



Screening of marine sediment-derived microorganisms and their bioactive metabolites: a review

Hongli Yao^{1,3,6} · Shuangping Liu^{1,2,3,4,5} · Tiantian Liu^{1,3,4,5} · Dongliang Ren^{1,3} · Qilin Yang^{1,3} · Zhilei Zhou^{1,2,3,4,5} · Jian Mao^{1,2,3,4,5}

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Abstract

Marine sediments are one of the largest habitats on Earth, and their unique ecology, such as high salinity, high pressure, and hypoxia, may activate certain silent genes in marine microbes, resulting in microbes, enzymes, active products, and specific metabolic pathways that can adapt to these specific ecological environments. Marine sediment-derived microorganisms and their bioactive metabolites are of great significance and have potential commercial development prospects for food, pharmaceutical, chemical industries, agriculture, environmental protection and human nutrition and health. In recent years, although there have been numerous scientific reports surrounding marine sediment-derived microorganisms and their bioactive metabolites, a comprehensive review of their research progress is lacking. This paper presents the development and renewal of traditional culture-dependent and omics analysis techniques and their application to the screening of marine sediment-derived microorganisms producing bioactive substances. It also highlights recent research advances in the last five years surrounding the types, functional properties and potential applications of bioactive metabolites produced by marine sediment-derived microorganisms. These bioactive metabolites mainly include antibiotics, enzymes, enzyme inhibitors, sugars, proteins, peptides, and some other small molecule metabolites. In addition, the review ends with concluding remarks on the challenges and future directions for marine sediment-derived microorganisms and their bioactive metabolites. The review report not only helps to deepen the understanding of marine sediment-derived microorganisms and their bioactive metabolites, but also provides some useful information for the exploitation and utilization of marine microbial resources and the mining of new compounds with potential functional properties.

Keywords Bioactive substances · Marine sediment · Microorganisms · Functional properties · Omics analysis

✉ Jian Mao
maojian@jiangnan.edu.cn
Hongli Yao
jnut-yaohongli@outlook.com
Shuangping Liu
liushuangping668@126.com
Tiantian Liu
liutiantian@jiangnan.edu.cn
Dongliang Ren
7200112086@vip.jiangnan.edu.cn
Qilin Yang
7210112065@stu.jiangnan.edu.cn
Zhilei Zhou
zhouz1985@126.com

- 1 National Engineering Research Center of Cereal Fermentation and Food Biomanufacturing, School of Food Science and Technology, Jiangnan University, Wuxi 214122, Jiangsu, China
- 2 Southern Marine Science and Engineering Guangdong Laboratory, Guangzhou 511458, Guangdong, China
- 3 Jiangsu Provincial Engineering Research Center for Bioactive Product Processing Technology, Jiangnan University, Wuxi 214122, Jiangsu, China
- 4 Jiangnan University (Shaoxing) Industrial Technology Research Institute, Shaoxing 31200, Zhejiang, China
- 5 National Engineering Research Center of Huangjiu, Zhejiang Guyuelongshan Shaoxing Wine CO., LTD, Shaoxing 646000, Zhejiang, China
- 6 Department of Biology and Food Engineering, Bozhou University, Bozhou 236800, Anhui, China

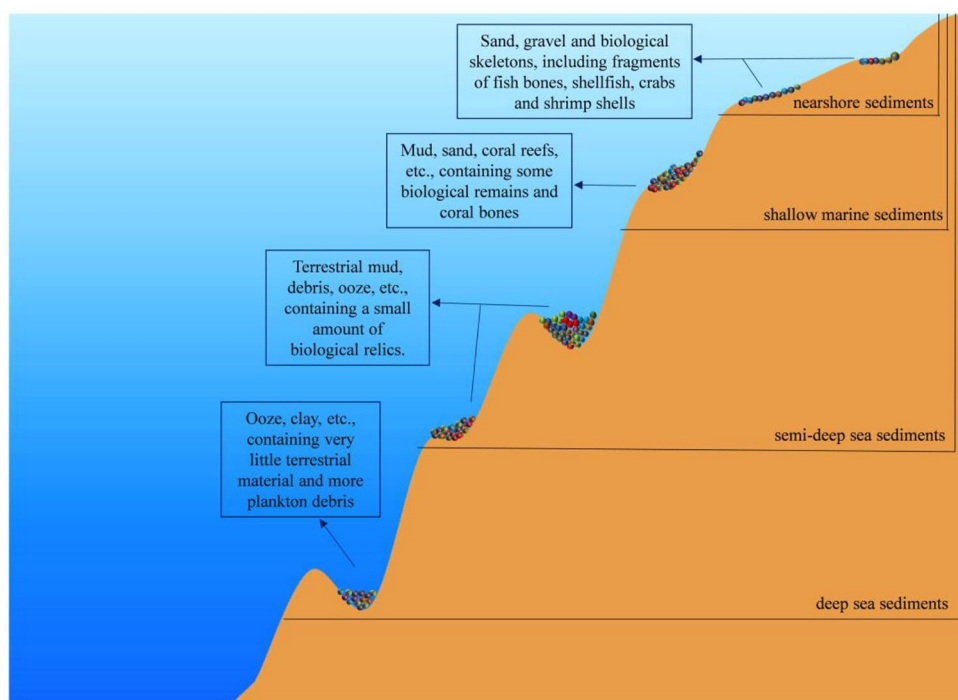
Introduction

Marine sediments are defined as deposits on the seafloor formed by various marine deposits, which make up more than 70% of the Earth's surface. There are many ways to classify marine sediments. For example, according to the lithology, marine sediments can be classified as conglomerate, sandstone, siltstone, and limestone (Tiwari and Mishra 2007; Awramik and Buchheim 2009). Depending on the grain size, they can be classified as boulder, medium gravel, gravel, sandy gravel, very coarse sand, coarse sand, medium sand, fine sand, very fine sand, silt, and clay, respectively (Callesen et al. 2018; Hassaan and El Nembr 2021). Conventional classification of marine sediments is based primarily on depth (Weltje and von Eynatten 2004). Generally, marine sediments may be divided into the following types: nearshore sediments, shallow marine sediments, semi-deep sea sediments, deep sea sediments, and other types (Li et al. 2021). The composition of marine sediments at different depths, including soil, gravel, biological debris, organic nutrients, minerals, salt concentrations, and certain compounds, is different (Hoshino et al. 2020), as shown in Fig. 1. Compared with land, the ocean has unique ecological characteristics such as high salinity, high pressure, low temperature, low oxygen, great variation of light intensity, and poor nutrition, which leads to the diversity of microbial species and metabolic pathways (Kim 2019; Bolser et al. 2023). Marine sediment is one of the largest habitats on Earth (Hoshino and Inagaki 2019). However, our understanding of its microbial diversity and function is relatively limited.

Marine microorganisms refer to all organisms that use marine water as their normal living environment, and include prokaryotes, eukaryotes, and viruses (Suttle 2007). Studies have shown that the marine environment contains about 3.6×10^{30} microorganisms (Egerton et al. 2018), while the total number of microbial cells in marine sediment is presently estimated as 2.9×10^{29} to 5.4×10^{29} cells, accounting for 0.18 to 3.6% of Earth's total living biomass (Hoshino et al. 2020). Marine microorganisms have a dual identity as producers and decomposers, and can participate in the entire process of decomposition, synthesis, and transformation of marine substances (Mishra et al. 2022). They not only purify, regulate and repair the marine environment and ecosystem, but also play an important role in the development of food, agriculture, medicine, energy, and other industries (Doley et al. 2020; Ghosh et al. 2022). For example, a strain of *Erythrobacter* sp. SDW2 from seawater that produces lutein can be used as an industrial microbe candidate in the production of food, cosmetics, and pharmaceuticals (Jeong et al. 2022). *Pseudomonas* GWSMS-1 strain from Antarctica, capable of producing cold-adapted chitinase, has been reported as a competitive candidate for biological control of plant pathogenic fungi (Liu et al. 2019). The collaboration of marine chitinase produced by deep-sea sediment-derived *Bacillus haynesii* with *Mucor* has also been reported to be effective in increasing bioethanol production (Govindaraj et al. 2023).

Marine microorganisms are often divided into culturable and unculturable microorganisms (Wang et al. 2021). For the screening of cultured marine microorganisms, the

Fig. 1 Major components of marine sediments at different depths



traditional culture-dependent approach is mainly through the design of appropriate screening media and culture conditions to obtain pure cultures (WagnerDöbler et al. 2002; Mu et al. 2021). Pure cultures are subsequently identified by physiological and biochemical characteristics and molecular biological conservative sequence methods. However, under standard laboratory conditions, more than 99% of marine microorganisms are uncultured, mainly due to a lack of information on the nutritional needs of uncultured microorganisms (Jiao et al. 2021). Traditional culture techniques are difficult to study those microorganisms that cannot grow in laboratory conditions, thus failing to reflect the abundance and scope of microbial diversity in nature, making it difficult to fully exploit and utilize the vast treasure trove of marine microorganisms as well (Lewis et al. 2021). Metagenomics is a culture-independent approach that can largely avoid the isolation and culture of microorganisms in order to analyze their genetic information and screen for functional genes (Berini et al. 2017). This method may be one of the more suitable methods to solve the problem of utilizing undeveloped genetic resources of uncultured microorganisms (Chin et al. 2022). In recent years, with the improvement of bioinformatics database construction and continuous innovation of analytical methods, multi-omics integration techniques have been rapidly developed, such as metagenomics, metaproteomics, metatranscriptomics and metabolomics (Miao et al. 2021). The combined application of multi-omics can help discover new microorganisms from marine ecological environments and provide unprecedented opportunities for screening of marine microorganisms that produce active compounds (Palazzotto and Weber 2018). In addition, the integration of these techniques can also help to explore the community structure of microorganisms and assess the complex relationship between microorganisms and the marine environment (Marfil-Santana et al. 2021), which can deepen the understanding of marine life.

