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Review

Marine actinomycetes: An endless source of potentially therapeutic novel secondary metabolites and other bioactive compounds

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ABSTRACT

Actinomycetes provide a potentially limitless source of novel bioactive compound, possessing a wide range of potential therapeutic uses. Around 25,000 microbial secondary metabolites have been recognized; actinomycetes produce some 75%, of them, with fungi yielding 15%, *Bacillus* spp. 6%, and other bacteria producing around 1–3%. Species of *Streptomyces* provide 50–60 percent of the known antibiotics. Over the last seventy or so years, a vast array of microorganisms has been isolated from soils and other readily accessible environments and the screened for antibiotics. Such screening programs have significantly reduced the likelihood that novel antimicrobial compounds, particularly active against drug resistant species, will now be found. Fortunately, unusual marine environments may act as a future source of actinomycetes and other microorganisms capable of producing new secondary metabolite possessing antifungal, antibacterial, anticancer, insecticidal, enzyme inhibitory and other therapeutic properties. The aim of this review is to highlight marine actinomycetes as a novel source of such potentially critical novel antibiotic and bioactive compounds.

Contents

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1. Introduction

Actinomycetes have a long history to be isolated from marine sources (Weyland, 1969), but at a frequency much lower than other environments, such as soils from which, due to drainage-supply, they largely originate (Goodfellow & Haynes, 1984). The ability of the marine actinomycetes to grow on a seawater-based

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medium does not provide *a priori* evidence that these organisms are obligate-marine and adapted to the marine environment, especially since non-marine actinomycetes are frequently salt tolerant (Okazaki and Okami, 1975). A significant understanding of the taxonomy and ecology of marine actinomyctes began to emerge around the mid-1980 s with the description of the first marine true actinomycetes taxon *Rhodococcus. marinonascens* (Helmke & Weyland 1984). Although this organism does not need marine water to grow, a physiological character which is generally linked to Gram-negative marine bacteria (Macleod, 1965), its isolation lead to the recognition that actinomycete are true residents of the marine water. This genera *Rhodococcus*, falls in the category of "un traditional actinomycete" essentially because of unicellular nature; we had to await until the early nineteen nineties for the unequivocal demonstration of the survival of this filamentous, marine water -adapted,actinomycetes populations (Jensen et al., 1991). These organisms are" obtained after marine Bahamian sediments and were the first marine-derived strains to be shown to have a clear requirement of seawater (i.e. sodium) for growth. Mincer et al. (2002) subsequently allocated the isolates to the genus *Salinispora*, which is made up of two species, namely S. *tropica* and S. *Arenicola.* (Maldonado et al., 2005); these are the lone actinomycetes defined to date for whom marine water is an absolute growing requirement.

Actinomycetes are the most widely exploited prokaryotes in biotechnology and, over the last eighty years or so and have providing the source of some two thirds of the presently utilizing bioactive metabolite (Anne Sofie et al., 2022), including anticancer compounds (Cragg et al., 2005). Based on this first-rate track record significant effort continues to be attentive on the separation of new actinomycetes from terrestrial environments. The success of such programmers has led to a situation of "diminishing returns", such that new classes of bioactive are becoming increasingly difficult to isolate (Sigwart et al., 2021). The obvious solution is use novel techniques and media in order to isolate potentially productive actinomycetes and secondly (and in tandem) to search novel environments, including unsearched areas of the sea, for novel organisms which might provide novel antibiotics and other bioactive compounds such as herbicides, insecticides, antiparasitic compounds, and waste-treatment enzymes like cellulase and xylanase (Saadoun and Gharaibeh, 2003). The chemical and biological diversity of organisms present the sea water environment is vast, and potentially provides an astonishing source for the finding of new antibiotics and anticancer drugs (Simmons et al. 2005). Despite this, it is eestimated that only 2% of sea water microorganisms have been use to culture on artificial medium (Bernan et al, 2004), let alone screened for their biotechnological potential (Fenical et al, 2002). Although Saudi Arabia has an extensive shoreline and lot of seawater resources are available in both the Red Sea and Arabian Gulf and on their littoral habitats these marine microbial resources are still largely unexploited in relation to secondary metabolites of medical potential. Saudi sea water environments therefore signify a vast reservoir of novel actinomycete taxa and therefore a prime source of latent, new bioactive secondary metabolites. The aim of this article is to summarize and review the available updated literature on the isolation of such novel marine actinomycetes in connection to their potential as sources of novel secondary metabolites.

