TPM Vol. 32, No. S6, 2025
ISSN: 1972-6325
https://www.tpmap.org/

MARINE-DERIVED COMPOUNDS: A NEW FRONTIER IN PHARMACEUTICAL RESEARCH

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Abstract
New 'validated' structures with novel methods of action that occupy chemical space relevant to biology may be found most abundantly in the understudied marine realm, which is also predicted to have the highest biodiversity. Effective medication development of these sometimes-complicated chemicals requires addressing a number of issues, including target identification and supply issues, but there are ways to get over these barriers. Technological developments in fields including fermentation, biotechnology, total chemical synthesis, nanoscale NMR for structure elucidation, and sampling techniques are critical to the efficacy of marine natural compounds as therapeutic leads. We demonstrate the high level of innovation in the marine natural goods sector, which we think will lead to the future release of a new generation of pharmaceuticals in stores and on the market.
Keywords: biotechnology, NMR, Several challenges, sampling strategies

1. INTRODUCTION

However, the focus shifted from the "natural drugstore" to completely synthetic pharmaceuticals because to the scientific renaissance and improved understanding of the pathology of many diseases, which made it possible to synthesize and develop pharmacological molecules against specific molecular targets. When high-throughput screening techniques were developed, this emphasis shifted to synthetic molecules. Although combinatorial chemistry was more attractive for drug discovery because it met this particular obligation before natural products, the 'faster' drug-discovery methods that aren't applicable to our chiral universe resulted in a 20-year decrease in the number of novel chemical entities in 2001. This was due to the need for a larger and faster compound library supply in order to have the ability to investigate a large number of chemical entities in a particular experiment at the same time [1].

Molecules with intricate structures and unique spatial configurations are frequently found in natural goods[6]. Since these chemical molecules were designed to interact with their biological targets in an efficient way and occupy a chemical space that is important to biology, they are confirmed starting points for medication development[4]. It is therefore not unexpected that 40% of the chemical scaffolds included in the Dictionary of Natural Products inhabit previously unheard-of chemical space that was previously empty of synthesized compounds[2]. Additionally, natural commodities were able to command a substantial market share and a clear popular preference due to their ingenuity.Natural products are connected to half of the top 20 nonprotein

medications, and half of all newly created medications during the reporting period are based on or derived from the structures of natural products[10].

Nowadays, almost all medications made from natural products have their origins on land. However, new sources, like those found in the ocean, will open the door for biological and chemical innovations as well[11]. Marine natural goods are more chemically innovative than terrestrial natural products, according to a head-to-head study by Kong and colleagues [3].A study comparing molecular scaffolds from the Dictionary of Natural Products with the Dictionary of Marine Natural Products found that over 71% of the molecular scaffolds in the Dictionary of Marine Natural Products were found only in marine creatures[12]. Additionally, the fraction of significant bioactivity in marine organisms is higher than that of terrestrial creatures[8]. For instance, in a National Cancer Institute preclinical cytotoxicity screen, approximately 1% of tested marine samples exhibited anti-tumor activity, but only 0.1% of studied terrestrial samples did the same. Additionally, the first marine drugs are currently on the market, and numerous others are in various stages of clinical research[9].

2. REVIEW OF LITERATURE

The renaissance of natural product-stimulated medicine development is being linked with the search for new natural supplies and animals, such as the marine environment, which makes up 70% of the earth's surface and is the largest undiscovered rich resource. A ten-year inventory from the first Census of Marine Life (2000–2010) has only recently shown an incredible amount of biodiversity[14]. With a focus on waters nearer the shore in the countries under study and so expected to have strong documentation, the study raised the estimate of known marine species from roughly 230,000 to almost 250,000. They also extrapolated their results to at least a million marine species and tens or even hundreds of millions of microbiological species (Census of Marine Life, www.coml.org)[16]. Venter has also emphasized the vast biodiversity of the marine microbial universe. The first ocean exploration genome project sampling mission (Global Ocean Sampling Expedition, 2003) increased the quantity of protein sequences in the NIH's GenBank and discovered 1.2 million new genes[15].

According to a recent study by Wolfe-Simon and colleagues, a bacterium from Mono Lake was able to adapt to its arsenic-rich environment, causing arsenate to replace phosphate in its macromolecules[18]. If true, this observation highlights the amazing capacity of microorganisms to adapt to their surroundings and trigger new metabolic reactions, despite the fact that the research is subject to harsh criticism.A similar idea might apply to the marine environment, where novel techniques and biochemical processes are induced by stress growth conditions. Bio-active secondary metabolites found in abundance in the marine environment may be able to treat a variety of illnesses [5].