The ocean is not only an important resource for microorganisms, but also an excellent source of natural bioactive molecules, new compounds, secondary metabolites and enzymes (Ameen et al. 2021; Ghosh et al. 2022). However, the bioactive marine microorganisms found so far may only account for about 1% of marine microorganisms (Li et al. 2021). This biological activity, which includes antibacterial, anti-cancer, anti-diabetes, anti-blood pressure, anti-inflammation, anti-virus, anti-oxidants and immunity (Song et al. 2021; Ghosh et al. 2022), has important implications for food, medicine and human nutrition and health. Therefore, it is of great scientific research and potential commercial application value to screen microorganisms with active components from marine sediments. In recent years, there have been endless reports on the production of bioactive substances by microorganisms from marine sediments

(Yang and Song 2018; Yurchenko et al. 2019; Han et al. 2020; Kikukawa et al. 2021), as well as numerous reviews on specific marine bioactive compounds, mainly around the source and function of specific bioactive substances (Cunha and Pintado 2022; Liu et al. 2022). The purpose of this review is to collect up-to-date research information on the active substances produced by different microorganisms in marine sediments. It also presents a number of methods for screening microorganisms and their applications to screening marine-derived microorganisms. In addition, the types, functional properties and potential applications of bioactive metabolites produced by marine-derived microorganisms are highlighted. This review may provide some useful information for the development and utilization of marine sediment-derived microbial resources and the excavation of bioactive matrix with potential functional characteristics.

Screening and identification of marine sediment-derived microorganisms

Development and renewal of traditional culture techniques and modern bioinformatics techniques

The establishment and development of traditional culture techniques has allowed us to isolate a large number of different microorganisms from ecological environments, and these techniques have been fundamental and instrumental in basic and applied research in microbiology for over a hundred years. The general process of traditional microbial culture is the design or simulation of suitable culture media and conditions for microbial growth, reproduction and metabolism based on the target organism or compound after sample acquisition. Then the pure culture (single strain and colony) obtained after separation and purification by various pretreatment strategies and techniques is analyzed and identified according to its structural, physiological and biochemical characteristics and conserved gene sequences (such as 16 S rRNA and ITS sequence) (Mohamed et al. 2021; Wang et al. 2021). To rapidly screen and isolate target strains from different ecological environments, identify and obtain their metabolites, the culture technology has been continuously developed and improved. Combined with sample pre-processing and modern biological devices, it has been developed into a variety of new methods and means for the study of novel target microorganisms and their potential activities, such as in situ culture technology and microfluidic droplet control technology (Wang et al. 2021; Imachi et al. 2022). An in situ cultivation device (the I-tip) has been used to cultivate microorganisms from Baikalian sponges (Jung et al. 2014). The I-tip method has produced cultures of 34 species from five major phyla,

Actinobacteria, *Alphaproteobacteria*, *Betaproteobacteria*, *Firmicutes*, and *Gammaproteobacteria*. The analysis and screening of *Phaeodactylum tricornutum* and *Nannochloropsis gaditana* using droplet-based microfluidic methods allows for rapid discrimination between individual *Phaeodactylum tricornutum* or *Nannochloropsis gaditana* cells engineered to express green fluorescent proteins from wild-type cells (Yu et al. 2021). Although these methods have many limitations, they contribute to the exploitation and utilization of the genetic resources of marine microbes to a certain extent, and they also provide a powerful means for the study of genetic diversity in the ocean (Imachi et al. 2022).

Due to the specificity of the growing environment, most marine microorganisms could be uncultured in the laboratory (Jiao et al. 2021; Mohamed et al. 2021). Advances in gene sequencing and bioinformatics have enabled humans to quickly sequence marine sediment samples (not just to identify specific genes) to study changes in metagenomic function and metabolism (Acinas et al. 2021), which avoids the limitation that many microorganisms may not be cultured in standard laboratories. This also makes it possible to study the microbial community structure and specific functional microbial strains in extreme marine environments. In recent years, gene sequencing technology has developed from the first generation (Sanger sequencing) to the second generation (Next-generation sequencing, NGS), and then to the latest third generation (Third-generation sequencing, TGS) (van Dijk et al. 2018; Hu et al. 2021; Athanasopoulou

et al. 2022). Compared with NGS technology, TGS based on single molecule real-time sequencing platform (for example, PacBio Sequel II platform, Pacific Biosciences Of California, Inc.) can extend the read length from hundreds of bases to thousands of bases, the maximum reading length is 20 kb, and the data of about 8 GB can be obtained after about 1 h of sequencing (Xiao and Zhou 2020; Athanasopoulou et al. 2022). Furthermore, innovative long-read technology makes genome sequencing a tractable procedure, reducing the average time of the library construction workflow and simplifying the ab-initio genome assembly process due to long reads (Athanasopoulou et al. 2022).

Although metagenomics has been intensively studied, it is difficult to give information on which microbial characteristics are truly associated with phenotypes relying solely on metagenomics analyses (Liu et al. 2021). Therefore, integrated meta-genomics approaches (as shown in Fig. 2) are expected to investigate interactions between microorganisms, between microorganisms and the environment, and between microorganisms and metabolites. Thousands of molecules in biological samples (DNA, RNA, proteins, and metabolites) can be measured simultaneously by using various combinatorial techniques for more efficient, rapid and accurate identification of microflora characteristics (Yu et al. 2019). It has been reported that the microbial methane oxidation at the sediment-water interface of a shallow marine methane seep has been studied by using metagenomics and metaproteomics (Taubert et al. 2019). The results

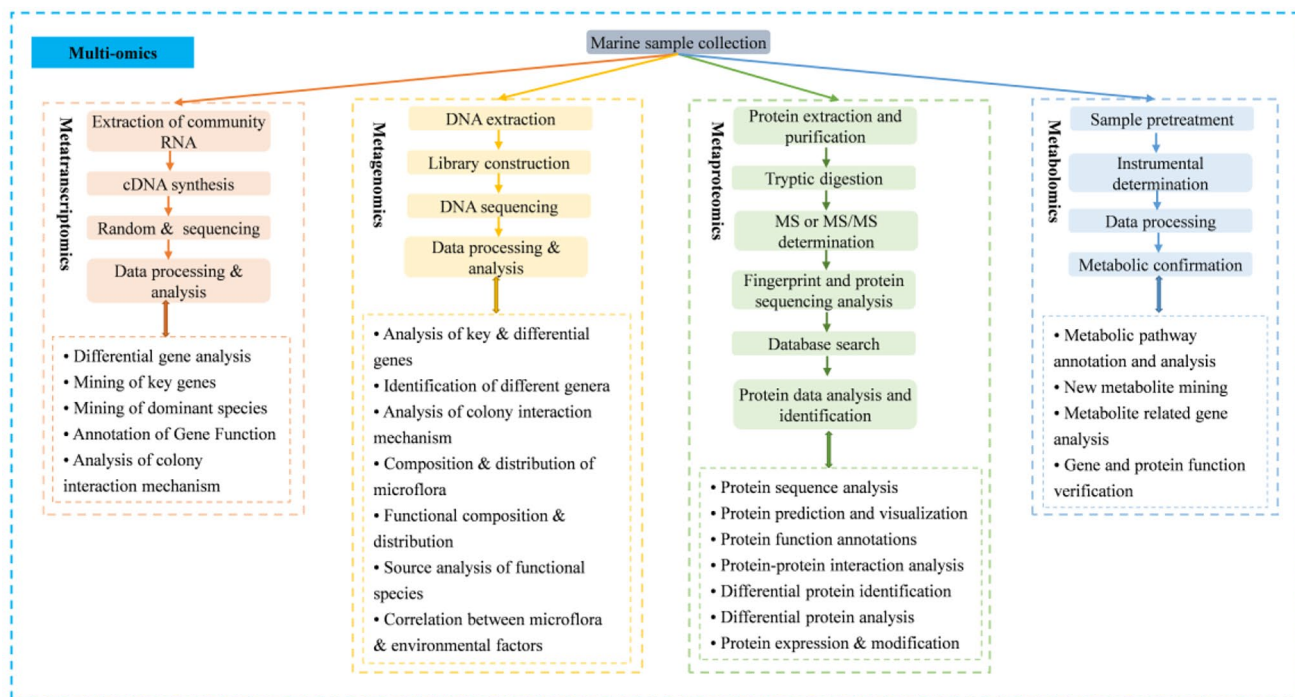


Fig. 2 The overall framework, technical process, function and application of multi-omics methods

have indicated that various members of the gammaproteobacterial family *Methylococcaceae* are the key players in methane oxidation. In complex ecosystems, metagenomic techniques reveal functional potential (Aguilar-Pulido et al. 2016; Yu et al. 2019). For example, metagenomics has been used to analyze the potential metabolic capacity of microbial communities in deep sediments in the southern Gulf of Mexico (Torres-Beltran et al. 2021). It has been shown that the metabolic cores of prokaryotic communities exhibit different functional signatures between the continental slope and abyssal plain. Metatranscriptomics and metabonomics can reveal active genes and metabolic responses to specific physiological processes. Metatranscriptomics has been used to explore microbial polyphosphate utilization in marine sediments (Jones et al. 2016). The results have shown that sulfur oxidizing microorganisms preferentially express polyphosphate degradation genes in anoxic conditions. Non-targeted metabonomics has been used to reveal the metabolic response of *Bacillus* to cyclotetramethylene-trinitramine stress (Yang et al. 2021a, b, c). The results have shown that the main differentially expressed metabolites during cyclotetramethylene-trinitramine stress are lipids and lipid-like molecules, and that the most significantly affected metabolic pathway is purine metabolism. Metaproteomics aims to study the composition and differential expression of proteins in cells. A novel gene encoding for a lipolytic enzyme has been identified using a functional metaproteomics approach and successfully expressed in *Escherichia coli* (*E. coli*) (Sukul et al. 2018). Currently, even though the ability to report comprehensive analyses of microorganisms in marine sediments using integrated metagenomics techniques is still limited (Yu et al. 2019), these new techniques have become indispensable tools for scientists to explore marine microbial resources and functional active components.

