Study on Marine actinomycetes and analysis of their secondary metabolites

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Abbreviations
PCR, polymerase chain reaction; MIC, minimum inhibitory concentration.

Citation

Abstract
Actinomycetes are relatively prevalent bacteria in the ocean, constituting 9% of the total number of marine bacteria. The advancement of science and technology has led to a more profound exploration of marine actinomycetes. These studies hold immense significance in comprehending the distribution and adaptation of marine actinomycetes within the oceanic environment, as well as uncovering new secondary metabolites. Based on differing lifestyles, marine actinomycetes can be categorized as free-living or co-epiphytic. The activity and metabolism of actinomycetes vary across diverse marine settings, including the deep sea, benthic regions, and marine organisms. Due to their distinctive biological traits and genetic background, these marine actinomycetes inevitably generate metabolites possessing unique structures. Research methodologies concerning marine actinomycetes predominantly encompass traditional pure culture techniques, molecular biology approaches, and the integration of metagenomics and bioinformatics. The exploration of varied methodologies proves pivotal for the analysis of metabolite processes. Through the cultivation of marine actinomycetes, numerous compounds featuring novel structures and significant activities have been isolated, furnishing a substantial foundation for new drug investigations. These encompass, but are not restricted to, peptides, antibiotics, terpenoids, ketones, quinones, macrolides, and pigments. The potential applications of marine actinomycines and their secondary metabolites extend beyond antibacterial and anti-tumor effects, exhibiting promising prospects in antifungal and antiviral domains. This paper provides a comprehensive review of the classification, resources, research methodologies, and habitats of marine actinomycetes. Furthermore, it delves into the classification of secondary metabolites and their functional activities, facilitating a more exhaustive analysis of the secondary metabolites produced by marine actinomycetes.

Keywords: Marine actinomycetes; secondary metabolites; research method; functional activity
Actinomycetes are a group of Gram-positive bacteria widely distributed and diverse in nature. Actinomycetes are closely connected to human endeavors. Up to now, actinomycetes remain a vital research domain for uncovering novel active substances. It is in aspects of lifestyle, movement patterns, and metabolism that their complexity becomes evident [1]. Being a significant source of fresh secondary metabolites for medicinal use, actinomycetes have a broad spectrum of research fields due to their abundant resources. As society progresses, the demand for new bioactive compounds keeps increasing. In recent years, the importance of terrestrial actinomycetes in drug research has waned. The oceanic environment is characterized by high pressure, salinity, and low temperature, and marine organisms exhibit intricate physiological traits. Therefore, actinomycetes isolated from the sea showcase a wide array of secondary metabolite structures and distinct biological activities [2]. They possess an exceptional capability to produce a diverse range of secondary metabolites with various biological activities, including antibacterial, antitumor, cytotoxic, cytostatic, antiparasitic, antiviral, and antioxidant properties [3–9]. The chemical composition of bioactive compounds sourced from marine actinomycetes forms the basis for novel medication development. In the years ahead, there will be an augmented demand for freshly synthesized bioactive compounds by marine actinomycetes. The scrutiny and exploration of marine actinomycete resources have expanded our understanding of these organisms and laid the groundwork for the creation of more potent secondary metabolites [10]. Marine actinomycetes manifest diverse biological activities linked to secondary metabolites, encompassing antibacterial, antiviral, and ant-tumor functions. Additionally, they play pivotal ecological roles such as chemical communication and the control of aquatic hazards [11, 12]. Therefore, delving into secondary metabolites generated by marine actinomycetes could open novel avenues for marine drug exploration and the production of biocontrol agents.

Research overview and resource analysis of Marine actinomycetes

The article on Marine actinomycetes was initially published in 1966, and development has been slow since that time. However, in the 2000s, there was a significant increase in the number of papers. As illustrated in Figure 1, upon utilizing “marine actinomycetes or marine actinobacteria” as the primary search term in the Web of Science core collection and filtering out non-Review literature, a total of 3274 articles were collected since 1991. This trend can be attributed to the ongoing advancement of science and technology, particularly the continuous enhancement of deep-sea exploration capabilities. The progress in sample collection and separation technology has led to the swift advancement of Marine actinomycetes research. Notably, in 2021, the number of Marine actinomycetes-related papers reached as high as 278, marking the highest count in any given year. This robustly indicates the increasing attention being dedicated to the study of Marine actinomycetes.

The United States, the United Kingdom, and Japan were the pioneers in initiating the study of Marine actinomycetes, with the United States emerging as the most influential nation in this field. It holds the second global ranking and receives significantly more citations than other countries. Although China entered this field later, its development has been rapid, boasting the largest number of published papers worldwide. However, China’s research in this domain is still in its early stages, leaving a considerable gap when compared to the research output of developed countries in Europe and the United States.

With the advancement of deep-sea actinomycetes sample collection and separation technology, an increasing number of deep-sea actinomycetes have been unearthed. These investigations hold profound significance in comprehending the distribution of Marine actinomycetes within the ocean and their ability to acclimate to the environment, as well as in uncovering novel secondary metabolites. Based on the lifestyle of Marine actinomycetes, they can be categorized into free-living actinomycetes and co-epiphytic actinomycetes. Free-living actinomycetes are widely dispersed in various natural settings, including soil, seawater, and mangroves. Mangroves, found in tropical and subtropical coastal regions, constitute a woody plant community within the coastal intertidal zone. Their distinct physical and chemical conditions, coupled with abundant humus, create an ideal environment for microbial diversity [13–17].

Co-epiphytic actinomycetes reside on plants or animals. Ordinary epiphytic actinomycetes have been identified in marine creatures such as Metopograpsus quadridentatus, sponges, sea cucumbers (Stichopus japonicus), Australian ascidians (ascidians), and deep-sea coral invertebrates. Furthermore, co-epiphytic actinomycetes have also been observed on marine vegetation like seagrasses and green algae [18–24]. Based on existing research outcomes, there is no conspicuous distinction in the genus classification between free actinomycetes and co-epiphytic actinomycetes. To date, multiple actinomycetes genera have been identified globally (Table 1). Although a few new species (genera) have been uncovered, their natural status remains uncertain. Currently, their adaptation to the marine environment can only be explored by integrating these phenotypic characteristics with genomic data.

