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Research review paper

Bio-mining the microbial treasures of the ocean: New natural products

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ABSTRACT

The biological resources of the oceans have been exploited since ancient human history, mainly by catching fish and harvesting algae. Research on natural products with special emphasis on marine animals and also algae during the last decades of the 20th century has revealed the importance of marine organisms as producers of substances useful for the treatment of human diseases. Though a large number of bioactive substances have been identified, some many years ago, only recently the first drugs from the oceans were approved. Quite astonishingly, the immense diversity of microbes in the marine environments and their almost untouched capacity to produce natural products and therefore the importance of microbes for marine biotechnology was realized on a broad basis by the scientific communities only recently. This has strengthened worldwide research activities dealing with the exploration of marine microorganisms for biotechnological applications, which comprise the production of bioactive compounds for pharmaceutical use, as well as the development of other valuable products, such as enzymes, nutraceuticals and cosmetics. While the focus in these fields was mainly on marine bacteria, also marine fungi now receive growing attention. Although culture-dependent studies continue to provide interesting new chemical structures with biological activities at a high rate and represent highly promising approaches for the search of new drugs, exploration and use of genomic and metagenomic resources are considered to further increase this potential. Many efforts are made for the sustainable exploration of marine microbial resources. Large culture collections specifically of marine bacteria and marine fungi are available. Compound libraries of marine natural products, even of highly purified substances, were established. The expectations into the commercial exploitation of marine microbial resources has given rise to numerous institutions worldwide, basic research facilities as well as companies. In Europe, recent activities have initiated a dynamic development in marine biotechnology, though concentrated efforts on marine natural product research are rare. One of these activities is represented by the Kieler Wirkstoff-Zentrum KiWiZ, which was founded in 2005 in Kiel (Germany).

Contents

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1. Introduction

In 1967, a small symposium was held in Rhode Island, USA, with the ambitious title "Drugs from the Sea". The catchphrase of the symposium title has endured over the decades as a metaphor for drug development from marine natural products, though the first genuine drug from the sea was a long time coming (Molinski et al., 2009). The need for novel substances for the treatment of severe human diseases such as cancer, microbial infections and inflammatory processes, combined with the recognition that marine organisms provide a rich potential source of such substances support the intensive search for new substances from marine organisms. In the past, often algae and marine invertebrates have been investigated. However, modern marine biotechnology has moved its focus to microbes and encompasses the discovery of new pharmaceuticals from marine microbes (Molinski et al., 2009; Mayer et al., 2010). In particular bacteria and fungi associated with marine macroorganisms such as sponges, corals and algae are potent producers of biological active substances with prominent activities not only against pathogenic bacteria, fungi, and viruses but also against tumor cells. The remarkably high hit rates of marine compounds in screening for drug leads makes the search in marine organisms quite attractive. Natural products in general play an important role in the development of drugs. 63% of new drugs were classified as naturally derived (unmodified natural product, modified natural product, or synthetic compound with a natural product as pharmacophore). Covering the period from January 1981 to the middle of October 2008 68% of anti-infectives (antibacterial, antifungal, antiparasitic, and antiviral) and 63% of drugs used in cancer treatment, respectively, were naturally derived (Cragg et al., 2009).

The research on biological active substances and their production has two major aspects. On the one hand the ecological role in microbe–microbe and microbe–host interactions and on the other hand their potential application in the treatment of diseases and other applications. In addition to the use as pharmaceuticals, marine microbes and their products are applied in materials technology, bioremediation and as marine biomedical model organisms. In this review, we discuss the potential and application of marine microbes in the production of natural products and in marine biotechnology.

2. Milestones in research on marine natural products

Over the late decades of the last century, studies on marine natural products largely involved the collection of organisms from the sea, their extraction and the analysis of these extracts. Numerous new compounds have been isolated and many were found with interesting biological activities, most of which were described from sponges, corals and other marine invertebrates. However, the application of many promising substances was hampered by disappointing difficulties regarding reproduction and scale up. In addition, problems to supply sufficient amounts of the pure substances limited further progress in many cases. Recovery rates of less than 1 g of substances such as halichondrin, ecteinascidin or bryostatin obtained from a ton of sponges, ascidia or bryozoa, respectively, as well as widely unsolved problems with the mariculture of most marine macroorganisms made it extremely difficult to produce substances in amounts sufficient for further studies (for review see Molinski et al., 2009 and Mayer et al., 2010). Alternative production processes solved these problems for several substances (Battershill et al. 1998, Duckworth et al., 2004). Therefore, only few marine natural products entered preclinical or clinical trials, although a large number has been described from marine biota and many have reached advanced states of applied research studies. The current pipeline of marine natural products was reviewed recently by (Mayer et al., 2010). In the following we will highlight success and problems of the development of some outstanding marine natural products.

The first discovery of a biologically active marine natural product was reported in the late 1950s by Bergmann (Bergmann and Feeney, 1951; Bergmann and Burke, 1956; Bergmann and Stempien, 1957). The discovery of unusual arabino and ribo-pentosyl nucleosides in marine sponges was the first demonstration that naturally occurring nucleosides could be found containing sugars other than ribose and deoxyribose. Chemical synthesis allowed the development of the derivatives ara-A (vidarabine) (Fig. 1) and ara-C (cytarabine) (Fig. 1), two nucleosides with significant antiviral and anticancer properties, respectively. Both have been in clinical use for decades now (Zhang et al., 2005).

After more than two decades of research and development, ziconotide, a synthetic form of ω-conotoxin MVIIA (Fig. 1), became the first marine-derived drug approved by the US Food and Drug Administration (Molinski et al., 2009).This powerful pain killer was isolated originally from a cocktail of peptides from the cone snail *Conus magus*. Due to the successful development of methods for chemical synthesis of this substance a rather timely performance of drug development including clinical trials was possible. Today this substance is one of the first "marine drugs" in clinical application for the treatment of chronic pain in spinal cord injury (approved in the United States in 2004) known under the trade name Prialt® (Terlau and Olivera, 2004).

Among those substances that have succeeded, pseudopterosin from the Caribbean horn coral *Pseudopterogorgia elisabethae* still is recovered from corals grown in mariculture in the sea off the Bahamas (Look et al., 1986). Pseudopterosin has potential activity against psoriasis and neurodermatitis, anti-inflammatory aspects and also against pain and rheumatic disease. The substance is in clinical trial phase II. However, the compound already has found its way to the marketplace. It is used as an additive preventing irritation caused by exposure to the sun or chemicals in a cosmetic skin care product (Rouhi, 1995).

As some of the most potent antitumor substances, the bryostatins were first isolated from the bryozoan *Bugula neritina* and already studied in the early 1980s (Pettit et al., 1982). However, all attempts