Actinomycetes in the marine environment Only 7–8% of the entire sea is represented by surface water, the remainder being profound sea, 60% of which is represented by water depths of more than 2500 m (Das et al, 2006; Bull et al., 2000). The deep sea environment is exceptional being categorized by low temperature, high pressure, nonexistence of light, and varying saltiness and oxygen content. Despite the huge geographical extent of deep water, scientific information and studies on microbial diversity in the environment remain restricted (Das et al., 2006), although studies show it is a source of antibiotic-producing microbes (Bull et al., 2000; Goodfellow and Williams, 1983) and Actinomycetes indigenous to the oceans have been demonstrated by culture independent methods (Ward & Bora, 2006). Such isolates contain species of *Salinispora* (Mincer et al., 2005) and *Marinispora* (Jensen et al., 1991), *Dietzia, Rhodococcus* (Heald et al., 2001), *Streptomyces* (Moran et al., 1995), and *Aeromicrobium marinum,* all of which have obligatory salt requirements (Bruns et al., 2003). Some of these isolates have been shown compounds like the salinosporamides, which are nowadays being showing promise in scientific trials as effective anti-cancer medicines (Feling et al, 2003).

1.1. Impact of actinomycetes on the marine environment

Actinomycetes are crucial to the functioning of the seawater environmental conditions (Das et al, 2006), playing critical roles in the decomposition and turnover of a extensive range of materials (Jensen et al., 2005; Lam, 2006;), with changes in specific enzyme-producing microbe reflecting the concentration of usual and natural substances and environmental conditions (Myronovskyi et al., 2020). Cellulolytic and chitinolytic activity in marine actinomycetes has been described by Chandramohan et al. (1972) and Pisano et al. 1992) respectively, and several scientifically relevant enzyme producing actinomycetes; actinobacteria have also been linked to the breakdown and recycling of a widespread variety of organic molecules (Weyland, 1969).

1.2. Actinomycetes as sources of novel antibiotics

Actinobacteria are a valued source of new biologically active chemicals (Adinarayana et al, 2006; Meanwhile the finding of streptomycin, a huge number of antibiotics has been obtained from different species of both terrestrial & marine *Streptomyces* and *Streptoverticillium*, as well as severals therapeutic molecules such as aminoglycosides, tetracyclines, chloramphenicol, & macrolides, as well as the recently discovered b lactam cephamycin group. Antibiotics derived from terrestrial sources, marine-derived antibiotics are often unique (Chen et al., 2021). Species of, *Streptosporangium, Microbispora, Micromonospora, Amycolatopsis,* Kibdelosporangium *Dactylosporangium, Planobispora, and Planomonospora, Actinomadura, Actinoplanes,* are among the least utilized genera of uncommon Actinobacteria that have been the focus of industrial screening (Lazzarini et al., 2000).

Actinomycetes are the exclusive producers of the following antibiotic classes: oligomycin-type large-membered macrolides, nigericin-type polyether antibiotics, nonactin type cyclopolylactones, anthracyclines, daunomycin type anthracyclines, aminoglycosides, streptothricins, actinomycins, and quinoxaline-peptides Polyene macrolides, (Kavitha and Vimala, 2020; Pereira et al., 2020). Some actinomycete strains produce a wide spectrum of antibiotics, while some produce individual antibiotics (Barka et al., 2016).

Since 2000, some thirty new antibiotics have been introduced, two being natural products (NP), twelve NP-derived compounds and sixteen synthetic antibiotics (Raissa et al., 2020). Twelve novel antibiotics from actinomycetes have been discovered as natural products or natural product-derivatives covering seven diverse antibiotic families (Table 1).

1.3. Antibiotics found in rare marine actinomycetes

Some one hundred novel bioactive chemicals have been discovered in thirty-eight rare actinomycete strains, all derived from fifteen species, namely: Salinispora (21 novel compounds), Nocardiopsis (13 novel compounds), Verrucosispora (19 nevel

Table 1
Marine actinomycetes produce secondary metabolites.

