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Review Article
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MARINE NATURAL PRODUCTS: A PROMISING FRONTIER IN MODERN DRUG DISCOVERY

KAVURI SATHVIKA*, KAMANI MANASA VANI, BUDAGALA GAYATHRI, CHANDU BABU RAO

Priyadarshini Institute of Pharmaceutical Education and Research, 5th Mile, Pulladigunta, Guntur-522017, Andhra Pradesh, India.

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***Corresponding Author**
Kavuri Sathvika

Abstract
The relevant biological activities, source organisms and country of origin. Pertinent reviews, biosynthetic studies, first syntheses, and synthesis that led to the revision of structures or stereo chemistries, have been included. analysis of the progress in the study of prokaryote involvement in macro-invertebrate MNP production is discussed. The biomedical potential of the sea has gone largely unexplored so far, despite the globe that it covers three parts of the planet surface and the fact that life on Earth originated from the sea. However, with the help of the professional deep sea divers, the marine researchers have archived access to all sorts of marine creatures like sponges, corals, sea urchins, sea squirts, hydroids, sea anemones, fishes and mollusks as well as to varied types of sea plants including algae and the other micro-organisms embedded in the sea bed. New Advancements in synthetic biology, genomic sequencing and bioinformatics are entitiling innovative solutions to these challenges, facilitating the identification, characterization, and sustainable production of marine bioactive compounds. versatile collaborations and public-private partnerships are essential for translating MNP discoveries into viable clinical applications. The results highlighted the overlooked prospective of marine natural products as high in resources for innovative solutions in the phase of escalating drug resistance and vacant void of therapeutic needs.

Keywords: *Marine biotechnology, herapeutic agents' bioactive compounds, pharmaceuticals drug discovery, marine natural products, therapeutic agents, bioactive compounds*

INTRODUCTION

Some of the new MNP structures or previously reported compounds where there has been a structural revision, or a newly established stereochemistry are shown in this review. It also covers previously reported MNPs with significant new bioactivities or ones that have been synthesized for the first time, but their structures are generally not shown. A symbol on the identifying diagram number is used to differentiate structures where the absolute configuration has been determined for all stereogenic centres, axes, and planes in a compound. Reports of new MNPs that were identified based solely on a combination of gene cluster information, MS data, and Global Natural Products Social (GNPS)-based molecular networking, with compounds not isolated and no NMR data recorded, are excluded from the review [1]. It makes it easier to find new sources for novel drug discoveries. Although acquiring larger amounts of marine compounds sustainably poses a challenge, many derived medicines have reached the clinical phases or are undergoing clinical trials.

The therapeutic promise of marine bioactivity is well demonstrated with the sea squirt-derived trabectedin and cone snail venom ziconotide. Marine biotechnology, metagenomics, and marine microbial culturing techniques have made marine bioresources more accessible. Marine Natural Products are now playing a vital role in developing future medicine innovations to treat cancer, neurodegenerative diseases, and antibiotic-resistant infections [2] Informatic tools are being developed for the efficient and targeted identification of Biosynthetic Gene Clusters (BGCs) encoding bacterial NPs of interest. For example, the ARTS tool enables the discovery of BGCs encoding for compounds with antimicrobial activity. Combination of improved tools for predicting structures from genomic information, such as antiSMASH v5, with programs that predict bioactivities from structures, are helping to sort through the enormous quantity of sequence information now available and thus focus on compounds of greatest potential. these are now reaching a more mature stage and have thus been used to increase titer of known compounds of interest, produce compounds deriving from cryptic gene clusters or eDNA, and has been the

identification of biosynthetic gene clusters for terpene biosynthesis in the genomes of marine corals, a discovery that overturns the long-held belief that these coral-derived compounds were the product of symbiotic associated marine microorganisms The increased availability of genome sequences [3].

