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Review

Pharmaceutically active secondary metabolites of marine actinobacteria☆

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ABSTRACT

Marine actinobacteria are one of the most efficient groups of secondary metabolite producers and are very important from an industrial point of view. Many representatives of the order *Actinomycetales* are prolific producers of thousands of biologically active secondary metabolites. Actinobacteria from terrestrial sources have been studied and screened since the 1950s, for many important antibiotics, anticancer, antitumor and immunosuppressive agents. However, frequent rediscovery of the same compounds from the terrestrial actinobacteria has made them less attractive for screening programs in the recent years. At the same time, actinobacteria isolated from the marine environment have currently received considerable attention due to the structural diversity and unique biological activities of their secondary metabolites. They are efficient producers of new secondary metabolites that show a range of biological activities including antibacterial, antifungal, anticancer, antitumor, cytotoxic, cytostatic, anti-inflammatory, anti-parasitic, anti-malaria, antiviral, antioxidant, anti-angiogenesis, *etc*. In this review, an evaluation is made on the current status of research on marine actinobacteria yielding pharmaceutically active secondary metabolites. Bioactive compounds from marine actinobacteria possess distinct chemical structures that may form the basis for synthesis of new drugs that could be used to combat resistant pathogens. With the increasing advancement in science and technology, there would be a greater demand for new bioactive compounds synthesized by actinobacteria from various marine sources in future.

Contents

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1. Introduction

New drugs, especially antibiotics, are urgently needed to counter and reverse the spread of antibiotic resistant pathogens (Payne et al. 2006; Talbot et al. 2006) and to combat life-threatening diseases such as cancer (Olano et al. 2009). Although considerable progress is being made within the fields of chemical synthesis and engineered biosynthesis of antimicrobial compounds, nature still remains the richest and the most versatile source for new antibiotics (Koehn and Carter 2005; Baltz 2006; Peláez 2006).

Actinobacteria, which are the prolific producers of antibiotics and important suppliers to the pharmaceutical industry, can produce a wide variety of secondary metabolites (Baltz 2005). Actinobacteria belonging to the family Actinomycetaceae are well known for their ability to produce secondary metabolites many of which are active against pathogenic microorganisms. Traditionally, these bacteria have been isolated from terrestrial sources, although the first report of mycelium-forming actinobacterium from the marine sediments appeared several decades ago (Weyland 1969). It is only more recently that marine actinobacteria have become recognized as a source of novel antibiotics and anticancer agents with unusual structures and properties (Jensen et al. 2005).

Marine actinobacteria are the best sources of secondary metabolites and the vast majority of these compounds are derived from the single genus *Streptomyces*, whose species are distributed widely in the marine and terrestrial habitats (Pathom-Aree et al. 2006a) and are of commercial interest due to their unique capacity to produce novel metabolites. It was also perceived that *Streptomyces* species will have a cosmopolitan distribution, as they produce abundant spores that are readily dispersed (Antony-Babu et al. 2008) and these filamentous bacteria are well adapted to the marine environment and can break down complex biological polymers (Anderson and Wellington 2001). In fact, the genus *Streptomyces* alone accounts for a remarkable 80% of the actinobacterial natural products reported to date, a biosynthetic capacity that remains without rival in the microbial world (Watve et al. 2001).

Marine actinobacteria are widely distributed in biological sources such as fishes, molluscs, sponges, seaweeds, mangroves, besides seawater and sediments. These organisms are gaining importance not only for their taxonomic and ecological perspectives, but also for their production of novel bioactive compounds like antibiotics, antitumor agents, immunosuppressive agents, enzymes, enzyme inhibitors, pigments (Dharmaraj 2010). In this review we focuses on novel bioactive compounds identified from marine actinobacteria and classified them in terms of their chemical structure, covering the literature to date.