<table>
<thead>
<tr>
<th>Actinomycetes</th>
<th>Bacteria</th>
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<tbody>
<tr>
<td>Free-living actinomycetes</td>
<td>Aeromicrobium, Dietzia, Friedmanniella, Jiangella, KocuriaActinomadura, Microbacterium, Marinactinospora, Arthrobacter, Brachbacterium, Brev-Bacterium, Nonomuraea, Corynebacterium, Chainia, NakaMurella, Saccharopolyspora, Rhodococcus, Streptosporangium, Salinispora, Verrucosispora, Salinibacterium, Amycolatopsis, Marinispora, Modestopacter, Sciscionella, Serinicoccus, Nesterenkonia, Williamsia, Nocardioides, Mycobacterium, Marinophilus</td>
</tr>
<tr>
<td>Actinomycetes in plants and animals</td>
<td>Actinomycorallia, Arsenicococcus, Agrococcus, Actinomycystospora, Actinoaurantiispora, Acidimicrobium, Demequina, Leifsonia, Microbispora, Mycobac, Rium, Isopericola, Microbrix, Tesseracoccus, Gordonia, Micrococcus, Prauserella, Glycomyces, Physiccola, Promicromonospora, Sanguibacter, Euzebya, Knoellia, Iamia</td>
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Distribution of marine actinomycetes in the ocean

Due to the attributes of high salinity, elevated pressure, low temperature, and limited nutrients, seawater hosts abundant biological resources. Marine organisms exhibit distinct features in metabolism, survival strategies, information transmission, and adaptability [25]. Marine microorganisms constitute pivotal elements of Marine biodiversity, and their extensive genetic diversity and metabolic variations have emerged over protracted biological evolution, conferring upon them substantial biosynthetic capability. Since the discovery of the inaugural Marine actinomycete by H. Weyland in 1969, scientists have identified numerous actinomycete species within marine life. Notably, differences exist in the activity and metabolism of actinomycetes across diverse marine environments [26].

Marine actinomycetes in seawater

The marine environment, characterized by low temperature, diminished oxygen levels, and elevated salinity, can foster a distinct microbial community in stark contrast to terrestrial ecosystems. Within such an extreme setting, the likelihood of encountering novel actinomycete groups endowed with unique biological activities is notably high.

Bai SJ and colleagues successfully isolated a Marine actinomycetes strain, B501, from seawater samples obtained from Xiamen Bay, China [27]. Subsequent analysis of the 16S r DNA sequence revealed a close kinship to Brevibacterium. Notably, activity testing underscored its algidclal potential against Alexandriella. These findings indicate that the identified actinomycetes in marine water harbours promise as a potential agent for algal control. Yang T et al., in their investigations, stumbled upon a cytotoxic Marine actinomycetes, AK432, at a depth of 800 meters in Sagami Bay, Japan [28]. Employing activity-tracing methods, they identified a new aromatic polyketone compound. This substance exhibited an IC50 value of 1.7µM, demonstrating cytotoxic effects on B16 cell lines. The presence of actinomycetes in seawater serves as a vital wellspring for the production of antibacterial metabolites, positioning it as a cradle for novel antibiotics.

Benthic marine actinomycetes

The lower regions of the ocean constitute the second largest ecological realm after marine waters. This expanse stands as the most biologically diverse zone worldwide, playing a pivotal ecological role. However, the understanding of this domain remains exceedingly limited. Marine benthos comprise organisms inhabiting the sea floor or sediment. Distributed throughout the ocean, they form the most expansive category of ecosystems.

Sobolevskaya et al. unearthed a novel dipeptide compound from the actinomycetes KMM 7210, sourced from sediment in the Sea of Japan [29]. This compound exhibited noteworthy biological activity against gram-negative bacteria. Yuan M et al. isolated 73 actinomycetes strains from the sediments of the Chukchi Sea's continental shelf in the Arctic Ocean [30]. Through phylogenetic analysis and activity assessment of 30 representative actinomycetes strains, they identified affiliations with 14 diverse genera, including Halobacterium, Streptomyces, and Nocardiia. Furthermore, 11 actinomycetes strains displayed antibacterial or antifungal activity, implying that Chukchi continental shelf sediments house abundant species diversity and potential for bioactive compound production. Undarbarrena A et al. scrutinized the diversity and activity of Marine actinomycetes extracted from marine sediments [31]. The research unveiled that Arthrobacter, Brevibacterium, Rhodococcus, and Streptomyces isolates exhibited potent inhibitory effects against Gram-negative bacteria such as Pseudomonas aeruginosa, Escherichia coli, and Salmonella enterica, as well as Gram-positive bacteria including Staphylococcus aureus. These findings underscore that Marine actinomycetes from this source and sediment remain promising sources for generating antibacterial metabolites. Benthic actinomycetes have recently emerged as primary subjects of research in the realm of new drug development due to their unique bioactive substances.

Marine actinomycetes living on marine plants and animals

Owing to the unique habitat of the ocean, Marine microorganisms and their metabolites yield numerous bioactive substances with innovative structures, encompassing compounds with anti-tumor, anti-inflammatory, antibacterial, anti-parasitic, and other properties. Marine microorganisms have evolved into a significant wellspring for new drug development [32-36]. Notably, co-epiphytic microorganisms associated with Marine animals and plants actively partake in the metabolic activities of these organisms. They assume a vital role in the ecological defense against infections and the phagocytosis processes of animals and plants [37].

Lin et al. undertook the isolation and purification of polyketones from strain 105SU.1.1a.3b [38]. This particular strain was identified in the liver and pancreatic tissue of a newfound trypanosoma species in the Philippines. Their investigation revealed that the crude extract from this strain displayed inhibitory effects on Bacillus subtilis. Romero et al. isolated L-13-ACM2-092 from soft corals within the coastal zones of Mozambique [39]. The metabolites derived from this compound exhibited inhibitory effects on both human lung adenocarcinoma and melanoma. Tian Yunfang et al., on the other hand, isolated 152 strains of Marine actinomycetes from various Marine animals within the intertidal zone of Zhoushan [40]. Through a screening process, they identified four potent actinomycetes with strong antibacterial properties, indicating their potential for further exploration.

Research methods of Marine actinomycetes

The uniqueness of the marine environment imparts distinct physiological characteristics and genetic metabolisms to Marine actinomycetes. Thus, selecting appropriate research methods to analyze their metabolites becomes of paramount importance. Currently, approximately 50% of the active substances originating from marine microorganisms are synthesized by Marine actinomycetes [41-43]. The exploration of secondary metabolites from Marine actinomycetes encompasses various facets of knowledge and technology, encompassing aspects like sampling and extraction, purification and separation, structural identification, and activity evaluation. Throughout this process, an array of methods and technical tools are required, including high-performance liquid chromatography and mass spectrometry. Functioning as the foundation and wellspring for identifying lead compounds, the analysis of metabolite research processes holds immense significance [44, 45].