Scientists so far have been completely dependent on the tropical forests and terrestrial ecosystems for unusual substances having medicinal properties, which have been used either in direct extracts or synthetic redesigns of the plant molecules. Anti-malarial drug quinine from the bark of the cinchona tree, aspirin from the willow bark, morphine from opium poppies, and Taxol to treat cancer from the yew tree of rainforests are a few such examples. The quest to find novel sources of medicines to fight developing antibiotic resistance and the diseases of the industrialized world has forced researchers to explore marine animals and plants, too. The recent studies on marine biota have proved that it, in fact, is a great storehouse of useful bio-chemicals and lifesaving medicines which otherwise are not found in terrestrial natural products. Marine organisms need these bioactive compounds for purposes such as reproduction, communication, and for their own protection against predation, infection, and competition. The biologically active chemical diversity from the vast plethora of marine organisms is now being translated into novel biomedicines having therapeutic activity [4].

MARINE MICROORGANISMS AND PHYTOPLANKTON

1 Marine-sourced bacteria

Actinobacteria were the most common source of bacterial MNPs, with 94 new structures reported. A sponge-derived Actino alloteichus cyanogriseus yielded three new cyclolipopeptides, cyanogripeptides A–C 1– Based on the annotations from the genome mining tool antiSMASH, the candidate biosyntheticgene cluster (BGC) cgpV was proposed to be responsible for the assembly of the compounds. A cyclic tetrapeptide, arthropeptide B 4, was isolated from Arthrobacter humicola sourced from composted material of marine origin,4 and a new diketopiperazine janibatide A 5 was reported from a deep-sea sediment-derived Janibacter sp.5 A new pyrroline, nocarpyrroline A 6, was reported from a krill-derived Nocardiopsis sp.,6, and two new furan derivatives, nicardifurans D 7 and E 8, were isolated from a sediment-sourced Nocardiopsis sp.7. A coral-derived Micromonospora sp. Yielded

2. Cyanobacteria:

The lower number of MNPs reported from cyanobacteria in 2023 also coincided with a decrease in the chemical diversity of new structures. Another general observation is an increase in the isolation of new NPs from mixed assemblages of cyanobacteria. Amixed cyanobacterial collection of predominantly Lyngbya and Dichothrix spp. yielded a new peptide–polyketide hybrid NP, iezoside B 111, 80while a South China Sea collection of Lyngbya sp. yielded two new aplysiatoxin analogues, neo-debromoaplysia toxin I 112, and neo-debromoaplysiatoxin J 113. 81 A new cyclic depsipeptide, alotamide B 114 was reported from a mixed assemblage comprised mostly of Moorena sp. (annotated as Moorena sp. in the manuscript)82 and a new cyclopropane-containing fatty acid derivative, benderadiene 115 was reported from a bloom forming assemblage of Lyngbya sp.83 Notably, there is still significant inconsistency in reporting of the correct naming of this genus with Moorena being the accepted genus name.

3. Marine-Derived Fungi

Marine fungi have emerged as another significant source of bioactive metabolites. Compounds isolated from *Acremonium*, *Alternaria*, *Amphicorda*, *Arthrinium*, and *Alfimbria* species include sesquiterpenoids, meroterpenoids, chromanol analogues, and alkaloids with anticancer, antimetastatic and calcium signaling inhibitory properties. Notably, Marinobazzanan reduced Structural Diversity of marine natural products and challenges in charecterization cancer cell migration and metastasis in experimental models, demonstrating the therapeutic potential of fungal metabolites.

4 Marine Sponges and Other Protists

Marine sponges (phylum Porifera), among the simplest multicellular organisms, are recognized as reservoirs of potent chemical defenses. To protect themselves from predators, they synthesize a wide range of toxic secondary metabolites, many of which exhibit anticancer and antiinflammatory activities. Stable isotope incorporation techniques have facilitated structural elucidation of several sponge-derived compounds. Other marine protists, such as *Thraustochytrium pachydermum*, have also produced unique sterol derivatives.

5 Green algae :

(*Chlorophyta*) represent an important but underexplored source of marine natural products with significant pharmaceutical potential. Adaptation to harsh marine conditions such as high salinity, intense light, and microbial competition has enabled these organisms to produce diverse secondary metabolites. Green algae synthesize bioactive compounds, including terpenoids, alkaloids,

Structural Diversity of marine natural products and challenges in charecterization

phenolics, polysaccharides, fatty acids, and pigments that exhibit antimicrobial, antiviral, anticancer, antioxidant, and anti-inflammatory activities.