Marine source	Compounds	Biological activity
Actinoalloteichus cyanogriseus	Cyanogrisides E–H	Cytotoxicity
Actinomadura sp.	Forazoline A	Anti-candida activity
Amycolatopsis sp.	Amycolactam	Cytotoxicity
Actinomycetospora chlora	Thiasporines A–C	Cytotoxicity
Amycolatopsis mediterranei U-32	Rifamycin	Antibacterial
Amycolatopsis sp.	Amythiamicins	Antibacterial
Actinomadura pelletieri	MM461156	Antiviral, antibacterial
Actinomadura verrucosospora	Verucopeptin	Antitumor
Actinomadura carminata	Carminomycin	Antitumor
Actinomadura rubra	Maduramycins	Antibacterial
Actinoplanes coloradoensis sp. nov.	Coloradocin	Antibacterial
Actinomadura sp.	ZHD-0501	Anticancer
Chiana rubra	Napyradiomycins	Antibacterial
Marinispora	Marinomycins	Anticancer, antibacterial
Micromonospora sp.	Levantilide C	Antiproliferative activity
Micromonospora sp.	Quinoline alkaloid	Antibacterial activity
Micromonospora matsumotoense	Paulomycin G	Strong cytotoxic activity
Micromonospora harpali	Tetrocarcin P	Antibacterial activity
Nocardiopsis sp.	Nocazines F and G	Excellent cytotoxicity
Nocardiopsis sp.	Nocardiamide A and B	Antimicrobial activity
Nocardia sp. SANK 64282	Spirocardins A and B	Antibacterial
Nocardiopsis alba	Isomethoxyneihumicin	Strong cytotoxicity
Pseudonocardia carboxydivorans	Branimycins B and C	Antibacterial activities
Salinispora tropica	Salinosporamide A	Anticancer; antimalarial
Streptomyces sp. CNQ-085	Daryamides	Anticancer, antifungal
Streptomyces sp.	Cyclomarin A	Anti-inflammatory, Antiviral
Streptomyces sp.	Piperazimycins	Anticancer
Streptomyces sp.	Staurosporinone	Antitumor; phycotoxicity
Streptomyces corchorusii AUBN (1)/7	Resistomycin	Antiviral
Streptomyces sp.	Streptokordin	Antitumor
Verrucosispora sp.	Proximicins	Antibacterial; anticancer

compounds), Marinispora (12 new compounds), Actinoalloteichus (11 new compounds), and Micromonospora (10 new compounds) (Subramani et al., 2013; Wang et al., 2021). Four new antibiotics from the sea water actinomycetes are now in scientific trials (Table 1), three of which remained derived from *Salinispora* species making the point that *Streptomyces* species currently are not usual and important biological source of novel antibiotics.

1.4. Anticancer molecules and drugs from marine actinomycetes

Cancer is a term that encompasses more than one hundred diverse diseases that emerge when physiology has been disrupted, allowing for uncontrolled cell-proliferation (Capon et al., 2000). It is now the major leading cause of mortality in the industrialized world, impacting one out of every three people and accounting for one out of every five fatalities worldwide (Capon et al., 2000). Anticancer agents have been derived from a variety of marine Actinobacteria which produce cell toxins, some of which have been found to have a variety of harmful chemicals some of which exhibit potent anticancer activity (Jeong et al., 2006).

1.5. Marine actinomycetes produce novel metabolites

Despite the fact that near about 40,000 diseases have been clinically identified, very few can be treated symptomatically, and even fewer can be cured (Jagannathan et al., 2021). New therapeutic agents are clearly urgently required (Wright and Sutherland, 2007), a need which is likely to be met by developing the plethora of available natural products (Cheng et al., 2021). Although the use of seawater actinomycetes as a basis of different secondary metabolites is still in its early stages, various novel compounds have recently been discovered (Lam, 2006). From 2005 to 2020, an array of potentially useful, novel secondary metabolites were identified from marine actinomycetes (Table 1);while not a complete list it does demonstrate the wide range of compounds discovered having an equally diverse range of biotechnological applications; compounds such as Spirocardins A and B, Salinosporamide A, Streptokordin, Staurosporinone, Tetrocarcin P and Carminomycin being of special interest.

2. Conclusions

Secondary metabolites derived from marine actinomycetes contain unique chemical Structures that are available for the development of novel medications. Marine Microorganisms are deal candidates as sources of novel secondary metabolites. Despite this, the use of seawater actinomycetes as a source of new secondary metabolites is still in its early stages, but even the current limited screening efforts have shown that the rate of discovery of novel secondary metabolites from marine actinomycetes surpasses that of their terrestrial counterparts. Our ability to isolate novel antibiotics from marine sources is clearly therefore crucial to our war against antibiotic resistant bacteria.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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