Screening and identification of marine sediment-derived microorganisms using dependent-culture and modern bioinformatics techniques

In recent years, interest in terrestrial microbial resources has gradually declined, while more researchers have focused on the exploitation of marine microbial resources, particularly those from marine sediments. Traditional isolation and culture technology is a common tool for screening marine microorganisms, which provides the basic conditions for the discovery of novel marine microorganisms and functional structural compounds. Using traditional culture and isolation techniques, 13 strains of marine bacteria have been isolated from 25 sediment and water samples taken from a shallow area off the west coast of Yemen. Based on morphology, biochemistry, and 16 S rRNA gene sequence, the

isolate 1S1 has been identified as strain *Streptomyces* sp.S1. Evaluation and analysis of its antibacterial potential and ethyl acetate extract suggest that the strain has the ability to produce a variety of antibacterial compounds (Mothana et al. 2022). Some marine microorganisms have special growth conditions, and are difficult to isolate and culture in the laboratory (Wang et al. 2021). Researchers usually need to find a suitable culture medium and design optimal growth conditions, or simulate a marine ecological environment suitable for the growth, reproduction, and metabolism of the target strain as far as possible to achieve the purpose of enriching microorganisms. For example, to obtain bioactive sulfate-enriched marine anaerobic bacteria, an anoxic enrichment medium containing mineral brackish marine media with sulfated polysaccharides as a substrate has been designed, and anoxic Black Sea sediment from a depth of 2100 m has been incubated continuously for several weeks to obtain microbial colonies (van Vliet et al. 2019). Community analysis using 16 S rRNA gene amplicon sequencing has shown that *Kiritimatiella* clade R76-B128 can be enriched in the concentrated solution with the sulfated polysaccharides fucoidan and iota-carrageenan as substrates. The results of sulfate esterase studies on two of these strains, F1 and F21, imply that they are the most abundant microorganisms encoding sulfate esterases available. The use of certain pre-processing techniques to enrich the target microbe before strain isolation can effectively increase the separation efficiency of the microbe (Mohamed et al. 2021; Mu et al. 2021). A total of 290 actinomycetes strains have been collected from 14 sediment samples from the Oman Sea using different media and heat treatments (Mohamed et al. 2021). The results of 16 S rRNA gene sequencing suggest that three of the strains may be *Streptomyces djakartensis*, *Streptomyces olivaceus*, and *Nocardioopsis dassonvillei*. The results of activity tests on ethyl acetate extracts from all strains suggest the widespread distribution of the antioxidant and cytotoxic compounds produced by *Actinobacteria* in the Oman Sea sediments.

Culture-independent metagenomics can provide a new perspective on uncultivated marine microorganisms by cloning and analyzing microbial DNA directly from environmental samples to address the central question of the production potential of bioactive substances. Using metagenomic sequencing of antibiotic resistance genes from 12 coastal sediment samples covering the urban coastline of Kuwait, 20 common resistance genes have been identified, ranging from 402 genes to 34 drug classes. 46% of the genes are from the phylum *Proteobacteria* (Habibi et al. 2022). Metagenomics can be used not only to discover these potentially functional genes, but also to explore differences in the community structure, function and metabolism of complex microorganisms in marine sediments (Gong et al.

2019; Parvathi et al. 2020). Comparing the taxonomic structure and genetic profiles of mangrove and non-mangrove sediment samples, *Proteobacteria*, *Bacteroidetes*, and *Firmicutes* are the most abundant bacterial phyla (Zhao et al. 2019b). Archaeal family *Methanosarcinaceae* and bacterial genera *Vibrio* and *Dehalococcoides* are significantly higher in the mangrove sediments than in the nonmangrove sediments. Functional analysis has shown that “Carbohydrate metabolism” is the most abundant metabolic category. The significant difference in carbohydrate metabolism between mangrove sediments and non-mangrove sediments is attributed to the higher contents of polyphenol oxidase, hexosyltransferase, and β -N-acetylhexosaminidase in mangrove sediments. Metagenomics can be used not only to explore the ecological structure and metabolic processes of complex microbial communities, but also as an indispensable method to rapidly mine the genes encoding bioactive metabolites in metagenomes. It provides a tool for the screening of uncultured microorganisms from marine sediment sources and the discovery of novel bioactive metabolites.

The emergence of multi-omics technique has accelerated the development of quantitative and high-throughput research. With the continuous proposal, development and updating of this technology, people have a deeper and clearer understanding of the structural and functional characteristics of microbial communities in marine sediments and their internal and external metabolism and synthesis mechanisms. Previous studies have reported the use of amplicon sequencing combined with in-depth metagenomics to study the composition and function of microbial communities in sediments collected from different marine environments (Zhang et al. 2022b). The results have shown that microbial communities in seamount sediments are more abundant and diverse than those in the cold seeps and marine trenches sediments. *Acinetobacter* dominates the cold seeps sediments and is replaced by *Halomonas* and *Pseudomonas* in seamount and marine trench sediments. Results from the exploration of microbial communities in the oligotrophic northern Indian Ocean using an integrated meta-omics-based approach suggest that metabolic regulation is an important mechanism for maintaining the stability of microbial communities dominated by *Prochlorococcus*, *Synechococcus*, and SAR₁₁ (Xie et al. 2022). In addition, multi-omics techniques can quickly identify not only genetic materials in marine sediments, but also new bioactive substances with specific functions. A metagenome and metatranscriptome-based integrated approach has been used to identify small RNAs in the microbiome of Guaymas Basin sediments (Nawaz and Wang 2022). The results show that 82% of the sRNAs are highly similar to the previously known sRNA in the Rfam database, and “18%” are putative novel sRNA motifs. A putative *cis*-acting sRNA potentially

binding to methyl coenzyme M reductase, a key enzyme in methanogenesis or anaerobic oxidation of methane, has been found in the genome of ANaerobic MEthane oxidizing archaea group 1, the dominant microorganism in the sample. Of course, mutli-omics techniques highlight a lot of interesting information about uncultured marine microorganisms, but independent culture methods are also needed to confirm potential activities. These techniques have become an effective tool for scientists to explore marine microbial resources and functionally active components.

Production of bioactive metabolites by marine sediment-derived microorganisms

The diversity of marine environments not only determines biological diversity, but also produces many types of compounds with novel chemical structures and remarkable physiological activity. The diversity of these compounds may far exceed that of terrestrial organisms (Dayanidhi et al. 2021). Studies have shown that the biosynthesis of natural products by these marine microorganisms depends on a variety of biological and abiotic factors in the marine environment, including temperature, nutrients, salinity, and their interactions with other microorganisms (Gozari et al. 2021). Marine bioactive substances are a broad category that includes not only antibiotics, sugars, proteins, peptides, amino acids, but also pigments, alkaloids, terpenes, saponins, and polyketones (Cunha and Pintado 2022; Ghosh et al. 2022). Some marine sediment-derived microorganisms and their bioactive metabolites, functions, and potential applications are shown in Fig. 3. The study of bioactive metabolites produced by marine sediment-derived microorganisms is of great significance both in theory and in the maintenance of human health.

Production of antibiotics as potential drugs

Antibiotics are generally considered to be substances produced by microbial metabolism that can inhibit the growth and reproduction of pathogenic microorganisms (or cancer cells) at very low concentrations. According to their chemical properties and structure, they can be divided into quinolones, β -lactams, macrolides, aminoglycosides, and other antibiotics (Ozumchelouei et al. 2020). According to their different functions, antibiotics can also be divided into antibacterial, antifungal, antiviral, and anti-tumor (Aminov 2009). In recent years, although most of the clinically available antibiotics come from terrestrial *Streptomyces*, as many infectious diseases become resistant to traditional antibiotics, the input and output rate of terrestrial antibiotics continues to decline, as well as the continuous development of



Fig. 3 Types, functions and potential applications of bioactive compounds produced by marine sediment-derived microorganisms

marine biotechnology and other reasons, many scientists and explorers turn their attention to the ocean to discover novel antibiotics (Durand et al. 2019). On the one hand, features of resource sustainability and abundant species of marine microorganisms may provide rich species or matrix materials for new drug discovery. On the other hand, the discovery of new marine antibiotics may overcome the dependence of human health on terrestrial antibiotics (Zhang et al. 2021a).

Screening of marine sediment-derived microorganisms producing antibiotics, especially actinomycetes (Qu et al.