IMPORTANCE OF MNPS IN DRUG DISCOVERY

The exploration of MNPs is crucial for several reasons

1 Chemical diversity:

Marine organisms produce a wide range of bioactive compounds that are often structurally distinct from terrestrial natural products. This chemical novelty is

essential for discovering new drugs with distinctive mechanisms of action.

2. Therapeutic potential

Numerous MNPs exhibit remarkable pharmacological properties, including anticancer, antimicrobial, and anti-inflammatory activities. For example, ziconotide, extracted from the venom of the cone snail, was the first marine-derived drug approved by the FDA in 2004.

3 Unmet medical needs

MNPs provide potential solutions for diseases that currently lack effective treatments. The increasing interest in marine pharmacognosy arises from the need for new therapeutic agents to inhibit various health challenges [2].

MNPS AS DRUG SOURCES

1distinctive features of marine-derived compounds

MNPs are distinguished by their chemical diversity and unique structural features that often differ significantly from terrestrial compounds. Key characteristics include:

1.1Chemical novelty:

precisely 71% of the molecular platforms found in MNPs are exclusive to marine organisms, highlighting their potential for novel drug discovery.

1.2Bioactivity :

MNPs exhibit a higher incidence of significant bioactivity compared to terrestrial natural products. For instance, preclinical screens show that about 1% of marine specimens exhibit anti-tumor activity, compared to 0.1% from terrestrial sources.

1.3Ecological roles:

Many MNPs serve as chemical shielding for marine compounds against predators and pathogens, which contributes to their bioactive properties.

2 Examples of successful drugs from marine sources

Several marine-derived compounds have effectively transitioned into clinical use, displaying the potential of MNPs in pharmacotherapy:

3.2.1Cytarabine (Ara-C)

The first FDA-approved marine-derived drug, approved in 1969 for cancer treatment, is derived from nucleosides extracted from the Caribbean sponge Tethya crypta.

3.2.2Ziconotide (Prialt®)

Approved in 2004 for severe chronic pain management, this drug is a synthetic equivalent of a peptide from the venom of the cone snail Conus magus.

2.3Trabectedin (Yondelis®)

This marine alkaloid, isolated from the tunicate Ecteinascidia turbinata, received EU approval in 2007 for treating soft-tissue sarcoma and relapsed ovarian cancer.

BIOACTIVE COMPOUNDS FROM NOVEL MARINE MICROBES

The discovery of the group of marine microbes from the coral reef sponges and from the marine precipitate has provided an opportunity to microbiologists to look for novel antibiotics. The studies have revealed a raised microbial population that is unparlleled bioactive in many sponges. Marine invertebrates such as corals and sponges are hosts to a multitude of microorganisms. The existence of a relationship between the microbes and the host organisms is not yet fully understood. The presence of micro-organisms in the marine invertebrates seems to play a role in keeping them healthy and nourished, besides producing defense chemicals to protect them from their predators. The ocean floor itself is the next major potential source of bioactive compounds. It is estimated that there are one billion living cells per cubic centimeter of seafloor sediment. The micro-organisms diversity of microorganisms in the deep ocean is boundless. These microbes can be used more efficiently, cost-effectively, and sustainably as compared to other marine organisms and can be gathered with little impact on the natural environment, in case they can be cultured in large quantities in lab. It is worth noticing that 70% of the naturally occurring antibiotics such as actinomycin, streptomycin, novobiocin are produced by soil based actinomycetes family. However, the discovery of many novel marine actinomycetes from the marine environment such as seafloor sediments, algae and sponges may lead to the availability of novel antibiotics which may overcome the iminant dagner of antibiotic resistance in future. Actinomycetes are responsible for the production of about half of the discovered bioactive secondary metabolites mainly antibiotics, antitumor agents, immunosuppressive agents and enzymes. Many new chemical compounds from the marine actinomycetes now stands isolated and ten new genera of microbes have been remarkably characterized including the genus *Salinispora* from about 2,500 new strains have been discovered.22 Marine bacteria *Salinispora tropica* isolated from the marine sediments produce a compound salinosporamide-A (NPI-0052, Fig.1), a novel β-lactone-γ-lactam, that exhibits cytotoxicity counter breast cancer, colon cancer, non-small cell lung cancer and melanoma orally active proteosome inhibitor that induces apoptosis in multiple myeloma cells with mechanisms distinct from the commercial proteosome inhibitor anticancer drug bortezomib.23 A novel metabolite diazepinomicin (ECO-4601), a uniquefarnesylated dibenzodiazepinone produced by marineactinomycetes (*Micromonospora* species) possesses antibacterial, anti-inflammatory and antitumor activities.24 Ithas broad spectrum of in vitro cytotoxicity and has signifies in vivo, activity against glioma, breast and Prostate cancer in mouse models.