In addition to their unique chemical composition, a few of those compounds have unique modes of action. There are good examples of this in the newly developed marine drugs. Ziconotide has incredibly potent analgesic effects through an entirely new mode of action. N-type voltage-sensitive calcium channels are reversibly blocked, and a subset of neurons, including primary pain-sensing nociceptors, have their firing activity inhibited. Ziconotide is the first N-type calcium-channel blocker and the first peptide generated from marine sources to be marketed as a drug. By interacting with the DNA minor groove to produce DNA damage and selectively affecting the transcription-coupled nucleotide repair mechanism, it preferentially induces apoptosis in cancer cells that express a lot more genes than normal cells.Similarly, unlike existing antimitotic medications, the recently licensed anticancer marine medication selectively inhibits microtubule elongation and sequesters tubulin through a novel microtubule-targeting method.This category includes just two cytotoxic chemicals from our group. As a result, advancements in target identification, structural determination, and sampling methodologies are crucial turning points in marine drugdiscovery.

3. MATERIALS AND METHOD

The ocean requires more sophisticated sampling methods and equipment, which may have been one of the main reasons it was not investigated for a very long period. From readily accessible marine samples collected close to shore, several compounds were identified; however, other remote oceanic regions may have unknown macro- and microorganisms and, as a result, new treatments. After soil-dwelling bacteria were known to produce antibiotics, Finical and associates set out to find potentially significant antibiotics in the deep-sea marine sediments, which are unreachable. By creating a system that uses comparatively small boats to gather samples from the sea floor at depths of more than 2000 meters, they were able to get around the access problem. The highly active proteasome inhibitor was therefore created by phylogenetically unique marine actinomycete strains, one of which is a prolific generator of bioactive secondary metabolites. NMR spectroscopy was still essential for elucidating structures, but it was still limited by its low sensitivity in comparison to other techniques, such as mass

spectrometry[13]. Recently, Molinski compiled those developments and gave a clear illustration of the significant influence of microscale methods on his group's more fruitful chemical analysis of rare marine specimens.

In an effort to find drug candidates that impact biological processes, phenotypic screening has drawn interest from both academia and industry. This type of mechanistic understanding is necessary to predict probable side effects and prevent expensive trial failures, but even if a hit molecule has been identified in one of those screens, figuring out its cellular target and mode of action remains a hurdle to its development into a drug. It provides biomarkers for clinical and preclinical trials and is also utilized for lead optimization. This step was made feasible by several important developments in drug target-identification techniques, which in turn increased the opportunities for drug development and discovery. There are two categories of target-identification techniques that use a phenotypic screen: direct techniques like protein microarrays, expression cloning, and affinity chromatography, and indirect techniques like global profiling techniques based on genomes, proteomics, or metabolomics.

One of the older methods for identifying targets is affinity chromatography. However, there are a few more changes that aim to address the shortcomings of this approach, which usually entails adding a label. One of the more sophisticated label-free techniques, known as "drug affinity responsive target stability," relies on the target protein's enhanced resistance to proteolysis by attaching to its substrate or bioactive chemical. The breakdown of nontarget proteins would be followed by target protein enrichment and detection. The fact that the molecular target of didemnid B, for instance, was initially identified using affinity purification techniques and subsequently validated by drug affinity responsive target stability further demonstrated the value of this innovative methodology. They found that the onellamides in fission yeast directly target ergosterol, the main sterol in fungal cell membranes, by using chemical-genomic profiling in fission yeast and fluorescence tagging to identify the compound's subcellular position. The sterol binding activity of the onellamides, however, is distinct from that of every other sterol binder that is now known, indicating that those marine secondary metabolites are members of a new and unidentified family of sterol-binding compounds. Apratoxin A competitively blocks the secretory route of many cancer-related receptors by inhibiting translational translocation, which has not yet been studied for anticancer drug development. Ultimately, the creation of therapeutic targets raises the possibility that a promising chemical obtained from marine sources may be investigated further. [7].