Traditional pure culture method

Isolation and culture methods are typically utilised to extract and refine Marine microorganisms from the environment, followed by the investigation of the diversity of Marine microorganisms through general biochemical traits or specific phenotypes. Stach et al. employed the traditional selective culture method to isolate a novel actinomycetes, Williamsia maris sp. However, this approach does not fully capture the present state of Marine microbial diversity. This is due to the strong selection effect exerted by the isolation and culture medium, which cannot comprehensively represent the ecological role of Marine microorganisms [46].

In the cultivation of Marine actinomycetes, pivotal conditions involve their nutritional necessities, growth factors, and organic and inorganic growth elements. Inappropriate culture conditions can lead to diminished production of active substances. For instance, the antibiotic production of Streptomyces declines as the nutrient level in the medium increases. To illustrate, a Streptomyces strain isolated from offshore sea mud generates a new antibiotic solely when the conventional yeast medium is diluted and supplemented with NaCl. However, as nutrient levels rise in the medium, the antibiotic yield diminishes [47]. Recognizing the limitations of traditional culture methods, researchers have explored techniques like surface fluorescence microscopy, transmission electron microscopy, scanning...
electron microscopy, and microbial quinone fingerprinting [48]. Although these methods offer notable advantages over traditional culture, they still struggle to capture specific alterations at the genus or species level.

**Molecular biology technology**

The shortcomings of conventional microbial culture methods can be addressed through the application of polymerase chain reaction (PCR), 16S rRNA sequence analysis, and ARDRA analysis. **Study on 16S rRNA gene sequence.** Bacterial species identification holds paramount significance within the realm of microbiology. Traditional methodologies for such identification are predominantly rooted in phenotypic characteristics, encompassing aspects like morphological traits and biochemical reactions. Prominent techniques include the surface solution method, the bifidum index method, and the digital coding method [49, 50]. The first two of these approaches are the most traditional, necessitating rigorous experimental conditions, intricate processes, and relatively modest accuracy. Such methods do not align with the contemporary trend towards automated bacterial identification. Even within a biochemical reaction of a specific bacterium, the reaction’s outcome is not entirely immutable, albeit with a low probability [51, 52]. It is upon this uncertainty that the digital coding method is predicated. It undertakes a comprehensive analysis of the likelihood of each biochemical reaction trampling across diverse bacteria.

In recent years, the rapid advancements in molecular biology have provided essential technical support for swift microbial species identification. The stability and precision inherent to molecular biology technologies compensate for the limitations of biochemical methods in microorganism identification. Since Carl Woese proposed the utilization of the 16S rRNA gene for biological phylogenetic studies during the 1970s, this gene has found extensive application in the biological classification and phylogeny of bacteria. The 16S rRNA gene harbours an abundance of information and is easily attainable in terms of gene sequencing, rendering it the optimal choice as a molecular marker in phylogenetic analyses [53]. In prokaryotes, there exist approximately 1–15 copies of the ribosomal gene [54]. Distinctions between varying copies of the 16S rRNA gene could potentially lead to the misclassification of certain species as novel entities [55].

Dong Lei Sun et al. conducted a comprehensive analysis of the entire genome information for 2013 bacteria and archaea. They discovered that the differences in the 16S rRNA gene exceeded 1% across 22.5% of the genomes. Notably, some species of bacteria exhibit substantial similarity in their 16S rRNA gene, even sharing identical base sequences. These factors can limit the 16S rRNA gene’s capacity for distinguishing between different bacterial species. When utilising the 16S rRNA gene for bacterial species identification, it becomes necessary to consider gene sequences from different copies of the 16S rRNA gene obtained from isolates. This approach yields more meaningful phylogenetic classification information [56].

Woese et al. employed 16S rRNA oligonucleotide sequence analysis to identify a distinct class of archaea exhibiting significant phylogenetic divergence from other bacteria. They established a 16S rDNA clone library for marine sediment samples obtained at varying depths. The population’s genetic diversity was computed through library sequences and specific probes for actinomycta. Subsequently, the data was processed using the LIBSHUFF program and the Simpson index was calculated. The outcomes revealed a gradual increase in the population genetic diversity of actinomycetes dominance, which, however, decreased with deeper ocean depths [57].

**Research method based on PCR technology.** PCR can be employed to specifically amplify segments of interest within the genomic DNA of Marine actinomycetes, such as sequences from representative genes. By sequencing and analyzing these amplified products, it becomes possible to explore the genetic diversity, functional genome, and metabolic pathways of Marine actinomycetes. This approach offers a potent avenue for delving deeper into their biological attributes. Liu et al. utilise T-RFLP technology to investigate microbial polymorphism, a technique successfully applied for the analysis and comparison of diverse microbial communities. It serves to examine the diversity and structural characteristics of microbial communities. The foundational principle of T-RFLP is the amplification of total DNA in the sample via PCR, with one end of a primer labelled with fluorescent agents like HEX, TET, or 6-FAM. This results in a PCR product featuring the fluorescent label at one extremity, which is then subjected to digestion by appropriate restriction enzymes. Although PCR technology has matured significantly, certain challenges remain. The generation of non-specific products can be mitigated by refining the Mg2+ concentration within the PCR reaction buffer [58].

**Combination of metagenomics and bioinformatics**

For the first time, certain scholars employed metagenomics to establish a comprehensive gene library within the surface sediments of national Marine reserves. By integrating bioinformatics, they conducted microbial classification, ushering in novel concepts and methodologies for the investigation of microbial diversity and the development of new bioactive substances (or acquisition of new genes) [59].

Metagenomics enables a comprehensive analysis of the genome structure of microbial populations without the necessity for strain purification. This technology has paved the way for numerous functional investigations. Concurrently, metagenomic analysis of these compounds lays a foundational framework for comprehending the molecular mechanisms underpinning them. This technique has the potential to uncover pharmacologically active substances from challenging-to-culture strains, thus streamlining timelines and reducing reliance on laboratory microbial cultivation [60].

With an increased grasp of the diversity exhibited by Marine actinomycetes and the identification of secondary metabolite gene clusters, the potential correlation between the diversity of their biosynthetic gene clusters, the relatedness of strains, and their distribution patterns has garnered substantial attention from researchers [61]. Presently, the fusion of ecological and phylogenetic approaches has emerged as a fresh investigative strategy in the quest for novel metabolites. Comparative genomic analysis of Amycolatopsis actinomycetes strains and their biosynthetic potential has unveiled four primary lineages, each exhibiting distinct capabilities in producing secondary metabolites [62].

