vitamin C) [44]. In *A. japonicus*, SUD disrupts normal physiological processes and induces oxidative stress. Studies assessing the activities of key antioxidant enzymes, superoxide dismutase (SOD) and catalase (CAT), alongside MDA levels, showed that diseased sea cucumbers had significantly increased MDA levels, indicating enhanced oxidative damage, while SOD and CAT activities were reduced, reflecting impaired antioxidant defenses. Metabolomic analysis further identified several upregulated metabolites associated with oxidative stress and cellular damage, highlighting an ongoing stress response. These findings underscore the critical role of oxidative stress in SUD pathogenesis and suggest that compromised antioxidant capacity may contribute to disease progression and severity. Understanding this relationship can inform strategies to mitigate the effects of SUD in sea cucumber aquaculture [3] (Tables 6, 7 and 8) (Fig. 2).

Table 6 Metabolic insights into SUD; focus areas, key findings, and implications

Focus area	Key findings	Implications	References
Energy Metabolism	Reduced glycolysis; increased lipid and amino acid catabolism	Shows metabolic shifts linked to survival strategies	[46]
Lipid Metabolism	Altered phospholipids, ceramides, fatty acids linked to membrane repair	Indicates lipid metabolism as biomarker for tissue repair	[3, 27]
Inflammatory Metabolites	Prostaglandins, leukotrienes, eicosanoids upregulated	Provides metabolic markers for inflammation monitoring	[3, 27]
Oxidative Stress & Antioxidants	MDA increased; SOD and CAT decreased; impaired anti-oxidant defense	Guides anti-oxidant-based interventions	[3, 44]

Discussion

In this review, we examined a range of studies that employed various omics techniques to investigate SUD in sea cucumbers, highlighting the significant progress made through these approaches. However, significant gaps remain in understanding the precise molecular mechanisms underlying these diseases. With an emphasis on genomics, transcriptomics, proteomics, and metabolomics, this systematic review integrates existing research to advance knowledge of the pathophysiology of skin ulcerations in sea cucumbers.

Table 8 Summary of omics approaches in SUD, outlining their primary focus and key applications

Omics Type	Focus	Key Applications
Genomics	DNA-level insights	Identifies genetic resistance markers, supports phage therapy
Transcriptomics	RNA expression	Reveals DEGs, biomarkers, immune pathways, regeneration
Proteomics	Protein expression	Profiles HSPs, immune proteins, ECM remodeling, IgY therapy
Metabolomics	Small molecules	Tracks metabolic reprogramming, oxidative stress, lipid changes

The application of omics approaches has enabled the identification of key biological processes involved in SUD and the discovery of important molecular signatures.

The increasing prevalence of SUD in sea cucumbers poses a significant threat to marine biodiversity, aquaculture sustainability, and ecosystem health. These diseases, marked by localized lesions that can progress to extensive tissue necrosis, arise from complex interactions among opportunistic pathogens, impaired immune defenses, and environmental stressors. Mortality in affected populations is often driven by microbial infections, environmental pollutants, and immune dysfunction. Given this multifactorial nature of SUD, understanding its molecular basis requires an integrative approach that combines multiple layers of biological information. Multi-omics strategies which include genomics, transcriptomics, proteomics, and metabolomics, offer a comprehensive view of disease progression

Table 7 Comparative overview of genomics, transcriptomics, proteomics, and metabolomics approaches in SUD research, highlighting key applications, strengths and limitations

Omics approach	Description	Key applications in SUD research	Strengths	Limitations	References
Genomics	Study of the complete DNA sequence of an organism	Identification of genetic mutations, polymorphisms and immune-related genes	Provides comprehensive understanding of genetic variation and potential disease predisposition	Functional insights are missed because it focusses on only DNA sequence.	[47]
Transcriptomics	Study of the RNA molecules (mRNA, non-coding RNAs) transcribed from DNA	Identification of differentially expressed genes associated with SUD	Highlights the functional response of genes in disease states	Only provides information on gene expression not mutations.	[48]
Proteomics	Study of proteins expressed in the organism	Analysis of protein changes in response to skin ulceration and infection	Directly correlates with cellular function and disease phenotypes	Requires complex technologies and may have issues with sample complexity.	[49]
Metabolomics	Study of small molecule (metabolites) in biological samples	Identification of metabolic disruptions in skin ulceration diseases	Offers insights into physiological changes, identifying potential biomarkers	Limited by the availability of known metabolites and their detection methods.	[50]