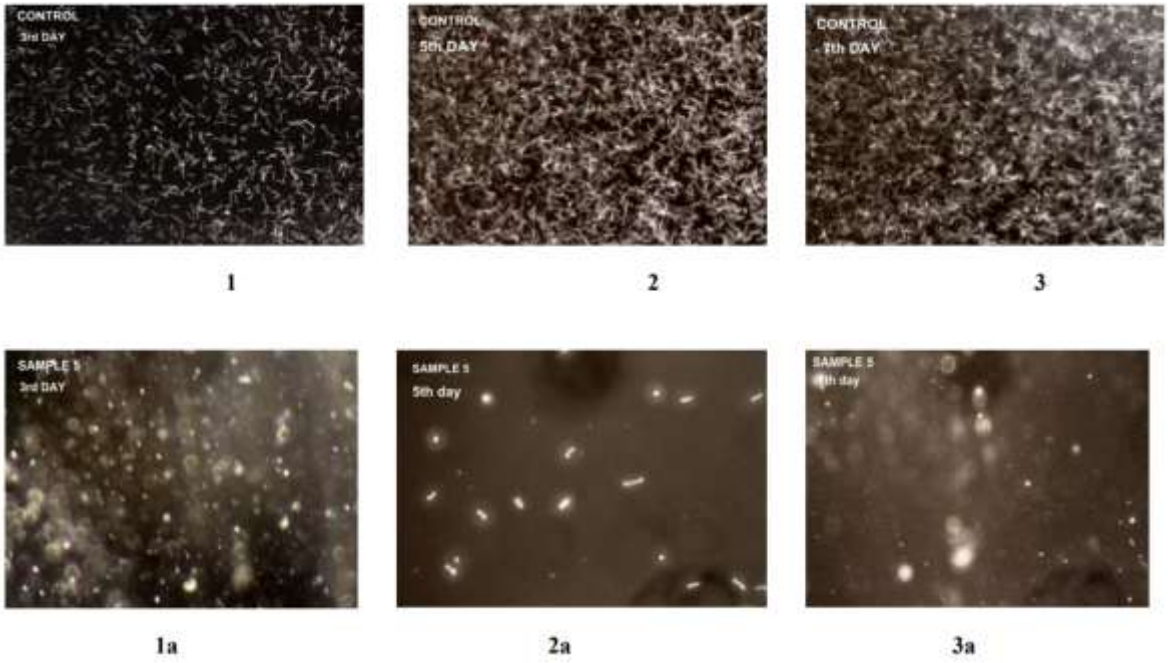

Figure 1: Salinem response

One of the largest obstacles in the medication discovery process for marine natural products is the supply problem. However, some excellent answers to this significant issue have just been made available, and the rapid advancements in several technologies provide more supply alleviation. These include advancements in biotechnology, fermentation, and synthetic chemistry. Despite the normal structural complexity of marine natural products, their overall chemical synthesis has made remarkable strides, which are typically publicized as soon as they are discovered. Two important advantages result from the successful development of a practical process for the full chemical synthesis of a bioactive compound.

4. RESULT AND DISCUSSION

The microbial gene clusters for bioactive secondary metabolites, which are active in their natural competitive context, can go dormant in non-competitive laboratory settings, according to genomic study. Mixed fermentation is a superior way to learn about the metabolic capability of cultivable bacteria. Watanabe's group also looked at the synergistic production of pyocyanin, a blue pigment, in mixed marine microbial cultures that did not produce any discernible metabolites in pure cultures. Moreover, mixed fermentation will increase the production of secondary metabolites that were previously undiscovered due to their levels below the detection limit. Biotechnology is transforming the marine natural products industry. By identifying the true producer of a secondary metabolite within a symbiotic relationship, researchers can prioritize organisms for drug discovery and better explore the ocean's microbial richness thanks to developments in molecular biology and analytical technologies. Furthermore, the developments coincide with the identification of many biosynthetic gene clusters and pathways, eventually enabling their manipulation [17].