5.THE STRUCTURAL DIVERSITY OF MNPS POSES BOTH OPPORTUNITIES AND CHALLENGES :

1 Methodology:

This study adopted a qualitative and exploratory research design to examine the role of marine biological resources and marine natural products in biomedical and pharmacological development. A systematic literature review, supported by descriptive analysis and case study evaluation, was employed to integrate scientific evidence and understand the relationship between marine biodiversity and drug discovery.

2 Research Design and Framework

The research framework followed the Systematic Literature Review (SLR) methodology guided by PRISMA guidelines to ensure transparency, reproducibility, and reduced bias. This approach enabled the identification, evaluation, and synthesis of scholarly studies focusing on bioactive marine compounds with therapeutic potential.

3Complex structures

The entangled structures of many MNPs complicate their characterization and synthesis. Advanced approaches such as NMR spectroscopy and mass spectrometry (MS) are essential for interpreting these structures.

4 Supply issues:

Many bioactive compounds are generated in low yields by their natural sources, necessitating innovative approaches such as synthetic biology or semi-synthesis to enhance availability.

5Metabolic stability:

Peptide-based drugs often face metabolic degradation challenges. Medicinal chemistry tactics are being employed to modify these compounds to improve their pharmacokinetic properties.

TECHNIQUES IN EXPLORING MNPS

Collection and identification of marine organisms

Advancements in sampling techniques have significantly improved the collection of marine organisms. Methods now include

1 metagenomics:

This approach allows researchers to analyze genetic material directly from environmental samples, facilitating the discovery of novel marine species and their associated bioactive compounds. *Remote sensing technologies.* These technologies aid in locating unexplored marine habitats, such as deep-sea environments, where unique organisms may reside. Extraction and Isolation of Bioactive Compounds. The extraction and isolation processes are critical steps in drug discovery

2 *Solvent extraction*

Traditional methods using organic solvents are commonly employed to isolate bioactive compounds from marine organisms. However, new methods such as microwave-assisted parentage are gaining traction due to their effectiveness.

3 *Chromatography techniques*

High-performance liquid chromatography and other chromatographic methods are essential for isolating pure compounds from complex mixtures.

POTENTIAL APPLICATIONS IN DRUG DISCOVERY

1 Anticancer agents

MNPs have shown significant potential as anticancer agents due to their unique bioactive compounds. The ecological role of these compounds often involves chemical defense mechanisms, which can be harnessed for therapeutic purposes. Significant examples include: *Trabectedin (Yondelis®)* isolated from the tunicate Ecteinascidia turbinata, which is the drug used for soft-tissue sarcoma and ovarian cancer. *Dola statin 10* Isolated from the sea hare Dolabella auricularia, has been developed into antibody-drug conjugates for targeted cancer therapy, demonstrating the potential for MNPs to enhance treatment efficacy while minimizing side effects.

2 Antimicrobial and antiviral compounds

The marine environment is a rich source of antimicrobial and antiviral agents, with many compounds exhibiting potent activity against a variety of pathogens. *Marine bacteria.* Certain marine-derived bacteria produce antibiotics that are effective against resistant strains of bacteria. For instance, Salinispora tropica has yielded compounds with significant antibacterial properties. *Antiviral activities of* MNPs have also shown promise against viruses, including those responsible for influenza and HIV. Research continues to explore the mechanisms by which these compounds exert their antiviral effects.