A comparative genomic exploration of 87 Streptomyces officialis strains revealed that the majority of species could be categorised into three clades (I, II, III). Clade I’s secondary metabolite biosynthesis gene cluster (SMBGs) is more specialised than those of Streptomyces from Marine sediments, encompassing commonly employed SMBGs. In contrast, Streptomyces within Clade II featured a higher abundance of SMB-GCs and elevated levels of secondary metabolites. Further statistical analysis demonstrated a certain correlation between its geographical distribution pattern and both system type and ecological characteristics [63].

**Marine actinomycetes culture process**

In the Marine ecosystem, diverse types of actinomycetes might exist across various regions. Therefore, prior to sample collection, it becomes crucial to select an appropriate sampling site in accordance with the research objectives and relevant literature references. To prevent sample contamination, the utilization of sterile instruments during collection is typically essential. For instance, custom-made material collectors, sterilized subsamplers, or specialised sampling equipment can be employed. During the collection process, the collection instrument should be fully immersed in seawater, and separate collections from both the surface and bottom layers are carried out [64]. It is customary to promptly treat the seawater from which the gene collection is expected to avoid potential contamination from external sources. The collected samples can be subjected to procedures like filtration and centrifugation to isolate actinomycete cells. Moreover, various culture media can be used to cultivate...
actinomycetes in order to obtain distinct types. It’s important to note that this step needs to be conducted under sterile conditions [65].

Before isolating Marine actinomycetes, suitable culture media must be prepared to furnish the required nutritional and environmental conditions for their growth. Typically, seawater or synthetic seawater mediums are used. Using the prepared medium, the collected samples are appropriately diluted. This step ensures each cell receives sufficient nutrients and space. The medium containing enriched actinomycetes is then plated [66]. Once the cells form colonies, individual colonies are scraped from the medium and transferred to fresh medium using tools such as a picking needle or trephine. The individual colony is confirmed as actinomycetes through morphological observation, physiological and biochemical tests, and its preliminary identification is established. Identified and purified actinomycetes strains are then preserved and managed for subsequent experimental research and application development [67].

To ensure that the isolated and purified actinomycetes strains are single and stable, they must be further separated using mediums and other methods to generate new single colonies. Morphological characteristics of actinomycetes, such as size, colour, and texture, are observed. Actinomycetes typically exhibit mycelial or branched forms, and certain species display distinctive fluorescence reactions or odours. Physiological and biochemical traits of actinomycetes strains are analysed to further confirm their identity [68]. This involves assessing factors like growth temperature range, metabolites, enzyme activity, and other indicators. Molecular biological identification techniques, such as 16S RNA sequence analysis, are used to ascertain the genetic information of actinomycetes, determining their species and subspecies classification. Secondary metabolites of Marine actinomycetes often possess strong biological activity, which can be assessed and verified through biological activity screening and other methods [69].

The verified strains are cultivated with controlled influencing factors to facilitate growth and multiplication. Marine actinomycetes require a medium with the appropriate concentration of sea salt for optimal growth. Generally, they can thrive in sea salt concentrations around 3%. Commonly used mediums include Zobell medium, ISP medium, and others. The suitable growth temperature for Marine actinomycetes lies between 28–30°C, although different strains possess varying ranges of temperature adaptability [70]. Cultivation is often performed on a constant temperature shaker to maintain the right temperature and oxygen supply. The optimum pH range for the growth of Marine actinomycetes is 7.0–8.5. Deviations from this range, whether too low or too high, can impede growth and metabolism, necessitating pH control during cultivation [71]. Marine actinomycetes require ample oxygen supply to thrive, necessitating favourable aeration conditions during culture. Most Marine actinomycetes are not reliant on light and can even be sensitive to it, hence they are typically cultured under conditions that avoid light. Different strains of Marine actinomycetes exhibit distinct culture time requirements. In general, it is advisable to culture at an appropriate temperature for approximately a week until cell density reaches a suitable range or attains the highest level of metabolite accumulation [72].

The secondary metabolite of marine actinomycetes

Due to its unique habitat, Marine actinomycetes have developed distinct metabolic pathways compared to other environmental microorganisms, resulting in secondary metabolites with novel structures and diverse types. As of 2019, a total of 313 natural products from Marine actinomycetes showcasing significant antibacterial activity have been documented, constituting approximately 87% of the overall reported natural products from this group. According to the analysis of articles concerning Marine actinomycetes in the Web of Science core collection, more than 300 newly identified active natural product molecules have been reported from 2020 onwards (97 in 2020, 99 in 2021, and 119 in 2022). Among these, the majority consist of polyketones and polypeptides.

Peptides

Peptides are organic compounds that are dehydrated from amino acids, contain carboxyl and amino groups, and are amphipathic compounds. Peptides are widely present in nature and play an important role in normal life activities. Marine actinomycetes are a rich source of peptide compounds, and peptides isolated from secondary metabolites of Marine actinomycetes are highly active.

Cheng Liang et al. found through experiments that Marine actinomycete Y12-26 can metabolize A substance with strong biological activity, Iturins A-2 (Figure 2A), which has a highly efficient and broad-spectrum antibacterial activity structure, is a cyclic lipopeptide compound composed of 8 amino acids and belongs to the substances in the family of subtitin [73]. It is mainly produced by the fermentation of yeast, and its isolation from the fermentation broth of Marine actinomycetes provides a new gene pool for the synthesis of subtilisin. The high yield strain can be obtained by optimizing the process, which can be used as a new biological insecticide.

Fiedler isolated three new aminofurans ProximicinsA (Figure 2B), B (Figure 2C) and C (Figure 2D) from Verrucosispora strain MG-37 [74]. Figure 2B showed low antibacterial activity, but showed good inhibitory effect on human tumor cell lines. Figure 2C showed a mild inhibitory effect on Gram-positive bacteria, but Figure 2D showed a weak inhibitory effect on Breviblis DSM 30. Proximicins compounds A, B and C have obvious inhibitory effect on the growth of gastric cancer and liver cancer cells, but have weak effect on MCF7.

Asolkar et al. isolated Arenamides A (Figure 2E) and B (Figure 2F) from the fermentation broth of strains from seafloor sediment samples of the Great Astriola Reef [75]. Figure 2E showed a significant cytotoxicity against HCT-116 cells with an IC50 of 13.2 µg/mL. However, Figure 2F also showed cytotoxicity against HCT-116 with an IC50 of 19.2 µg/mL.