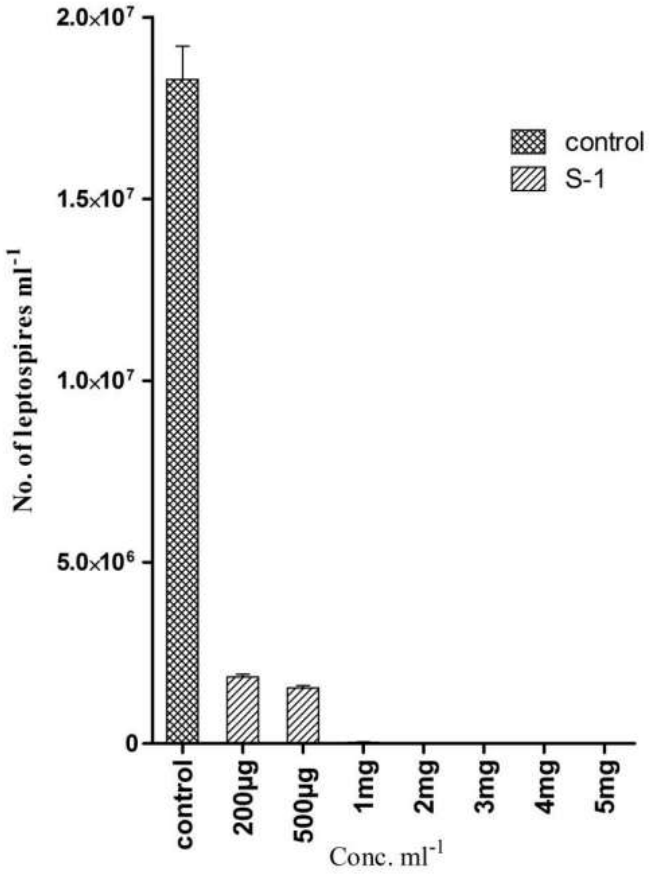

Figure 2: Minimum inhibitory concentration

Novel techniques to medication development and optimization include in vitro multienzyme synthesis and biosynthetic genetic engineering. Additionally, microbial chemical factories are increasingly being investigated for the simple and effective manufacture of laboriously fully synthesized lead compounds. Genomic sequencing is becoming increasingly affordable. Whole-genome sequencing directs the identification of gene clusters for previously discovered chemicals, demonstrating the synthesis capacity of an organism. It also directs genome mining, a novel drug-discovery method that forecasts the potential chemical structures of as-yet-undiscovered natural molecules.Again, genome sequencing serves as a roadmap for the creation of new methods and approaches for the benefit of natural product medication discovery. Natural Product Searcher, a web-based application created lately by Sherman and associates, provides a quick way to look for possible natural product biosynthetic clusters in a microbial genome sequence.

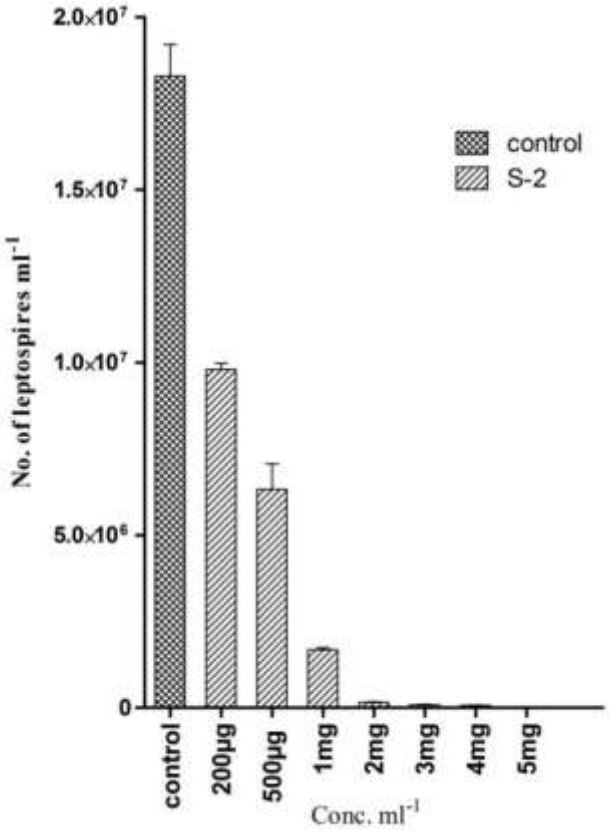

Figure 3: Minimum inhibitory concentration of S2

The scan outputs are structural assembly predictions represented by PKS, NRPS, or hybrid NRPS/PKS clusters, and secondary metabolic structures are generated in a text format compatible with standard chemistry software programs. The promising potential for genome mining-based natural product discovery was further illustrated by comparable results from an in-silico analysis of PKS gene clusters by Mohanty et al.

5. CONCLUSION

The vast majority of medications are modelled using scaffolding made of terrestrial natural resources. On the other hand, when high-throughput screening technology was introduced, natural compounds were disregarded for drug development. Effective medication development of these frequently complex structures requires overcoming certain obstacles, such as the supply and target identification issues. Since the first marine natural products have reached the pharmaceutical market and a number of potential candidates are already in advanced study, the answer is in the yes. Could the oceans provide a sufficient supply of marine drugs? Technological developments in fields including genetic engineering, total chemical synthesis, biosynthesis, nanoscale NMR for structural elucidation, and sampling techniques are critical to the efficacy of marine natural materials as therapeutic leads. It will be common practice to predict drug and biosynthetic possibilities using whole-genome sequencing. We think that successful marine drug discovery and development will be made possible by the enormous amount of innovation in marine natural products. It also serves as the basis for our conviction that a new class of pharmaceuticals made from marine natural ingredients will eventually overtake the market and pharmacies.

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