3 Neuroprotective agents

MNPs are being investigated for their neuroprotective properties, which could lead to new treatments for neurodegenerative diseases

3.1Peptides from marine sources:

Compounds such as conotoxins from cone snails have demonstrated potential in modulating neurotransmitter systems and protecting neuronal cells from degeneration.

7.3.2 Bioactive lipids

Certain lipids derived from marine organisms exhibit anti-inflammatory and neuroprotective effects, suggesting their utility in treating conditions like Alzheimer's disease.

CHALLENGES AND LIMITATIONS IN MARINE NATURAL PRODUCTS (MNPS) RESEARCH

Despite the immense therapeutic potential of marine natural products, their exploration and development face several scientific, environmental, legal, technical, and financial challenges that limit their large-scale utilization in drug discovery.

1. Accessibility and Sustainability of Marine Resources

One of the primary obstacles in marine pharmacognosy is the limited accessibility to marine ecosystems. Many biologically rich environments, particularly deep-sea habitats, coral reefs, and extreme marine zones, remain largely unexplored due to technological difficulties, high operational costs, and harsh environmental conditions.

2. Legal and Ethical Considerations

Marine natural product research is further complicated by various legal and ethical issues. International frameworks, including the Convention on Biological Diversity (CBD), regulate access to genetic resources and emphasize fair and equitable benefit-sharing among nations and communities. Researchers and industries must comply with these regulations to maintain ethical standards and avoid legal disputes.

9. FUTURE DIRECTIONS IN MARINE NATURAL PRODUCTS (MNPS) RESEARCH

1. Emerging Technologies in Marine Pharmacognosy

The future of marine pharmacognosy appears highly promising due to the integration of advanced technologies that enhance the discovery, production, and development of marine-derived drugs.

2. Synthetic biology:

Has emerged as a powerful tool in this field. By engineering microbial hosts to express biosynthetic pathways of marine organisms, researchers can produce valuable marine-derived compounds on a large scale. This approach helps overcome supply limitations associated with low natural yields and reduces dependence on harvesting marine species, thereby supporting both sustainability and commercialization.

3.Genomic approaches

Also play a crucial role in accelerating discovery. Modern genomic sequencing and bioinformatics techniques enable the identification of biosynthetic gene clusters responsible for the production of secondary metabolites. Understanding these genetic pathways facilitates the prediction, identification, and production of new bioactive compounds, even from organisms that are difficult or impossible to culture.

CONCLUSION

Marine natural products (MNPs) represent a valuable and largely untapped source of novel bioactive compounds with significant potential for drug discovery. Although recent years have seen a decline in the discovery of new prokaryote-derived marine metabolites, this trend may reflect the increasing difficulty of identifying truly unique marine microorganisms rather than a lack of potential. Many easily accessible marine microbes produce metabolites similar to those of terrestrial organisms, reducing chemical novelty. Nevertheless, continued exploration of marine biodiversity remains highly promising. Since the 1980s, scientific evidence has demonstrated that many compounds previously attributed to marine invertebrates are actually synthesized by associated microbial symbionts. Structural similarities between metabolites from marine organisms and terrestrial bacteria first suggested this relationship. Subsequent studies confirmed that several complex polyketides and peptides originated from bacteria living within sponges and other invertebrates. This understanding shifted research focus from harvesting macro-organisms to cultivating marine microorganisms, offering a more sustainable and scalable approach to production. Marine-derived compounds have already contributed significantly to modern medicine. Clinically approved drugs such as cytarabine and trabectedin for cancer therapy, vidarabine as an antiviral agent, and ziconotide for chronic pain management demonstrate the therapeutic value of MNPs. Furthermore, numerous compounds exhibiting anticancer, antimicrobial, antiviral, antiinflammatory, and neuroprotective activities are currently undergoing preclinical and clinical evaluation. These successes highlight the high probability of discovering effective drugs from marine sources.

AUTHOR CONTRIBUTIONS

All authors are contributed equally.

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