![Peptides](https://example.com/peptides.png)
Antibiotics
With the continuous renewal of the medical industry, the discovery of antibiotics shows an upward trend. However, in the annual report of antibiotics, there are not many real new structures or new lead compounds, and few new targets or new types of varieties. Marine actinomycetes are the main source of antibiotics, and researchers are still trying to screen new antibiotics from the secondary metabolites of actinomycetes. Screening pathways for general antibiotics fall into two categories (Figure 3).

The secondary metabolites of actinomycetes are very important sources of antibiotics, and about 70% of the most widely used antibiotics are from actinomycetes. Under the selective pressure of the special Marine living conditions of Marine actinomycetes, Marine actinomycetes can accumulate new metabolites completely different from terrestrial actinomycetes by regulating the secondary metabolic pathway, thus shifting attention to rare and unique new actinomycetes in the ocean [76]. Secondary metabolites of Marine actinomycetes play an important role in cell communication, antibody immunity, and aquatic disaster prevention [77–79].

Lu Jiansheng et al. discovered and isolated chromomycin A2 (Figure 4A) by analyzing the secondary metabolites of WBF16 [79]. Figure 4A was the main metabolite with good biological activity and could be used for industrial production. Figure 4A is a yellow powder dissolved in chloroform, methanol, which is not easily dissolved in water and remains stable in acid. Activity assays showed that Figure 4A was significantly toxic to both KB and human lung cancer A549, and its toxicity was similar to that of doxorubicin, but more toxic to SMMC-7721 cells.

Zhang Bing isolated two lobophorin whorl-like antibiotics, lobophorin M (Figure 4B) and lobophorin H (Figure 4C), from Marine Actinomycete SS92 [80]. The lobophorin family of compounds is structurally diverse, most of which are isolated from Marine actinomycetes. These compounds have various biological activities such as antibacterial, anti-tumor and anti-inflammatory. Figure 4B and Figure 4C showed strong inhibitory activity against MRSA, and compound 8 was also found to have inhibitory activity against Salmonella typhimurium.

Yang Zhenzheng et al. studied the metabolite of strain M324 with broad-spectrum antibacterial effect in Lianyangang sea mud, and found that it had strong polarity, slightly dissolved alcohols, could be adsorbed by weakly polar macroporous resin, and desorb in low concentration of methanol solution [81]. The compound has a sugar ring structure and is an antimicrobial with a neutral glycoside. Its antibacterial activity was significantly higher than that of some traditional antibacterial activities. If cheap raw materials can be used for fermentation, then it is very beneficial for the economic development of industrialization.

Ye Liang [82] identified the species of Marine actinomycyes WBF7 and conducted a preliminary study on its anti-tumor metabolites. The Marine actinomycete WBF7 belongs to Streptomyces globossi cinerea, and this is the first time that this species has been isolated from a Marine environment. Strain WBF7 can produce strong anti-tumor active metabolites, which are stable under acid-base and heating conditions, and most of the active substances have medium polarity. Further work on the metabolites of strain WBF7 will hopefully find novel lead compounds for antitumor drugs.

Terpenoids
Terpenoids encompass all polymers of isoprene and their derivatives, denoted by the general formula \(\text{C}_n\text{H}_{2n}\). Apart from terpenes, there exists a variety of oxygen-containing derivatives such as alcohols, aldehydes, ketones, carboxylic acids, esters, and saponins. Following these are nitrogenous compounds, and to a lesser extent, sulfur-containing compounds. Numerous terpenoids hold significant roles in natural medicine and pharmaceutical development. While terpenoids are widely present in plants, their detection in Marine actinomycetes remains relatively limited.

Charles and colleagues isolated Marinone (Figure 5A) from Marine actinomycete CNB-632. The structure of Figure 5A shared similarities with another compound, Debrromarinone, both of which demonstrated notable inhibitory effects on Gram-negative bacteria [83]. Debrromarinone exhibited an minimum inhibitory concentration (MIC) of 1 to 2 \(\mu\)g/mL against Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, and Streptococcus pyogenes, whereas Marinone displayed an MIC of 1 \(\mu\)g/mL against Bacillus subtilis.

Wu and co-workers collected samples from the coastal intertidal zone of Qingdao, subjected them to separation, and identified three new paclitaxel sesquiterpenes, namely, Figure 5B, Figure 5C, and Figure 5D, within the secondary metabolites [84]. These compounds were initially screened for activity, revealing inhibitory effects on Bacillus subtilis, Escherichia coli, and other microorganisms. The biological activities of the three sesquiterpenes were evaluated. Notably, Figure 5B-D exhibited no effect on Bacillus subtilis, Streptomyces virgenes, Staphylococcus aureus, and Escherichia coli, and they showed no significant inhibitory effect on Chlorella.

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Ketones
Ketones are compounds where the carbonyl group is connected to two hydrocarbon groups. Their structure is intricate and varied, and they are pervasive in our daily lives. Ketones belong to the ketone family, encompassing antitumor drugs, pesticides, immunosuppressants, and food additives used in the food industry.

Cui Monina and collaborators discovered that the secondary metabolites of Streptomyces sp. AH17-3 were gemicidin A (Figure 6A) and gemicidin B (Figure 6B) [85]. Figure 6A and Figure 6B were initially identified in Marine actinomycetes, and compound 14 exhibited weak cytotoxic activity with an IC50 of 3.5 × 10^3 M. The primary synthetic pathway is the novel PKS pathway, capable of generating pyrone compounds from isoleucine as a substrate. Figure 6A inhibited Na^+ / K^+ -ATP pump and plant germination, while Figure 6B didn't exhibit any of the aforementioned activities.

Zhao Yunyu and colleagues extracted three monomers, 7,4',dihydroxyisoflavone (Figure 6C), 5,7,4'-trihydroxyisoflavone (Figure 6D), and butenolactone I (Figure 6E), from the fermentation broth of Marine actinomycete strain 6-1 [86]. Figure 6C boasts anti-cancer properties, osteoporosis prevention, cardiovascular and cerebrovascular disease prevention, immune enhancement, and antibacterial effects, serving as an effective approach for preventing and treating various chronic ailments. Figure 6D functions as a tyrosine kinase inhibitor that can suppress the body's immune function. Its structure resembles that of estrogen, thus it exhibits certain inhibitory effects on osteoporosis. Figure 6C and Figure 6D are both isoflavones, holding broad application potential and currently being research focal points worldwide. Figure 6E, which inhibits maturation promotion factor and impedes cell regeneration, has been employed in in vitro fertilization in animals like pigs, cattle, and sheep.