Multi-Omics Workflow

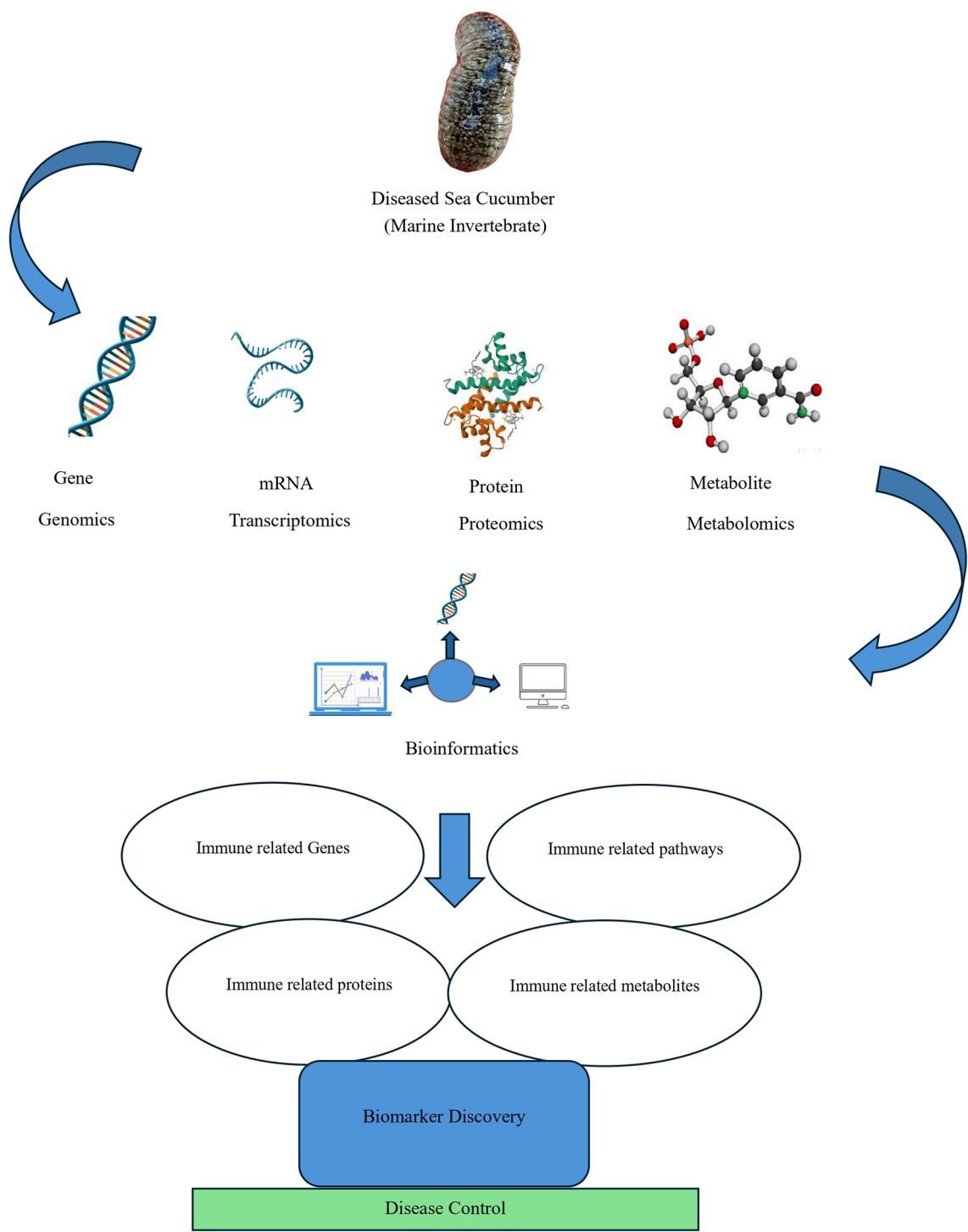


Fig. 2 Multi-omics application in sea cucumber with skin ulcerative disease

and host-pathogen dynamics, enabling the identification of molecular signatures linked to resistance, susceptibility, and adaptation.

Genomics has become a powerful tool for identifying genetic determinants of disease susceptibility and resistance in marine invertebrates. Advances in high-throughput sequencing have enabled comprehensive characterization of host genomes, facilitating the discovery of immune-related genes, stress-response pathways, and molecular markers associated with pathogen recognition. Recent genomic studies have shed light on host-pathogen interactions, revealing how sea cucumbers activate innate immune responses to *Vibrio* infections through the expression of pattern recognition receptors and antimicrobial peptides. Moreover, genomic characterization of bacteriophages targeting *Vibrio* species has opened new possibilities for biological control, offering promising alternatives to antibiotics in aquaculture. For instance, phage vB_VcyS_Vc1 has demonstrated strong efficacy against *V. cyclitrophicus* and has markedly improved survival in infected juvenile sea cucumbers. These findings underscore the potential of genomics-based interventions to strengthen host resilience and reduce disease outbreaks.

Transcriptomics complements genomics by providing dynamic insights into gene expression changes during disease progression and environmental stress. In *A. japonicus*, hundreds of differentially expressed genes have been identified in response to *V. splendidus* infection, particularly those involved in immune pathways such as MAPK, chemokine signaling, and lysosome mediated defense. Transcriptomic profiling also highlights the essential role of stress-response genes, including heat shock proteins, in mitigating damage caused by environmental fluctuations and pathogen invasion. In addition, transcriptomics has uncovered novel regulatory mechanisms such as circRNAs and m6A modifications that influence immune modulation and apoptosis, offering potential biomarkers for SUD resistance. Collectively, these findings underscore the complexity of immune regulation and provide opportunities for selective breeding programs aimed at enhancing disease tolerance in aquaculture species.

