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Marine microorganisms as a promising and sustainable source of bioactive molecules

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A B S T R A C T

There is an urgent need to discover new drug entities due to the increased incidence of severe diseases as cancer and neurodegenerative pathologies, and reducing efficacy of existing antibiotics. Recently, there is a renewed interest in exploring the marine habitat for new pharmaceuticals also thanks to the advancement in cultivation technologies and in molecular biology techniques. Microorganisms represent a still poorly explored resource for drug discovery. The possibility of obtaining a continuous source of bioactives from marine microorganisms, more amenable to culturing compared to macro-organisms, may be able to meet the challenging demands of pharmaceutical industries. This would enable a more environmentally-friendly approach to drug discovery and overcome the over-utilization of marine resources and the use of destructive collection practices. The importance of the topic is underlined by the number of EU projects funded aimed at improving the exploitation of marine organisms for drug discovery.

1. Introduction

Oceans cover nearly 70% of the earth surface and host a huge ecological, chemical and biological diversity (Argulis and Schwartz, 1982; Pomponi, 1999; Jimeno et al., 2004; Kijjoa and Swangwong, 2004). The first living organisms appeared in the sea more than 3500 million years ago (Macdougall, 1996; Argulis and Schwartz, 1982) and evolutionary processes have equipped many marine organisms with the appropriate mechanisms to survive in a hostile milieu in terms of extreme temperatures, changes in salinity and pressure, and attack by bacteria and viral pathogens (Jimeno et al., 2004). The harsh chemical and physical conditions of the sea have also favored the production of a great variety of novel molecules in marine organisms that are unique in terms of diversity, and structural and functional features with respect to compounds isolated from terrestrial plants (Kathiresan et al., 2008) and represent a reservoir of new bioactive compounds with a great pharmaceutical potential (Reen et al., 2015). Nevertheless, the marine habitat is still poorly explored. It is estimated that, in spite of 250 years of taxonomic classification and over 1.2 million species already catalogued in a central database, some 91% of species in the ocean still await description (Mora et al., 2011). The microbiota appears to be a promising and endless source for new drug development (Gerwick and Fenner, 2013) with new chemotherapeutants, especially novel antibiotics to combat diseases and drug-resistant pathogens that are becoming a significant threat to public health (Xiong et al., 2012). Currently, 16 of 20 marine antitumor compounds in clinical trials are derived from microbial sources and many more are expected to enter in the drug discovery pipeline (Xiong et al., 2013). For this reason there is a renewed interest in exploring the marine environment, especially as concerns the microorganisms that live in the oceans, with the aim of identifying novel chemical entities as sources for new lead compounds.

In this review we give a general overview on drug discovery in recent years, focusing in particular on microorganisms, including sponge-associated bacteria and marine photoautotrophs such as microalgae and cyanobacteria. We also present some of the innovative approaches being developed in this field, such as new cultivation methods and molecular biology tools that may help in disclosing the huge potential of marine microorganisms.

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Innovation in the field is going hand in hand with the funding of several FP7 and H2020 projects projects (e.g. MaCuMBA, www.macumbaproject.eu; PharmaSea, www.pharma-sea.eu; MicroB3, www.microb3.eu; Bluegenics, http://www.bluegenics.eu/) under the topic "Blue growth", with the ambition to overcome major bottlenecks that have slowed down the marine biotechnology pipeline in the past. A common final goal of all of these projects is to achieve a more environmentally-friendly approach to drug discovery to overcome negative impacts on the environment linked to the over-utilization of marine resources and the use of destructive collection practices.

2. Progress in marine natural product discovery: an historical overview

The medicinal use of natural products goes back thousands of years (Chast, 2008). The earliest records referring to the utilization of natural resources as medicines can be traced back to the ancient Egyptians but there are also archaeological findings revealing that even older cultures found herbs and plants useful for the treatment of diseases and discomforts (Halberstein, 2005). Also in ancient Greece as well as in Asia and South America, herbal remedies were important in the past. In some cultures as for example in China, traditional medicine is still widely employed even today (Cheung, 2011).