Rhamnoside soybean isoflavone (Figure 6F) is synthesized by Marine actinomycete Y12-26, attaching a rhamnose to each hydroxyl group of daidzein. The glycosylated daidzein may also harbor antitumor activity similar to daidzein. It exhibits the highest activity compared to other glycoside isoflavones [87].

Streptomyces sp. isolated from sea squirts by Buedenbender et al. obtained Herbimycin G (Figure 6G), an Ansamycins compound, through fermentation extraction [88]. In this assessment, the resistance of Figure 6G to chloroquine (3D7) and chloroquine resistance (Dd2) was gauged, and its inhibitory effect on both parasites surpassed 75%. Moreover, Figure 6G showed no cytotoxicity and exhibited good water solubility.

Figure 6 Ketones isolated from secondary metabolites of Marine actinomycetes. (A–B) gemicidin A, gemicidin B, two compounds found for the first time in Marine actinomycetes; (C–E) 7,4'-dihydroxyisoflavones, 5,7,4'-trihydroxyisoflavones, crotonolactone –I, three monomers were extracted from the fermentation broth of Marine actinomycete strain 6-1; (F) Rhamnoside soy isoflavones, the structure consists of a rhamnose attached to each hydroxyl group on both sides of daidzein; (G) Herbimycin G, resistant to chloroquine (3D7) and chloroquine (Dd2).

Quinones
Quinones are aromatic compounds with two double bonds and a cyclic diketone structure of six carbon atoms, such as benzoquinone and o-benzoquinone. Quinones share traits with open-chain binary ketones, engaging in addition and reduction reactions, but lack the characteristics of aromatic hydrocarbons. Derivatives of quinones include naphthoquinones, phenanthraquinones, anthraquinones, and so on. These compounds are either derived from quinones or can be readily converted into quinones, playing a significant role in quinone biosynthesis. Depending on their chemical structures, quinones can be categorized as benzoquinones, naphthoquinones, anthraquinones, and benzoquinones. Some of these quinones exhibit antibacterial and anti-tumor properties.

2-methyl-5,6,7-trimethoxy-1,4-naphthoquinone (Figure 7A), a secondary metabolite from Marine actinomycete WBF16, was first isolated from a marine microorganism. The presence of compounds like soy isoflavones, genistein, and soy saponins posed challenges in isolating Figure 7A from WBF16. Consequently, efficiently eliminating the interference of chemical components in the medium to separate secondary metabolites is a noteworthy issue to address [89].

Thiciana and colleagues gathered samples from the northeastern coast of Brazil, isolated the Micromonospora sp. strain, and purified four novel anthraquinone compounds, compounds Figure 7B–E [90]. Figure 7B and Figure 7D demonstrated cytotoxicity against HCT-8 human adenocarcinoma cells, boasting IC50 values of 12.7 and 6.2 μM, respectively, while Figure 7B and Figure 7D displayed no cytotoxicity against HCT-8 human adenocarcinoma cells. Anthraquinones exhibit activity 80 to 100 times higher than their corresponding glycosidic groups. The anthraquinone doxorubicin, used as a positive control, was 141 and 69 times more active than Figure 7B and Figure 7D, respectively.

A Marine actinomycete strain BCC45596, isolated from Sichang Island, Thailand, produces two structurally novel glycosylated anthraquinones, Urdamycinone A (Figure 7F) and Urdamycinone B (Figure 7G). These compounds have displayed growth inhibition effects on Mycobacterium tuberculosis and Plasmodium, making them promising lead compounds for developing anti-tuberculosis drugs and anti-parasite agents [91].

Li Yang and colleagues isolated two new polycyclic anthraquinone compounds, N-acetyl-N-demethylmayamycin (Figure 7H) and streptanthraquinone A (Figure 7I), from Marine Streptomyces 182SMLY [92]. Both anthraquinones markedly inhibited the proliferation of four distinct glioma cell lines, featuring IC50 values ranging from 0.5 to 7.3 μM, and they also induced apoptosis of glioma cells. Compound 28 additionally hindered the growth of S. aureus, demonstrating a MIC of 20.0 μM.

Macrolide
Macrolides are substances characterized by their macrolide ring structure. Most macrolides are microorganism-derived secondary metabolites, and they have found extensive application in treating respiratory and digestive disorders.

Kwon et al. isolated Marinomycins A to D (Figure 8A–D) [93]. Activity tests revealed robust antibacterial and cytotoxic properties in all four compounds, with Figure 8A being the most potent. These compounds demonstrated tissue-selective cytotoxic activity in NCI60 cancer cell line tests, with Marinomycins A displaying significant inhibition against six out of eight melanoma cell lines. Particularly noteworthy was SKMEL-5, with an IC50 of 5.0 nmolL⁻¹. The average IC50 values for Figure 8B and Figure 8C were 0.9 and 0.2 μmolL⁻¹, respectively. Importantly, these compounds exhibited minimal inhibitory effects on non-leukemia cancer cells, with an IC50 of about 50 μmolL⁻¹. This not only underscores their strong tissue selectivity but also suggests that if developed into drugs, the potential for myelosuppression-related side effects could be limited.

Williams P. G. et al. isolated three novel macrolide compounds, arenicolides A–C (Figure 8E–G), from various strains of Halosporium

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obligate marine actinomycetes [94]. All of these compounds feature an unsaturated macrocyclic lipid structure with a 26-membered ring and encompass several neighboring hydroxyl and methoxy components.

Buchanan isolated Sporolides A (Figure 8H) and B (Figure 8I) from strain CNB-392 [95]. Unfortunately, the strain did not exhibit any biological activity during screening. Figure 8H and Figure 8I did not demonstrate activity against vancomycin-resistant Enterococcus faecalis and methicillin-resistant Staphylococcus aureus. The highest concentration for human colon cancer testing was 78 μg/mL, with an upper limit of 250 μg/mL in antimicrobial assays.

**Figure 7 Quinones isolated from secondary metabolites of Marine actinomycetes.** (A) 2-methyl-5,6,7-trimethoxy-1,4-naphthoquinone, a secondary metabolite of Marine actinomycyes WBF16; (B–E) Four anthraquinone compounds isolated from strain Micromonospora sp.; (F–G) Urdamycinone A, Urdamycinone B, two novel glycosylated anthraquinone compounds inhibited Mycobacterium tuberculosis and Plasmodium; (H–I) N-acetyl-N-demethylmayamycin, streptoanthraquinone A, both anthraquinones could significantly inhibit the proliferation of glioma cell lines.