2018), for the development of novel marine drugs is one of the important directions in the exploitation of marine sediment microbial resources in recent years. Some information on antibiotic production by marine sediment-derived microorganisms is given in Table 1. Structural formula of antibiotics with potential functional properties are shown in Fig. 4. It has been reported that 28 strains of actinomycetes have been isolated from sediments ranging from 98 to 2974 m deep in the South China Sea, of which 4 strains have anti-*Mycobacterium phlei* activity and 5 strains have

Table 1 Antibiotics produced by marine sediment-derived microorganisms and their biological activities reported in recent five years

Specific microorganisms	Source	Bioactive compounds ^a	Bioactivity	Reference
<i>Streptomyces</i> sp. OPMA00071	Okinawan marine sediments	JBIR-150 ¹	Cytotoxicity	(Kawahara et al. 2018)
<i>Salinispora</i> sp. NHF45, <i>Nocardioopsis</i> sp. NHF48, and <i>Streptomyces</i> sp. NHF86	South China sea sediments	Rifamycin B ² , an analogue of paulomenol ³ and α -pyrone compound ⁴	Antibacterial	(Yang and Song 2018)
<i>Streptomyces fradiae</i> VITMK2	Marine soil sediments of Pichavaram, Tamil Nadu, India	9(10 H)-Acridanone ⁵	Antiviral	(Manimaran et al. 2018)
<i>Streptomyces chartreusis/cacaoi/sampsonii/qinglanensis/diastaticus</i>	Northern Oman Sea sediments	Ethyl acetate culture extracts	Antibacterial and antitumor	(Gozari et al. 2019)
<i>Streptomyces monashensis</i> sp. MUSC 1J ^T	Sarawak mangrove soil	Fermentation broth extract	Anticancer and antioxidant	(Law et al. 2019)
<i>Salinispora arenicola</i>	Marine Sediments of St. Peter and St. Paul Archipelago, Brazil	Salinaphthoquinones A-E ⁶⁻¹⁰	Antibacterial	(da Silva et al. 2019a; Silva et al. 2019b)
<i>Streptomyces</i> sp. ZS-A45	Marine sediments of Zhoushan Island	Nitricquinomycins A-C ¹¹⁻¹³	Antibacterial	(Zhou et al. 2019)
<i>Bingchengensis</i> ULS14	Lagos Lagoon sediment	ULDF 4 and 5 ^{14,15}	Anticancer	(Davies-Bolorunduro et al. 2019)
<i>Streptomyces</i> sp. RKND004	Prince Edward Island Sediment	Terrosamycins A and B ^{16,17}	Antibacterial and anticancer	(Sproule et al. 2019)
<i>Streptomyces</i> sp. RMS518F	Sediments of the Red Sea in Sharm el-Sheikh	Viscosine ¹⁸	Antibacterial and anticancer	(Selim et al. 2019)
<i>Streptomyces</i> sp. EG1	Sediments from the northern Mediterranean coast of Egypt	Mersaquinone ¹⁹	Antibacterial	(Kim et al. 2020)

Table 1 (continued)

Specific microorganisms	Source	Bioactive compounds ^a	Bioactivity	Reference
<i>Streptomyces griseorubens</i> DSD069	Philippine marine sediments	Bisanhydroaklavinone ²⁰ and 1-Hydroxybisanhydroaklavinone ²¹	Anticancer	(Paderog et al. 2020)
<i>Streptomyces</i> sp. Shell-016	Shell sediments in Binzhou shell dike island and Wetland National Nature Reserve, China	Shellmycin A-D ²²⁻²⁵	Anticancer	(Han et al. 2020)
<i>Streptomyces xinghaiensis</i> SCSIO S15077	The South China Sea sediment	Tunicamycin ²⁶	Antibacterial	(Zhang et al. 2020)
<i>Streptomyces</i> sp. DSD011	Marine sediments in near the coast of Islas de Gigantes, Iloilo	Fridamycin A and D ^{27,28}	Antibacterial	(Sabido et al. 2020)
<i>Verrucosipora maris</i> AB-18-032	Sediments from the Sea of Japan	Abyssomicin C ²⁹	Antibacterial	(Fiedler 2021)
<i>Pseudoalteromonas xiamenensis</i> STKMTI.2	Man-grove sediments of Setokok Island, Indonesia	Ethyl acetate extracts	Anti-vibrio	(Handayani et al. 2022)
<i>Streptomyces</i> sp. EG32	Sediments of the northern coast of Mediterranean Sea, Egypt	Chlororesistoflavins A and B ^{30,31}	Antibacterial	(Kim et al. 2022)
<i>Actinoalloteichus cyanogriseus</i> 12A22	Sediments of the South China Sea	Cyclo-(L-Pro-D-Pro-L-Tyr-L-Tyr) ³² and 2-hydroxyethyl-3-methyl-1,4-naphthoquinone ³³	Antibacterial and antitumor	(Zhang et al. 2021b)

Table 1 (continued)

Specific microorganisms	Source	Bioactive compounds ^a	Bioactivity	Reference
<i>Streptomyces</i> sp. KMM 9044	Marine sediment in the north-western part of the Sea of Japan	Streptocinnamides A and B ^{34,35}	Antibacterial	(Makarieva et al. 2022)
<i>Aspergillus</i> sp. YQ-13	Sediment Kueishantao hydrothermal vents off Taiwan	3-hydroxy-2-(2-hydroxy-6-methoxy-4-methylbenzoyl)-5-methoxy-benzoic acid methyl ester ³⁶	Antioxidant	(Tao et al. 2018)
<i>Aspergillus flocculosus</i>	Vietnamese marine sediment	Drimane sesquiterpenoid derivatives 7 and 8 ^{37,38}	Anticancer and neuroprotection	(Yurchenko et al. 2019)
<i>Phomopsis tersa</i> FS441	Deep-sea sediments	Phomeroids A and B ^{39,40}	Anticancer	(Chen et al. 2020)
<i>Aspergillus niveoglaucus</i>	Vietnamese marine sediment	Niveoglaucins A and B ^{41,42}	Neuroprotection	(Yurchenko et al. 2020)
<i>Gallaecimonas mangrovi</i> HK-28	Man-grove sediments from Hainan province, China	Gallaecimonamides A-C ⁴³⁻⁴⁵	Antibacterial	(Ding et al. 2020)
<i>Bacillus</i> sp. ZJ318	Arctic Ocean marine sediments	Macrolactin J ⁴⁶	Antibacterial	(Zhang et al. 2022a)

^aThe numbers in this column represent the number of compounds, and the structural formula of the numbered compound corresponds to Fig. 4

anti-methicillin-resistant *Staphylococcus aureus* activity (Yang and Song 2018). Through 10 L scale fermentation experiment, a new bioactive α -pyranone compound has been determined. These new substances offer the possibility of discovering new drugs. Another study has reported that 172 strains from marine sediments at depths of 42 to 3763 m in the Arctic Ocean have been isolated, one of which has been identified as *Bacillus* ZJ318 based on 16 S rRNA sequencing analysis (Zhang et al. 2022a). The ethyl acetate extract of this strain has been shown to have a strong inhibitory effect on *Staphylococcus aureus*, and subsequently a known macromolecular lactide has been obtained by chromatographic separation and HPLC purification. Ethyl acetate culture extracts of actinomycetes isolated from marine sediments in other regions have also been shown to be toxic to some tumor cells, but not to normal cells (Gozari et al. 2019). These studies suggest that these ethyl acetate extracts

may have some degree of cell-selective inhibition, but further analysis of the composition of the ethyl acetate extracts is needed. In addition, it can also be studied from the aspects of intracellular and extracellular structural characterization, cellular metabolic processes, and pharmacokinetic model design to clarify the mechanism by which these extracts inhibit cell selectivity and screen more potential drugs or novel compounds.

Streptomyces, as soil saprophytes and common antibiotic-producing bacteria (Yang et al. 2020), have been reported to have antibiotic biosynthesis gene clusters (Romano et al. 2018). A new tetracene derivative has been isolated from marine-derived *Streptomyces* organic matter in the search for a new antibiotic against methicillin-resistant *Staphylococcus aureus*. This derivative has antibacterial activity against methicillin-resistant *Staphylococcus aureus*, and its minimum inhibitory concentration is 3.36 $\mu\text{g/mL}$ (Kim et al.