Availability and accessibility has made terrestrial plants the preferred choice and the main source in traditional medicine. Macroalgae are one of the few marine organisms that have been used in traditional medicine as many are easily collectable (Dias et al., 2012). Ancient maritime people, notably the Chinese and Japanese, ate a variety of ionidine-rich seaweeds that undoubtedly accounted for their low incidence of goiter (Thakur et al., 2005). Chinese Pharmacopoeia recommends recipes for a number of disorders such as pain, menstrual difficulties, abscesses and cancer (Ruggieri, 1976). Coral reef products have also been traditionally used for treating various disorders in Taiwan, Japan, China and India. Historical records show that human beings have been aware of the venomous nature of some sea creatures for at least 4000 years (Colwell, 2002). Is has been known for centuries that sponges contain bioactive compounds that are of potential medical importance. Richter in 1907 outlined that the active component of the roasted bath sponge, used already by Roger cosmetics against struma, is rich in iodine (Thakur et al., 2005). In the 19th and early 20th centuries, cod liver oil was used as a nutritional supplement. However, only in the middle part of the 20th century did scientists begin to systematically probe the oceans for medicines. In the early 1950s, Ross Nigreli of the Osborn Laboratories of the New York aquarium extracted a toxin from cuvierian organs of the Bahamian sea cucumber, *Actynopyga agassizi*. This toxin was named "Holothurin", and showed some antitumor activity in mice (Nigreli et al., 1967). Although "Holothurin" was never commercialized, the search for drugs from the sea has continued ever since. Before 1985, the number of new natural products discovered annually was less than 100; in 1987 there was a marked increase in the number of marine natural products reported annually to over 300 (Blunt et al., 2007). The number of new products per year remained at a constant level of about 500 in the late 1990s. During the period 1996–2005 there was, however, a stasis in the number of new compounds reported (Blunt et al., 2007; Hu et al., 2015). This was mainly due to the fact that many of the larger pharmaceutical companies had decommissioned their natural product programs during the 1990s and early 2000s since traditional extract-based screening methods resulted in the continuous re-discovery of previously isolated compounds (Dias et al., 2012). Moreover, there were problems related to supply and the long time required to develop a natural product from an extract to hit. The advent of automated high throughput screening (HTS) technologies relying on combinatorial chemistry to generate large compound libraries was thought to be the future source of numerous novel carbon skeletons and drug leads or new chemical entities. Classical natural product chemistry was thus largely replaced by molecular target based drug discovery using large compound libraries to obtain efficient "hits" During the late 1990s synthetic chemists realized that these libraries lacked the complexity of the intricate natural products synthesized by nature (Newman, 2008) and focused their efforts on the synthesis of compounds resembling natural products (mimics) or that were based on natural product topologies. However, of the 1184 new compounds approved between the years 1981–2006 as drugs for the treatment of human diseases, only 30% were synthetic.

With improvements in diving techniques and remotely operated vehicles, the oceans were within reach and the number of marine natural products identified has virtually soared, now exceeding 28,175 chemical entities (Jaspars et al., 2016), with hundreds of new compounds still being discovered every year (Blunt et al., 2015, 2016; Hu et al., 2015) (Fig. 1). The diversity of secondary metabolites produced by marine organisms has been highlighted in several reviews (Munro et al., 1999; Faulkner, 2000; Proksch et al., 2002; Haefner, 2003; Jimeno et al., 2004; Jha and Zirong, 2004; Molinski et al., 2009; Kong et al., 2010; Montaser and Luesch, 2011; Blunt et al., 2013; Mehbub et al., 2014). They range from derivatives of amino acids and nucleosides to macrolides, porphyrins, terpenoids to aliphatic cyclic peroxides and sterols. There is strong evidence on the role of these metabolites in chemical defence against predators (Schupp et al., 1999; Pisut and Pawlik, 2002) and epibionts (Wahl et al., 1994; Thakur and Anil, 2000; Thakur, 2001; Thakur et al., 2003). In fact, studies on marine natural products include different aspects: i) diversity of chemical compounds produced by different organisms; ii) their potential function in nature; iii) strategies for their use for human benefit (Müller et al., 2003).

3. Success stories: marine-derived drugs approved for human therapy

With the combined efforts of marine natural products chemists and pharmacologists, a number of molecules are already on the market, or in clinical and pre-clinical trials. These products have been obtained from invertebrates such as sponges (Thakur and

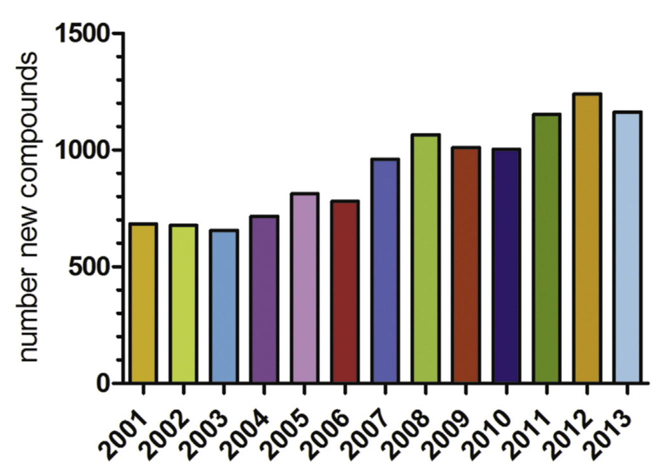

Fig. 1. Number of new compounds isolated from marine organisms in the years 2001–2013.