2. Marine actinobacteria as a novel source of bioactive compounds

Marine actinobacteria are the most economically and biotechnologically priceless prokaryotes. Representative genera of actinobacteria include *Streptomyces*, *Actinomyces*, *Arthrobacter*, *Corynebacterium*, *Frankia*, *Micrococcus*, *Micromonospora* and several others. Secondary metabolites produced by the marine actinobacteria possess a wide range of biological activities (Oldfield et al. 1998; Mann 2001; Berdy 2005; Manivasagan et al. 2013). The genus *Streptomyces* alone produces a large number of bioactive molecules. It has an enormous biosynthetic potential that remains unchallenged without a potential competitor among other microbial groups. A large number of *Streptomyces* spp. have been isolated and screened from soil in the past several decades (Watve et al. 2001). Consequently, chances of isolating a novel *Streptomyces* strain from terrestrial habitats have diminished. Above 500 species of *Streptomyces* account for 70–80% of relevant secondary metabolites, which have a wide range of activities such as antibacterial, antifungal, anticancer, antitumor, cytotoxic, cytostatic, anti-inflammatory, anti-parasitic, anti-malaria, antiviral, antioxidant and anti-angiogenesis, *etc*. (Table 1). Small contributions care from other genera, such as *Saccharopolyspora*, *Amycolatopsis*, *Micromonospora* and *Actinoplanes*. An important reason for discovering novel secondary metabolites is to circumvent the problem of resistant pathogens, which are no longer susceptible to the currently used drugs (Lam 2006; Ekwenye and Kazi 2007). The number of deaths due to these clever pathogenic organisms is on the rise. Secondary metabolites from marine actinobacteria may form the basis for the synthesis of novel therapeutic drugs, which may be efficient to combat a range of resistant microbes (Fenical and Jensen 2006).

Existence of cousins of terrestrial actinobacteria has been reported in the relatively untapped marine ecosystem. Immense diversity of this habitat along with its underexploitation is the fundamental reason for attracting researchers toward it for discovering novel metabolite producers. There is an occurrence of distinct rare genera in the marine ecosystem as evidenced by the taxonomic description of the first marine actinobacteria *Rhodococcus marinonascens* (Helmke and Weyland 1984). Actinobacteria comprise about 10% of the bacteria colonizing marine aggregates and can be isolated from marine sediments (Ward and Bora 2006). Many actinobacterial isolates from deep oceans contain non-ribosomal polyketide synthetase (NRPS) and polyketide synthetase (PKS) pathways, the hallmarks of secondary metabolite production (Salomon et al. 2004). Actinobacteria have also been isolated from free swimming as well as sessile marine vertebrates and invertebrates (Ward and Bora 2006). Unusual actinobacteria belonging to *Micrococceae*, *Dermatophilaceae* and *Gordoniaceae*, have been isolated from sponges (Lam 2006). Tetrodotoxin-producing actinobacteria most closely related to *Nocardiopsis dassonvillei* have been isolated from puffer fish ovaries (Wu et al. 2005).

Researchers are finding new genera from marine environments on a regular basis and discovering new metabolite producers never reported earlier. Actinobacteria genera identified by cultural and molecular techniques from different marine ecological niches include *Actinomadura*, *Actinosynnema*, *Amycolatopsis*, *Arthrobacter*, *Blastococcus*, *Brachybacterium*, *Corynebacterium*, *Dietzia*, *Frankia*, *Frigoribacterium*, *Geodermatophilus*, *Gordonia*, *Kitasatospora*, *Micromonospora*, *Micrococcus*, *Microbacterium*, *Mycobacterium*, *Nocardioides*, *Nocardiopsis*, *Nonomurea*, *Psuedonocardia*, *Rhodococcus*, *Saccharopolyspora*, *Salinispora*, *Serinicoccus*, *Solwaraspora*, *Streptomyces*, *Streptosporangium*, *Tsukamurella*, *Turicella*, *Verrucosispora* and *Williamsia* (Ward and Bora 2006). In spite of the improvements being made in the cultural methods for the isolation of rare marine actinobacteria, many of these organisms still remain unculturable and have to be detected by using molecular techniques (Stach et al. 2003; Mincer et al. 2005). Metagenomic methods, therefore will be useful for characterizing microbes that cannot be cultivated and can also be used to isolate their genes (Tringe et al. 2005).