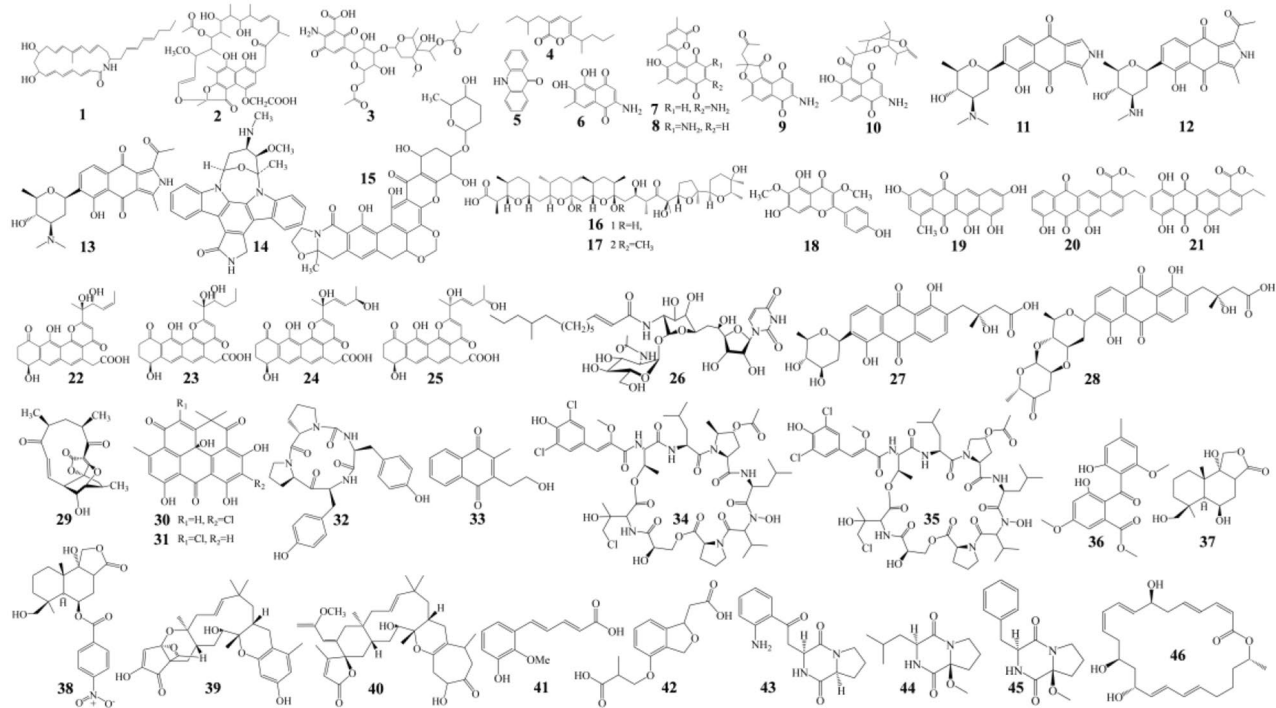


Fig. 4 Molecular structural formulae of novel compounds produced by marine sediment-derived microorganisms as potential antibiotics. The different numbers are consistent with the number labels of bioac-

2020). *Streptomyces griseus* is a species of *Streptomyces*. A crude extract of *Streptomyces griseus* isolated from marine sediments has also been shown to have high antibacterial activity against *Staphylococcus aureus*, and these antibiotic compounds have been identified as two anticancer anthracycline derivatives (Paderog et al. 2020). Similarly, *Streptomyces* sp. shell-016 isolated from shell sediments collected from Binzhou Shell Dike Island and Wetland National Nature Reserve in China can also produce new anticancer compounds (Han et al. 2020). After isolation and purification of these substances by HPLC, their toxic effects on five cancer cell lines have been confirmed. The IC_{50} values of their toxic effects on cancer cells ranged from 0.69 to 26.3 μ M.

Fungi can also produce certain antibacterial substances. For example, the fungus *Trichoderma* sp. JWM29-10-1 has been isolated from hydrothermal vent sediments on in Guishan Island, Taiwan, and five new polyketones and seven known compounds have been identified by spectroscopic analysis (Lai et al. 2022). Two new polyketones have shown not only strong antibacterial activity against *Helicobacter pylori*, but also significant inhibitory effects on the growth of gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus*, *Enterococcus faecalis*, and vancomycin-resistant *Enterococcus faecalis*. Similarly, four new compounds and five known metabolites have been isolated

compounds in Tables 1, which represent different bioactive compounds as potential antibiotics

from marine sediment-derived fungi in Vietnam. Some of these metabolites may be cytotoxic to prostate cancer cells, breast cancer cells, and neuroblasts (Yurchenko et al. 2019). In addition to the aforementioned microorganisms, since the first isolation of antibiotic-producing marine microorganisms, *Pseudomonas*, *Micrococcus*, *Bacillus*, and many undetermined new bacteria have been reported to be capable of producing a wide variety of antibiotics and their derivatives (Jose and Jha 2017; Guo et al. 2022). These special microorganisms have been found to be of great practical significance for the excavation of new antibiotics and the treatment of drug-resistant infectious diseases. Currently, most studies use traditional culture-dependent and 16 S rRNA sequence analysis to obtain target microorganisms, which are then combined with NMR, MS, HPLC and other chromatographic separation techniques to obtain corresponding novel compounds. These technologies provide some potential support for the development of novel drugs (Yurchenko et al. 2019; Han et al. 2020). It is believed that these new drugs will play a huge role in human health and disease treatment in the future.

Production of enzymes and enzyme inhibitors

Although a large number of enzymes have been recognized, these enzymes are often required to be stable under harsh

conditions such as high temperatures, extreme pH, high salt concentrations, and organic solvents (Gohel and Singh 2018). Therefore, it is still an important and urgent task to find new enzymes with special properties from special environments. In recent years, studies on specific functional enzymes and microbial screening in special extreme marine sediments have been reported, such as esterase (Lu et al. 2018), lipase (Verma et al. 2021), protease (Pessoa et al. 2017; Sun et al. 2020), amylase (Goel et al. 2022), agarase (Leema Roseline and Sachindra 2018), chitinase (Vasquez et al. 2021), and others.

Marine sediments are not only a resource bank containing huge biodiversity, but also a natural reserve for obtaining enzymes with potential for novel biocatalysts for biotechnology applications. Information on enzyme production by microorganisms from marine sediments over the past 5 years is given in Table 2. It has been reported that a novel esterase (Est3-14) has been screened and identified from marine environmental genomic DNA libraries by constructing fosmid genomic library and screening genes on a large scale (Lu et al. 2018). After purification, the enzyme can be used to prepare free all-trans-astaxanthin in a biphasic system, with a hydrolytic conversion ratio of up to 99.3% (Lu et al. 2018). 3-Deoxy-D-arabino-heptulosonate-7-phosphate synthase has been screened from a metagenomic library of subtropical marine mangrove sediments by a similar screening method, and has been successfully overexpressed in *E. coli* (Zhao et al. 2019a). The activity for the recombinant enzyme is the highest at pH 8.0 and 40 °C (Zhao et al. 2019a). It is not uncommon to screen for enzymes with special functional properties from marine sediments (Lu et al. 2018; Zhao et al. 2019a). Due to their superior properties, these enzymes have potential applications in food, medicine, agriculture, detergents, dyes, environmental protection and the chemical industry (Sun et al. 2020; Ben Ayed et al. 2021; Edoamodu and Nwodo 2022; Wu et al. 2022).

The metabolic diversity of microorganisms allows them to survive in harsh environments, which may be related to their own ability to produce enzymes (Zhang and Kim 2010). The Arctic bacterium *Colwellia hornerae* PAMC 20,917 strain, isolated from the offshore sediment near Ny-Ålesund, Svalbard, can grow best on marine agar at 10 °C due to the production of a cold-adapted and thermolabile alkaline phosphatase (Kim et al. 2018). Protease and amylase-producing microorganisms in extreme environments are often screened and widely used in many industrial fields. Recent studies have reported that *Colwellia* sp. NB097-1, isolated from a marine sediment sample from the Bering Sea, can produce a cold-adapted protease (Zhang et al. 2018). Heat resistance of proteases is an important property that can be used in food processing products,

detergents, pharmaceuticals and other industries (Sun et al. 2020). It has been reported that a heat-resistant serine protease (pF1AL2) has been screened from the genomic library of marine sediment microorganisms in the East China Sea (Sun et al. 2020). pF1AL2 has high stability under alkaline conditions, retaining more than 95% of its activity after 24 h at pH 11.0. This enzyme can be placed at 70 °C for 6 h and still maintain 80% activity, and has certain salt and acid resistance. Amylase is one of the most productive and widely used industrial enzymes, accounting for about 30% of the total sales of enzymes in the world (Paul et al. 2021). A gene encoding *BmaN* of the amylase from marine *Bacillus megaterium* NL3 has been expressed in *E. coli* (Shofiyah et al. 2020). This alpha-amylase has been obtained and has a maximum activity at pH 6.0 and 60 °C with a specific activity of 28.7 U/mg.

Although enzymes can be obtained from a variety of sources, including animals, plants, and microorganisms, the use of microorganisms to obtain the enzyme is one of the most common and desirable methods used in industry. Chitinase produced by marine microorganisms can hydrolyze chitin to release β -N-acetyl-D-glucosamine and N-acetyl chitin oligosaccharides (Liu et al. 2019). Chitin is a major resource for the preparation of chitin oligosaccharides and chitosan oligosaccharides, which have applicable values in the fields of medicine, food, health care, and environmental protection (Guan et al. 2019). Chitin, which belongs to the class of renewable resources, is abundant in the marine environment. In order to improve the degradation efficiency of chitin, it is particularly important to find efficient chitin-degrading bacteria and chitinase with higher activity from the marine environment. It has been reported that chitinase production in cold-adapted bacteria screened from the Maritime Antarctic has increased by a factor of 7.7 up to more than 330 U/L after optimizing culture conditions (Vasquez et al. 2021). Another study has reported the production of highly active chitinase by *Pseudomonas* from marine sediments on the Fildes Peninsula in Antarctica (Liu et al. 2019). When applied to cotton and cucumber, it can effectively suppress fungal-induced wilt disease and will play an important role in agricultural biocontrol.