Proteomics provides an additional layer of insight by characterizing protein expression patterns linked to immune defense, stress adaptation, and tissue remodeling during SUD. Proteomic analyses have shown the upregulation of heat shock proteins, antioxidant enzymes, and immune-related proteins in response to infection, highlighting their crucial roles in maintaining cellular homeostasis. Investigations into therapeutic approaches, including chicken egg yolk antibodies (IgY) and bioactive compounds such as polydeoxyribonucleotide (PDRN), have demonstrated promising effects in enhancing immune function and

reducing oxidative damage. These findings emphasize the value of proteomics in identifying functional protein networks involved in disease resistance and tissue repair, thereby informing the development of immune-supportive therapies for managing SUD in aquaculture systems.

Metabolomics reveals the biochemical alterations associated with disease progression and environmental stress. In sea cucumbers affected by SUD, metabolomic profiling has identified major disruptions in energy metabolism, lipid composition, and oxidative stress regulation. Elevated levels of oxidative stress markers such as malondialdehyde (MDA), together with reduced antioxidant enzyme activity, indicate an imbalance in redox homeostasis that worsens tissue damage. Shifts in key metabolites, including amino acids, phospholipids, and osmotic regulators, highlight how metabolic reprogramming occurs during infection and tissue repair. Comparative studies on estivation in *A. japonicus* demonstrate similar adaptive strategies, with energy metabolism shifting from carbohydrate utilization to lipid and amino acid catabolism, accompanied by enhanced antioxidant defenses to sustain cellular viability under hypometabolic conditions. These parallels suggest that metabolic flexibility is fundamental to stress resilience in marine invertebrates and may guide strategies to improve disease tolerance in aquaculture.

Towards multi-omics integration

The integration of genomics, transcriptomics, proteomics, and metabolomics offers a transformative framework for unraveling the pathophysiology of SUD. By combining these complementary datasets, we can construct comprehensive molecular interaction networks that clarify the relationships between genetic regulation, protein function, and metabolic adaptation during disease progression. Emerging approaches including single-cell omics, CRISPR-based functional genomics, and machine learning-driven data integration promise to advance our understanding of cell-type-specific responses, gene functions, and predictive biomarker discovery. Moreover, coupling multi-omics data with microbiome profiling and environmental parameters will be essential for characterizing host microbe interactions and forecasting disease outbreaks in the context of climate change and anthropogenic stressors.

Despite these advances, several limitations persist. Many studies remain confined to single-omics analyses or focus narrowly on specific tissues or developmental stages. Functional validation of candidate genes and proteins is limited, while the integration of environmental variables with omics profiles continues to be a major challenge. Furthermore, the high costs and technical complexity of multi-omics

approaches hinder their widespread application in non-model marine invertebrates.

Addressing SUD in marine invertebrates requires collaborative, interdisciplinary research that bridges molecular biology, ecology, and environmental science. By fostering partnerships between aquaculture practitioners, molecular biologists, and environmental scientists, we can translate multi omics insights into effective disease management strategies. Ultimately, a systems-level understanding of SUD pathogenesis, supported by multi-omics integration and emerging technologies, will be essential to safeguard marine biodiversity, improve aquaculture resilience, and mitigate the growing threat of disease in marine ecosystems.

Conclusion

Skin ulcerative disease in sea cucumbers is a multifactorial condition with significant ecological and aquaculture consequences. This review highlights key advances in understanding SUD pathophysiology through the integration of multi-omics approaches genomics, transcriptomics, proteomics, and metabolomics. Each approach provides critical insights into immune responses, stress adaptation, metabolic changes, and the complexity of host-pathogen interactions. Integrating these datasets enables the identification of predictive biomarkers, functional pathways, and potential therapeutic targets, including innovative interventions such as phage therapy and IgY-based treatments.

Emerging technologies such as single-cell omics, CRISPR-based functional genomics, and machine learning-driven data integration provide powerful opportunities to uncover cell-type-specific responses, improve predictive modeling, and design targeted interventions. However, limitations persist, including tissue-specific variability, incomplete functional validation, and the complexity of environmental influences, highlighting the need for continued research. Effectively addressing SUD will require interdisciplinary collaboration that integrates molecular biology, ecology, and environmental science to develop sustainable and practical disease management strategies.

Ultimately, multi-omics integration offers a powerful framework for advancing our understanding of SUD, supporting the development of effective mitigation strategies, strengthening aquaculture resilience, and protecting marine biodiversity. This review provides a comprehensive reference and roadmap to guide future research aimed at understanding and controlling SUD in marine invertebrates.

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Declarations

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