**Figure 8 Macrolides isolated from secondary metabolites of Marine actinomycetes.** (A–D) Marinomycins A–D, all the four compounds had strong antibacterial and cytotoxic activities; (E–G) Arenicolides A–C, they all have an unsaturated macrocyclic lipid structure with a 26-membered ring; (H–I) Sporolides A, Sporolides B, compounds isolated from strain CNB-392.
Pigments
With the continuous improvement of people's living standards and health awareness, more and more synthetic pigments are being banned due to their toxicity to the human body. Natural pigments, on the other hand, are garnering increased attention for being safer and more environmentally friendly. Natural pigments are found in nature and readily decompose without accumulating in organisms. Beyond being non-toxic and devoid of side effects, they also provide certain nutritional elements to the body, often exhibiting remarkable medical and health benefits. Marine actinomycetes, known for producing distinctive bioactive substances, have increasingly captured attention for their pigments.

S. violaceoruber can produce actinorhadin or its analogs, which often exhibit varying colors based on pH levels. For instance, S. coelicolor appears blue at pH 9.0–12.0, transitions to purple at pH 7.0, and then turns red at pH 3.0–5.0 [96].

In a study by Zhang Aimei et al., the stability of the green pigment produced by Streptomyces viridis was investigated [97]. It was observed that the pigment was not resistant to hydrogen peroxide, while sodium sulfite had a hyperchromic effect on it. An actinomycete strain isolated from a marine mangrove was able to produce a pink pigment that exhibited dye retention and stability even after three washes on cotton cloth and wool.

Liao Zhenlin and colleagues determined the spectral characteristics and stability of the extracted yellow pigment from Vernua orange under various conditions such as temperature, pH, illumination, ultraviolet light exposure, and exposure to metal ions [96]. It was found to be stable in acidic and neutral environments, with less stability in alkaline conditions. The pigment demonstrated robust stability to ultraviolet rays and remained stable when exposed to K⁺, Na⁺, Mg²⁺, Ca²⁺, and other metal ions. However, it lacked resistance to common bacteria, mold, and yeast. The yellow pigment produced by the marine actinomycete Hespera displayed the fundamental qualities needed to become a potential food additive in the field of food technology.

In research by Zhang Min et al., a physical and chemical analysis of the peach pigment from the marine actinomycete strain H-109 was conducted [98]. The resulting pigment had a peach hue and exhibited the highest solubility in acetone. It proved to be insensitive to sunlight and ultraviolet radiation, displaying a prolonged stable period. Although the pigment's solubility was affected by pH changes, it showcased bright color and stability at a pH of 7. While the pigment content was low, it remained unaffected by temperature and exhibited good stability. However, at higher concentrations, its stability was significantly influenced by temperature and prone to precipitation. At concentrations above 0 °C, A530's solubility in acetone yielded bright color and a higher absorption rate. This pigment displayed high homology with iGluRs, providing a foundation for further research on the subcellular localization of AGLRs.

Functional activity of secondary metabolites
The potential application of Marine actinomycetes and their secondary metabolites extends beyond antibacterial and anti-tumor properties, demonstrating promising research and application possibilities in antifungal and antiviral domains [99]. Certain metabolites hold significant importance in drug development, environmental conservation, and food safety. These aspects collectively underscore the research value and potential applications of Marine actinomycetes' secondary metabolites [100].

Antibacterial activity
The inhibitory effect of antibacterial action metabolites on pathogenic bacteria is attributed to the selective impact of antibacterial substances on specific bacterial targets, disrupting the biochemical metabolic processes, affecting structure and function, impairing growth and reproduction capabilities, and resulting in bacterial eradication or inhibition. Various metabolites possess distinct mechanisms of action, categorised into four main types (Figure 9).

Zhang et al. isolated an actinomycete strain, Micromonospora sp. WMMC-218, from Symplegma brekenhiemli, a sea squirt collected in Stanblum State Park, Florida, USA [101]. Within the secondary metabolites of this actinomycete, two compounds-Micromonohalimanes A and B-were identified and evaluated for their activity against Staphylococcus aureus ATCC 33591. Among them, only Micromonohalimanes B exhibited significant anti-MRSA activity. In 2017, Branna et al. isolated Branimycins C from the fermented extract of an actinomycete strain, Pseudonocardia carboxidivorans M-227, retrieved from the deep sea seafloor canyon of Aviles, Spain. This compound demonstrated anti-MRSA activity [102].

Antifungal activity
Fungal infections are illnesses caused by fungi, and the symptoms and severity of such infections vary based on the pathogen, host, and environment. In recent years, fungal infections have been on the rise globally, posing a significant threat to human health. Fungal infections are becoming progressively more prevalent. Studies have revealed that parasitic bacteria and mycotoxins present substantial risks to human health. Individuals with weakened immune systems and those who are on prolonged courses of antibiotics and hormones are particularly vulnerable to mycotoxicosis. Moreover, some fungal infections have developed resistance to drugs, creating significant challenges in their treatment. Consequently, there is an increasing need for novel antifungal medications. The types of antibacterial agents available are limited, and their detrimental effects on the ecological environment have greatly restricted their use. Thus, the quest for effective antifungal drugs is an urgent clinical imperative.

Streptomyces sp. ACT2, possessing antifungal activity, was isolated from estuarial sediments in a mangrove forest on the southwest coast of Tamil Nadu, India, using cross-strip and AGAR well diffusion methods. Active components identified against dermatophytes are bahamaloide and polypene-polyols, which are substances exhibiting commendable therapeutic effects against dermatophytes [103].

Xu et al. isolated two novel amide compounds, antimycin A(1) and antimycin A(2), from the culture medium of the Marine actinomycete Streptomyces antibioticus H74-18 [104]. These compounds exhibit potential inhibitory effects against Candida albicans, with MICs of 5 and 10 μg/ml, respectively.

2-pyrroliac, isolated from the secondary metabolite of the Marine sediment-derived actinomycete Streptomyces sp. AHMU XC 2026, displayed modest inhibitory activity against Pyricularia oryzae HNM 1003 in rice. There is ample room for modifying its structure and enhancing its antifungal activity. Concurrently, 2-pyrrolic acid is also a primary secondary metabolite of this strain [105].