Enzyme inhibitors are substances that specifically act on certain groups of enzymes, reducing their activity or even completely disabling them, mainly from plants, microorganisms and chemical synthesis. Some information on the enzyme inhibitors of marine microorganisms in the last five years is collected and showed in Table 3. In addition to the traditional screening and isolation of drug-derived bacteria, marine microorganisms and extreme microorganisms are new microbial groups among various enzyme inhibitors. *Actinomycetes* in marine sediments are the most common source of enzyme inhibitors (Imada 2005). Several new

Table 2 Enzymes produced by marine sediment-derived microorganisms reported in the past five years

Source	Specific microorganisms	Bioactive compounds	Function	Potential Application	Reference
Marine mud	/	Esterase	Preparation of the free all-trans-Astaxanthin	Food	(Lu et al. 2018)
Marine sediments of Ezhara beach, Kannur, Kerala	<i>Pseudomonas aeruginosa</i> KU1	Fibrinolytic enzyme	Fibrinolysis	Biopharmaceutical industry	(Kumar et al. 2018b)
Marine sediments from the east coast of India	<i>Acinetobacter</i> sp. PS12B	Agarase	Hydrolysis of seaweed and production of biofuels	Food and biofuels	(Leema Roseline and Sachindra 2018)
Marine sediment from the Fildes Peninsula, Antarctica	<i>Pseudomonas</i> GWSMS-1	Chitinase	Biological control	Agriculture	(Liu et al. 2019)
Black Sea sediments	<i>Kiritimatiellaota</i> strains F1 and F21	Sulfatase	Removal of sulfate groups from polysaccharides	Food and medicine	(van Vliet et al. 2019)
Marine sediments from the Gulf of Mannar biosphere reserve, Tamil Nadu	<i>Nocardioopsis</i> sp.	Inulinase	β -2,1 glycosidic bond of hydrolyzed inulin	Food	(Neha et al. 2022)
Marine sediment from the Bering Sea	<i>Colwellia</i> sp. NB097-1	Proteases	Cold-adapted hydrolyzed protein	Molecular biology, meat tenderizing and detergent industry	(Zhang et al. 2018)
Sediment of a hot spring in Indonesia	<i>Bacillus</i> sp. HT19	k-carrageenase	Degradation of carrageenan	Plant protection	(Li et al. 2019)
Marine sediments of the Red Sea, Saudi Arabia	<i>Bacillus velezensis</i>	Glutaminase-free L-asparaginase	Antitumor action	Biopharmaceutical industry	(Mostafa et al. 2019)
Subtropical marine mangrove wetland sediments	/	3-Deoxy-D-arabino-heptulosonate-7-phosphate synthase	A key rate-limiting enzyme in aromatic amino acid anabolism	Production of aromatic amino acids	(Zhao et al. 2019a)
Marine sediments of southern India	<i>Virgibacillus</i> sp. UR1	Urease	Cycle urea to nitrogen	Calcite precipitation and biocementation process	(Sarkar and Suthindhiran 2020)
Marine sediments in the East China Sea	<i>Anaerolineaceae bacterium</i>	Serine protease	High proteolytic activity	Detergent, pharmaceutical, food	(Sun et al. 2020)
Arabian Sea sediments	<i>Bacillus aryabhatai</i> B8W ₂₂	Chitin deacetylase	Chitin-degrading	Biomedicine	(Pawaskar et al. 2021)
Marine water sediments from Cove Rock and Bonza Bay beach of the Eastern Cape Province, South Africa	<i>Enterobacter asburiae</i> ES1 and <i>Enterobacter</i> sp. Kamsi	Laccases	Degrading- Bisphenol A	Environmental protection, food, dye and chemical industry	(Edoamodu and Nwodo 2022)
Marine sediment from the Kanniyakumari coast, Southern Tamil Nadu, India	<i>Bacillus halodurans</i>	Protease	Hydrolysis of protein	Detergent	(Balachandran et al. 2021)
Sediments from the hot water of Genow	<i>Bacillus subtilis</i> strain HR02	Protease	Hydrolysis of protein	Detergents, agricultural, textiles, paper, food and pharmaceutical industries	(Homaei and Qeshmi 2022)
Offshore sediment near Ny-Alesund, Svalbard	<i>Colwellia hornerae</i> PAMC 20,917	Alkaline phosphatases	Cold-active and thermolabile enzymes	Food, chemical synthesis, and bioremediation	(Kim et al. 2018)
Sediment and sponge samples from coastal sides of Turkey	<i>Penicillium polonicum</i> MF82	Phytase	Degradation of myoinositol hexakisphosphate	Food, environmental protection and pharmaceutical industries	(Kalkan et al. 2020)
Marine sediment from the East Sea near Korea	<i>Paraglaciicola agaritytica</i> NO2	Haloalkane dehalogenases	Catalytic halide hydrolysis	Biocatalysis, environmental protection and biosensor	(Mazur et al. 2021)
New Caledonian mangrove sediments	/	Peroxidases	Dye-decolorizing	Dye and textile industry	(Ben Ayed et al. 2021)
Black Sea marine sediment	<i>Streptomyces</i> sp. K47	Alkaline proteases	Degradation of various proteins	Therapeutic, cosmetic and food industry	(Corbaci and Ozcan 2021)
Sediments of mangrove wetlands in Qinzhou Bay, China	<i>Aspergillus fumigatus</i> df347	Chitinase	Preparation of chitin oligosaccharides	Food, medicine, agriculture and environmental protection	(Wu et al. 2022)

/ represents that no relevant information is involved in the reference

Table 3 Enzyme inhibitors produced by marine sediment-derived microorganisms reported in the past five years

Source	Specific microorganisms	Bioactive compounds	Function	Potential Application	Reference
A deep-sea sludge in the South China Sea	<i>Geosmithia pallida</i> FS140	Angiotensin-converting enzyme inhibitors	Inhibition of angiotensin-converting enzyme	Biomedical industry	(Sun et al. 2018)
Marine sediments from the Arabian Sea	<i>Oceanimonas</i> sp. BPMS22	Protease inhibitors	Anticoagulant activity	Biomedical industry	(Harish and Uppuluri 2018)
Marine sediments from different locations of Havelock Island	<i>Nocardia</i> sp. SCA21	4-bromophenol and Bis (2-ethylhexyl) phthalate	Inhibition of α -glucosidase and α -amylase	Biomedical industry	(Siddharth and Rai 2019)
Marine sediments from Yellow Sea, Shandong Province, China	<i>Streptomyces</i> sp. HO1518	Acylated Aminooligosaccharides	Inhibition of α -amylase	Biomedical industry	(Liu et al. 2018)
Marine sediment from the Rizhao coastal area, Shandong Province of China	<i>Streptomyces</i> sp. HO1518	D6-O-acetyl (or isobutyryl)-acarviosatin II03	Inhibition of α -glucosidase and lipase	Biomedical industry	(Xu et al. 2020)
A sediment sample of Tokyo Bay	<i>Aspergillus</i> sp. BFM-0085	Protuboxepin A and K	Inhibition of Alkaline phosphatase	Biomedical industry	(Ohte et al. 2020)

acylated aminooligosaccharides and their homologues have been isolated from the marine-derived *Streptomyces* strains (Xu et al. 2020). The evaluation of their inhibitory activity on α -glucosidase and pancreatic lipase has been performed. The results suggest that D6-O-isobutyryl-acarviosatin II03 and D6-O-acetyl-acarviosatin II03 of the two isolates have the most effective inhibitory effect on α -glucosidase and lipase. These studies have some potential applications in the development of multi-target antidiabetic drugs. Similarly, *Nocardia actinomycetes* SCA21 isolated from marine sediments can produce two active compounds, 4-bromophenol and Bis (2-ethylhexyl) phthalate, which have significant inhibitory activity on α -glucosidase, but phthalate ester has lower activity on α -amylase (Siddharth and Rai 2019).

Bacteria and fungi in marine sediments are also important sources of enzyme inhibitors. A moderately salt-tolerant marine bacterium that may produce trypsin inhibitors from marine sediments was reported, and a protease inhibitor, serine protease, was isolated and purified, which could be used as a potential anticoagulant (Harish and Uppuluri 2018). It is speculated that the anticoagulant activity of this enzyme inhibitor may be due to the inhibition of clotting factors, but its anticoagulant mechanism needs to be discussed. Active compound inhibitors isolated from marine microorganisms may have significant inhibitory effects on microbial populations. Tyrosol isolated from marine-derived fungi can reduce the trypsin activity and proteolysis activity of other microorganisms to 57.8% and 9.9%, respectively, and inhibit the ability of microorganisms to produce certain secondary metabolites (Chang et al. 2019).

Screening microorganisms with special functional enzymes and enzyme inhibitors from marine sediments has been one of the important directions in the exploitation of marine resources. Characteristics of ecological environments and multi-functional catalytic activity make marine microorganisms capable of producing special enzymes and

enzyme inhibitors with great potential for industrial production, but it is a complex and difficult process from laboratory screening to commercial application. A great deal of research and exploration is still needed. Large-scale development and commercial production of marine microbial enzymes and enzyme inhibitors will be just around the corner as various advanced technologies continue to develop and countries focus on the research field of marine enzymes and enzyme inhibitors.

Production of potential bioactive sugars

Functional sugars are a class of carbohydrates with specific effects, including bioactive oligosaccharides, alditols, and polysaccharides (Abbasi et al. 2021). Due to their effects on human health, functional sugars are widely used in food, medicine, and human health, such as anticancer, antiviral, hypoglycemic, antioxidant, anticoagulant, and antibacterial (Casillo et al. 2018; Lin et al. 2019; Wang et al. 2020; Kuda et al. 2021). It is common to extract functional polysaccharides from marine algae by some methods (Cui et al. 2018; Aullybux et al. 2019; Kuda et al. 2021; Wassie et al. 2021). However, studies have shown that microorganisms isolated from marine sediments can secrete polymers, which usually exist in the form of extracellular polysaccharides (Roca et al. 2016; Aullybux et al. 2022). In fact, marine bacteria, fungi and yeast can all produce extracellular polysaccharides (Dewapriya and Kim 2014). Marine bacteria are common microorganisms that produce bioactive polysaccharides, including *Alteromonas*, *Halomonas*, *Pseudoaltermonas*, *Bacillus*, *Lactobacillus*, and *Polaribacter* (Dewapriya and Kim 2014; Sahana and Rekha 2019). The extracellular polysaccharides secreted by them are the source of new bioactive polysaccharides. A marine bacterium *Alteromonas* sp. PRIM-28, isolated from the Malpe region of the west coast of India, has been reported to produce extracellular

polysaccharides with biological properties (Sahana and Rekha 2019). Its extracellular polysaccharide is a repetitive unit composed of manuronic acid, glucose and *N*-acetyl glucosamine repeating units in the ratio 1:3.67:0.93. It has the property of promoting cell proliferation and is a potential versatile bioactive polymer for wound care. The structure and function of extracellular active polysaccharides from different marine microorganisms are diverse. A strain of *Bacillus cereus* isolated from the Saudi Red Sea coast can produce sulfate-free extracellular polysaccharides, which is composed of glucose, galacturonic acid and arabinose with a molar ratio of 2.0:0.8:1.0, respectively, and has been proved to have antioxidant, anti-tumor, and anti-inflammatory activities (Selim et al. 2022). It is not only marine bacteria that produce extracellular polysaccharides, but also marine fungi are thought to be promising producers of bioactive polysaccharides. Four fungal isolates have been obtained from marine sediments collected from the coast of El Max, Alexandria, Egypt (Amer et al. 2020). One of the strains providing the highest extracellular polysaccharide production (4.98 g/L) has been identified as *Aspergillus terreus* based on 18 S rRNA gene sequence analysis. For the first time, the anticoagulant and cytotoxic activities of extracellular polysaccharides from the fungal *Aspergillus* species have been determined. It is generally believed that microbial polysaccharides from marine sediments are popular among researchers because of their novel functions, safety, and stable chemical and physical properties.

Polysaccharides are also the main building blocks of peptidoglycan and lipopolysaccharides, which make up the cell walls of most prokaryotes (Osibe et al. 2020). For microorganisms themselves, the functions of these extracellular polysaccharides include surface adhesion and colonization, protection of bacterial cells, and support for biochemical interactions between bacteria and their surroundings (Casillo et al. 2018). At the same time, due to the secretion of microorganisms, polysaccharides occupy a certain position in marine components. With the growing interest in renewable resources, these extracellular polysaccharides have been used to develop some important biotechnology products, such as thickeners, stabilizers, and texture agents in the food industry, flocculants in the wastewater treatment industry, or anti-aging molecules in the cosmetics industry (Zikmanis et al. 2020). These extracellular polysaccharides are also used as conversion substrates for bioenergy and biomaterials, which can reduce economic dependence on fossil fuels (Pagliano et al. 2017).

Functional oligosaccharides are functional sugars that can improve human health to a certain extent. Most of them are low-level polysaccharides, which are connected by 2–10 monosaccharides through glycosidic bonds to form straight-chain or branched-chain polysaccharides (Patel and Goyal

2011). Common functional oligosaccharides from marine and marine microorganisms include chitosan oligosaccharides (Kumar et al. 2018a), algal oligosaccharides (Jagtap and Manohar 2021; Xie and Cheong 2022), agar oligosaccharides (Jiang et al. 2021), and carrageenan oligosaccharides (Li et al. 2020). These biological activities include antioxidant, anti-tumor, anti-inflammatory, antibacterial, anticoagulant, and immunity boosting, and can be widely used in food, medicine, cosmetics, agricultural and aquatic products, and other fields (Zhu et al. 2021).

In recent years, with the protection of the marine ecological environment and resources, it is no longer possible to meet the functional oligosaccharide demand simply by certain extraction, separation and purification methods, which require large ecological and labor costs to obtain the corresponding oligosaccharides from the ocean. To meet the demand for functional oligosaccharides, researchers are increasingly focusing on how to obtain functional oligosaccharides through special microorganisms or efficient and specific enzymatic degradation. Bacteria from marine sediments are often used as the primary source of polysaccharide-degrading enzymes. A cold-adapted chitinase (EaChi39) has been purified from *Exiguobacterium antarcticum* DW2 screened from the east coast of the Bohai Sea in China, capable of fully converting colloidal chitin into *N*-acetyl glucosamine and oligosaccharides (Fu et al. 2020). This enzyme may be a good candidate for bioconversion of seafood byproducts. *Pseudoalteromonas carrageenovora* ASY5 screened from marine mangroves can produce ι -carrageenase that can degrade ι -carrageenan into disaccharides and tetrasaccharides (Xiao et al. 2018). A novel polysaccharide lyase, AlgSH17, has been identified from the marine bacterium *Microbulbifer* sp. SH-1 isolated from coastal soil collected in Zhangzhou City, Fujian Province, China (Yang et al. 2021a). Oligosaccharides with degree of polymerization ≥ 4 can be degraded into disaccharides and trisaccharides by cleavage of internal glycosidic bonds, and disaccharides and trisaccharides can be further digested into monosaccharides by external dissolution.

Alginate lyases are the enzymes commonly used to degrade fucoidan, a series of alginate lyases with different product distributions have been obtained by screening special microorganisms (*Serratia marcescens* NJ-07 and *Vibrio* sp. NJU-03) (Zhu et al. 2018a, b). The bifunctional alginate lyase FsAlgB can recognize tetrasaccharides as minimal substrates and cleave glycosidic bonds between subsites of -3 and +1, which is very important for the production of alginate oligosaccharides (Zhu et al. 2019). In addition, the acquisition and characterization of some polysaccharide-degrading enzymes is important for the agricultural, food, environmental protection, and pharmaceutical industries. For example, a thermostable κ -carrageenase isolated from

sediment samples collected from hot springs on the island of Kalanda, Indonesia can degrade κ -carrageenan in vitro, enhance cucumber resistance to cucumber mosaic virus, and improve the activity of antioxidant enzymes in infected plants (Li et al. 2019). By characterizing a new α -neoglycosaminidase, it has been found that the hydrolase can prepare medium-chain and long-chain agarose oligosaccharides, which can be used as functional food additives (Jiang et al. 2020). In summary, the discovery and screening of polysaccharide-degrading bacteria or enzymes from marine sediments can not only effectively increase the yield of functional oligosaccharides and the efficiency of converting polysaccharides into more bioactive oligosaccharides, but also provide more resources for the development of new functional oligosaccharides.

Protein degradation and active peptide production

Clastic proteins and lipids exist widely in the marine environment as biological macromolecules, in which clastic proteins are the largest component of marine organic matter (Liu 2022). These biological macromolecules can interact with and adsorb plastic particles (such as microplastics and nanoplastics) as marine pollutants (Liu et al. 2020). This interaction may affect the physical and chemical properties of plastics and macromolecules, including plastic toxicity, nutrient transport, and biological activity, which may have negative impacts on marine ecosystems and the cycle of organic compounds. In recent years, researchers have been actively searching for marine microorganisms that can degrade these biological macromolecules (Pelikan et al. 2021). Marine archaea may play a key role in protein remineralization in marine sediments (Yin et al. 2022). Meta-genomics has been used to analyze the archaea for the degradation of detrital proteins in different marine sediments. It has been found that three archaeal phyla (uncultivated *Thermoplasmata*, SG8-5; *Bathyarchaeota* subgroup 15; *Lokiarchaeota* subgroup 2c) actively perform protein catabolism. The characteristics, nutritional interactions and genomic characteristics of protein- and lipid-degradable bacteria in subarctic marine sediments have been analyzed by metagenomic technique. The results show that *Psychrilyobacter atlanticus* is an important primary protein-degrading bacterium, and that *Pseudomonas aeruginosa* can degrade not only primary proteins but also primary lipids (Pelikan et al. 2021). These microorganisms play an important role in improving the marine environment and promoting the circulation of marine compounds.

In recent years, there have been extensive studies on bioactive peptides, especially their functions, such as blood pressure lowering, antioxidation, antiviral, antibacterial, and cholesterol lowering (Akbarian et al. 2022).

Angiotensin-I-converting enzyme inhibitory peptides derived from marine organisms have been reported to have blood pressure lowering effects with no side effects (Feng et al. 2021). Antioxidant peptides isolated, identified, and characterized from snakehead soup after simulated gastrointestinal digestion suggest a higher antioxidant capacity for fractions with molecular weight less than 3 kDa (Zhang et al. 2021a, b, c). A multi-functional antimicrobial peptide (Epinecidin-1) produced by the orange-spotted grouper has been reported to have not only antibacterial, antifungal and antiviral effects, but also anticancer and immunomodulatory effects (Neshani et al. 2019). These bioactive peptides have potential applications in medicine, food and cosmetics industries due to their special functions (Cunha and Pintado 2022). The main sources of bioactive peptides from marine organisms are seaweed, shellfish, and fish, which are mainly obtained by extraction. The most common method is to hydrolyze the raw material with enzymes found in bacteria or fungi, such as acid protease, trypsin, papain, and alkaline protease, which hydrolyze large-molecule proteins into small-molecule active peptides (Cunha and Pintado 2022).