Antiviral activity
Certain secondary metabolites of Marine actinomycetes have demonstrated antiviral effects, with some components also displaying antiviral properties. These natural products possess unique structures and remarkable activity, making them promising novel antiviral lead compounds with significant application potential.

Figure 9 Mechanism of action of sterilization
Marine actinomycin X2 exhibits antiviral effects against CVB3 prior to viral adsorption, and its anti-CVB3 effect becomes more pronounced with increasing concentration. However, the inhibitory effect of actinomycin X2 diminishes after the virus adheres to host cells. Additionally, Marine actinomycin X2 down-regulates the mRNA and protein expression of ICAM-1 in CVB3-induced ECV304 cells. Following CVB3 infection over time, there is an elevation in ICAM-1 gene and protein expression, yet actinomycin X2 can mitigate this heightened expression within a specific timeframe [106].

Antiviral and larvicial properties are present in compounds extracted from Marine actinomycetes, sourced from Nocardia alba KC711971. These compounds were assessed against Newcastle disease virus and infectious bursal disease virus, and the bioactive compounds obtained displayed antiviral potential. The compound exhibits notable antiviral activity, effectively combating both NDV and IBDV poultry viruses [107].

**Cytotoxic activity**

Cytotoxicity pertains to cellular damage induced by specific substances, primarily evidenced through cell demise, disruptions in metabolism, and similar phenomena. The cytotoxicity assay stands as a vital technique for assessing the harm inflicted by chemicals upon cells. Currently, this technology has gained widespread employment in drug screening, environmental pollution monitoring, and related domains. Numerous distinct methods are accessible for identifying cytotoxic effects. Traditional techniques encompass assessments of cell membrane permeability, ATP content, and cell proliferation, among others. The degree of cytotoxicity is closely intertwined with its potential risks to the human body. The scientific evaluation of cytotoxicity holds significant importance for drug research and development, environmental protection, and food safety. For instance, during the drug development process, it becomes imperative to conduct toxicological studies on candidate compounds, enabling the selection of compounds with favorable effectiveness and safety profiles. Cytotoxicity assessment serves as a pivotal approach for gauging the severity of substance-induced harm, thereby furnishing an effective supplementary tool for drug research and development, environmental protection, and food safety.

Li et al. isolated a novel diamide compound, N1-acetyl-N7-phenylacetylcadaverine (3), from the ethyl acetate extract of the culture medium of a Streptomyces strain derived from the seabed mud of Bohai Bay [108]. This compound exhibited moderate cytotoxicity activity against HL-60 cells, with an IC50 value of 58.43 µM. Izumikawa et al. separated compound JBIR-31 (8), a fresh analogue of teleocidin, from a newly discovered strain of sponge-derived actinomycetes [109]. This compound displayed slight cytotoxic activity against Hela cells and human malignant pleural mesothelioma.

**Antitumor activity**

The focal point of research concerning Marine microbial natural products lies in the development of anti-tumor drugs. Microorganisms within the ocean, particularly those residing in its depths, generate a plethora of structurally unique compounds due to their distinctive habitat conditions, such as elevated salinity, high pressure, low temperature, and limited nutrients. Concurrently, their structural diversity affords access to numerous natural products endowed with crucial physiological activities. For instance, these products manifest anti-cancer, antibacterial, anti-HIV, anti-allergic, and other beneficial effects. The ocean harbors a diverse array of microorganisms, characterized by distinct living patterns and metabolic pathways when compared to terrestrial organisms. It is precisely this distinct attribute that empowers us to uncover anti-tumor agents from the marine realm [110].

Thiocoraline was extracted from strain L-13-AM2Q-092, which was isolated from soft corals collected off the Mozambique coast by Romero et al. Thiocoraline displayed approximately 5 times greater cytotoxic potency against lung adenocarcinoma and melanoma cells compared to its activity against colon adenocarcinoma cells (IC50 values of 0.002 and 0.01 µM, respectively) [111].

Antimycin A1a represents a secondary metabolite derived from novel actinomycetes in marine sediments procured from the New Zealand coast, Papua New Guinea. This compound exhibited robust effectiveness against Western equine encephalitis virus in cultured cells, characterized by a half-maximal inhibitory concentration of under 4nM and a selectivity index exceeding 550. Analogues of Antimycin A1a have demonstrated antiviral capabilities, and mechanistic investigations corroborate that these secondary metabolites originating from Streptomycetes strains function through the inhibition of the cellular mitochondrial electron transport chain, thereby impeding de novo pyrimidine synthesis [112].

**Summary and prospect**

The majority of reported actinomycetes originate from coastal waters, leaving substantial scope for further investigation into the active constituents of actinomycetes from more distant offshore waters. Presently, numerous other scarce or unidentified actinomycetes remain undiscovered. While some advancements have been made in the screening, isolation, purification, and pharmacology of their active components, only a limited number of these have been commercialized, and their yield remains low. This can be attributed to a certain lack of focus in the current active ingredient screening procedures and the challenge posed by the relatively low yield of natural active compounds, which hinders meeting production demands. Additionally, some natural products exhibit a certain level of toxicity, a primary constraint to their widespread application.

In light of the existing challenges, genetic analysis and exploration technologies can be employed to selectively isolate marine actinomycetes, thereby reducing the randomness in the screening process. Further analysis of the biosynthetic pathways of active compounds, coupled with the utilization of genetic engineering techniques to activate and regulate the expression of pivotal synthase genes related to active compounds, alongside the optimization of breeding, fermentation, and separation and purification processes, could stimulate the expansion of active compound production. Given the ongoing advancement of science and technology, the study and application of active products derived from marine actinomycetes possess considerable potential and promising prospects.

The ocean harbors a wealth of actinomycetes. Actinomycetes inhabiting distinct marine environments exhibit unique metabolic pathways and structurally innovative metabolites, offering substantial potential for new drug development. Actinomycetes sourced from marine sediments have remained a focal point of recent research, with approximately half of marine-derived actinomycetes that produce active secondary metabolites originating from these sediments. Notably, the compounds isolated thus far from actinomycetes of varied distribution showcase diverse structural attributes and biological activities, rendering them all of substantial research value. Consequently, marine actinomycetes represent an extensive repository of resources. Secondary metabolites extracted from marine actinomycetes have served as the cornerstone for new drug exploration and development. As the techniques for the isolation and cultivation of marine actinomycetes and the refinement of secondary metabolite purification continue to advance, more research findings are poised to contribute to the betterment of human society in the future.

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