Peptides with different sources, structures, compositions, and sequences have different biological activities and flavor characteristics. Most of the current research on marine peptides has focused on the extraction of marine organisms. However, with the utilization and large-scale development of marine resources, it is urgent to establish a friendly marine ecological environment. Therefore, bioactive peptides obtained by screening marine-derived microorganisms can effectively solve human dependence on marine non-renewable resources and enrich the sources of marine functional peptides (Johny and Suresh 2022). A strain of *Bacillus velezensis* FTL₇ with strong ability to produce antimicrobial peptides has been isolated from marine sediment samples on the west coast of South India (Johny and Suresh 2022). The strain has shown antibacterial activity against a broad range of foodborne pathogenic bacteria such as *Listeria monocytogenes* Scott A, *Bacillus cereus*, *Salmonella* Typhimurium, *Staphylococcus aureus*, and *Escherichia coli*. It has been reported that marine-derived fungi *Aspergillus allahabadii* and *Aspergillus ochraceopetaliformis* have been isolated from marine sediments (Hwang et al. 2019). Four novel peptides have been isolated from these microorganisms after being cultured. By studying the effect of these new peptides on enzymes, it has been found that these new peptides can inhibit the enzymes sortase A (a kind of enzyme) and isocitrate lyase to a certain extent, which has potential application value in biomedical and chemical industries (Hwang et al. 2019). A marine strain of *Aspergillus fumigatus* BTMF9 isolated from marine sediment samples and terrestrial decayed samples has also been reported (Raghavan et al. 2021). An antimicrobial peptide

under high temperature and extensive pH conditions has been obtained by ammonium sulfate precipitation and gel chromatography. The antimicrobial peptide is sensitive to proteolytic enzymes and is expected to become a novel anti-infective drug with strong anti-biofilm potential (Raghavan et al. 2021).

Non-ribosomal peptide is one of the most common drugs in clinic, and one of its sources is marine-derived microorganisms. Recent studies have reported that the diversity of microorganisms and their non-ribosomal peptides and polyketone biosynthesis genes in marine sediments have been explored by metagenomics (Wei et al. 2018). Most of the bacteria in marine sediments are *Proteus* and *Bacteroides*. *Actinomyces* producing non-ribosomal peptides and polyketones account for only 0.82% of all bacterial species. Most microbes are uncultured. In addition, the marine sediments may have the ability to synthesize new natural products and the distribution of non-ribosomal peptide gene clusters in this environment is more than that of polyketone gene clusters. In a search for bacteria producing non-ribosomal peptides and genes encoding non-ribosomal peptide enzymes, the results of a multi-omics analysis of coastal sediments in the Yucatan have revealed that *Proteobacteria* and *Firmicutes* are the phyla with the highest representation of non-ribosomal peptide-producing organisms (Martinez-Nunez and Rodriguez-Escamilla 2020). Whole genome sequencing of a novel marine bacterium, *Bacillus velezensis* FTL₇, which has an effective production capacity of antimicrobial peptides, has shown that genes responsible for the synthesis of non-ribosomal peptides and bacteriocins are present in the strain (Johny and Suresh 2022). It also suggests that *Bacillus velezensis* is already an excellent producer of antimicrobial peptides.

Production of some small-molecule metabolites

Some compounds such as alkaloids, pigments, polyketones, and alkenes are common metabolites of microorganisms. Some of these small molecular metabolites are also considered as potential marine antibiotics because of their medicinal value. In recent years, as science has developed and marine resources have been continuously excavated, new microorganisms have been discovered from marine sediments. It has been reported that a new quinoline alkaloid and two new bisabolane-type sesquiterpene derivatives have been isolated from the deep-sea derived fungus *Aspergillus* sp. SCSIO06786 after culture on rice medium (Pang et al. 2020). These compounds have a certain inhibitory effect on pathogenic bacteria. In addition, four new prenylated indole alkaloids and four new chromone derivatives have been obtained by culturing *Penicillium* sp. SCSIO041218, a fungus derived from mangrove sediments (Yang et al.

2018). Recent studies have also reported that a kind of actinomycetes, *Salinospora arenicola*, isolated from sediments of the St. Peter and St. Paul Archipelago, Brazil, can produce a variety of indole and pyruvate derivatives (Silva et al. 2019a, b).

In addition to alkaloids, pigment-producing microorganisms isolated from marine sediments are also common. Fourteen strains have been reported from 180 sampling sites in pristine Andaman Islands, India (Ramesh et al. 2020b). Two red-pigmented strains, BSE6.1 and S2.1, have been identified for their active compounds. It has been found that hypocrellin is the dominant chemical component, and both strains exhibit potential multifaceted applications, such as antibacterial, antioxidant, food colorant, and staining properties (Ramesh et al. 2020b). Furthermore, whole genome and 16 S rRNA sequence analysis of strain S2.1 has shown that it is a new species of *Zoosporidium* (Ramesh et al. 2020a). Bacteria are often thought to be the main microorganisms responsible for producing lycopene. A new rose-red pigment-producing bacterium isolated from the cordgrass *Spartina alterniflora* sediments has been reported to produce both heptylprodigiosin and cycloheptylprodigiosin, which have dyeing and antibacterial activity (Huang et al. 2020). Carotenoids, which are important natural pigments, is considered as one of the representative alkenes. Carotenoids have anti-oxidant, immunological, anti-aging, and anti-cancer effects, and are widely found in animals, plants, fungi, and algae (Delgado-Vargas et al. 2000). However, a recent study has shown that *Saccharomyces cerevisiae* screened from marine sediments can produce carotenoids, with a maximum total carotenoid concentration of 987 g/L at optimal culture conditions, which is potentially commercially valuable (Zhao et al. 2019c). Similar reports have been made of a bacterium, *Sphingomonas* sp. SG73, isolated from deep-sea sediments collected in Suruga Bay, Shizuoka, Japan, which produces a polyhydroxyl yellow carotenoid (Kikukawa et al. 2021).

Polyketones are also the main bioactive polymeric compounds derived from marine microorganisms, including macrolides, tetracyclines, anthracyclines, polyethers, and others. Polyketones are usually synthesized by polyketone synthase using small molecular carboxylic acids as precursors, and their structures are complex. Many polyketones are often considered as antibiotics. Marine fungi are rich in polyketones, which account for about half of all novel structural compounds from all sources (Yang et al. 2021b). The deep-sea fungus *Leptosphaeria* sp. SCSIO 41,005 can produce a variety of polyketones, such as isobenzofuranones and isoprenones (Luo et al. 2017). Some of the marine polyketones come from marine actinomycetes. It has been reported that seven kinds of pradiomycin polyketones have been isolated from the dichloromethane extract

of *Streptomyces* CGMCC 4.7309 from marine sediments (Gao et al. 2018). The relationship between structure and antioxidant activity of these compounds has been subsequently studied. The results show that these compounds may be effective natural antioxidants with considerable medicinal value. At present, many small molecular metabolites from marine sources have not been discovered, and the biosynthesis mechanisms that produce small molecules with potentially functional properties from most marine sedimentary sources have not been elucidated. It is more challenging to explore the biological and pharmacological activities of new compounds and other secondary metabolites from marine sources.

Conclusions

Marine sediment is an integral part of the marine ecosystem and is rich in microbial resources. The exploration of marine sediment-derived microorganisms not only helps to understand the community structure and functional characteristics of microorganisms in marine ecosystems, but also to obtain many useful metabolites from microorganisms. These metabolites are widely used in food, medicine, agriculture, environmental protection and other industries. However, there are many challenges and problems associated with the study of marine sediment-derived microorganisms and their bioactive metabolites. First, while marine microorganisms are widely distributed in marine sediments, some microorganisms that produce bioactive metabolites with special functions may be present in marine sediments with special ecological environments. It is difficult to collect and obtain marine sediments in these special ecological environments, such as the deep sea, polar region, and hydrothermal zones. Second, microorganisms and their communities in marine sediments are diverse, and various microorganisms have different requirements for culture media and conditions. The growth and metabolic activity of microorganisms varies significantly in different culture media and environments. As a result, the screening of marine sediment-derived microorganisms for the production of bioactive metabolites is largely blind and uncertain, and suffers from problems such as low screening efficiency and difficulty in culture of microorganisms. In addition, although the active materials obtained from marine sediment-derived microorganisms are novel in structure and unique in activity, their low yields make them difficult to isolate and identify. These issues limit the commercial use of active metabolites produced by marine sediment-derived microorganisms.

Marine sediments are one of the sources of novel microorganisms, in which many organisms with functional properties and bioactive metabolites have yet to be discovered.

How to better tap the potential of the active substances produced by marine sediment-derived microorganisms is a challenge and task for every marine microorganism worker. In the future, directions for investigating marine sediment-derived microorganisms and their bioactive metabolites are suggested as follows. The development of accurate and intelligent marine sediment sampling equipment can provide some guarantees for the collection of marine sediment in some special ecological environments. The screening space is further expanded to look for strains that produce novel or highly active bioactive substances. By using multi-omics techniques and modern biotechnology to analyze the community structure, functional characteristics, and genetic evolution of microorganisms in different marine sediments, the functional genes of marine microorganisms and their specific functions can be found quickly and accurately, and thus the resource base and functional gene bank of marine sediment-derived microorganisms can be established. Combined with microbial culture-dependent techniques, the composition and conditions of the culture medium are reasonably designed. Using molecular biology techniques, marine sediment-derived microorganisms can be identified. Meanwhile, with the combination of genetic engineering, cell engineering and protein engineering, high yields of bioactive metabolites from marine microorganisms can be obtained by expressing functional genes associated with bioactive metabolites. The range of industrial applications of marine sediment-derived microorganisms and their bioactive metabolites can be broadened by the use of sophisticated separation, purification and identification devices to analyze the structure-function relationship of bioactive metabolites and further assess their safety and functionality.

At present, although there are many difficulties in the study of marine sediment-derived microorganisms and their bioactive metabolites, with the development and mutual penetration of biology, chemistry, physics, pharmacy, computer and other related disciplines, as well as the cooperation of various advanced technologies and means, the development, production and application of marine sediment-derived microorganisms and their bioactive metabolites can be promoted. Large-scale, industrial production of these bioactive compounds is just around the corner. In the future, marine sediment-derived microorganisms and their bioactive metabolites will make a greater contribution to humanity as they are better understood and studied.

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Declarations

Competing interests The authors declare no conflict of interest.

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