

Actinobacteria from Algerian ecosystems as a rich source of bioactive molecules promising for new potential drugs

Secondary metabolites are molecules not essential for the growth and development of microorganism, mainly having a defence role. They have shown a great potential for the discovery of drugs and their study still draws attention to the development of more effective therapeutic agents.

Actinobacteria are well known for their high biosynthetic ability to yield secondary metabolites, that are characterized by peculiar molecular structures often highly complex and rich in stereogenic centers, produced in enantiomerically pure form. These molecules display a broad spectrum of biological activities including antibiotic, antifungal, antitumor, antioxidant, effects as plant promoting growth and immunosuppressive property. Of note that among the bacteria known for their secondary metabolism, Actinobacteria produce about two-thirds of all derived active natural products in current clinical use.

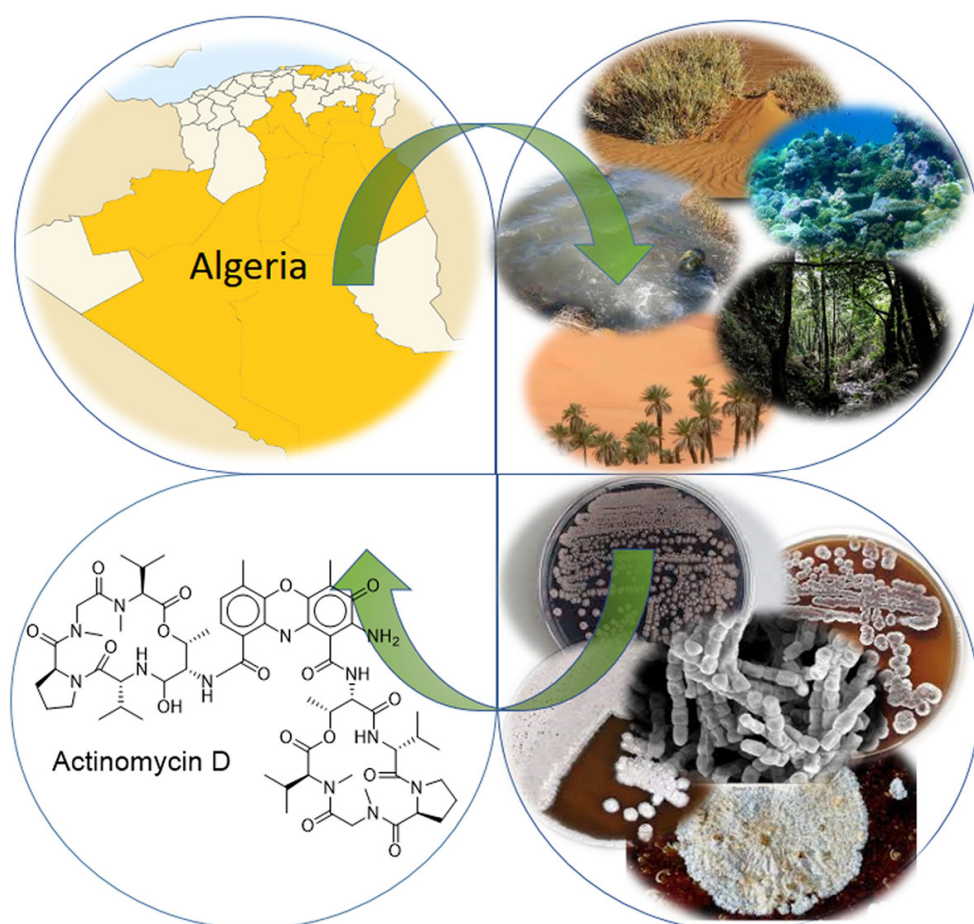


Fig. 1. Distribution of the explored Algerian ecosystems and Actinobacteria species diversity investigated for novel bioactive molecules.

Actinobacteria are ubiquitous and represent the most dominant bacterial population within soils. An increasing number of novel and rare actinobacterial taxa continues to be reported from natural habitats and the study of extreme and underexplored environments, such as marine, forest, semi-arid and desert ecosystems has focused a growing interest. These environmental features affect the biodiversity, that is very rich in actinobacteria, and to a great biodiversity corresponds a wide chemodiversity of metabolites. Therefore, the potential of this approach consists in the discovery of novel strains with new metabolic pathways and new gene clusters offering a successful chance to discover novel bioactive metabolites.

Algeria has a great climatic diversity ranging from mountains in the Northern regions to the world's hottest Saharan desert in the Southern region, passing through semi-arid areas. As recently reported in our overview on this topic, the exploration on rare and novel genera and species of Actinobacteria present in Algerian habitats started several decades ago. Twenty-nine newly discovered rare Actinobacteria species were reported in the period 2002-2019, isolated from different ecosystems, mainly from the Saharan soils and palm groves, where 38% of the most abundant genera belong to *Saccharothrix* and *Actinopolyspora*.

A transdisciplinary research, closely combining studies on biology and chemistry of natural products is essential to identify the molecular structures of the metabolite responsible for the bioactivity. The biological work can include the selection of nutritive sources and culture conditions applying a statistical approach to optimize the metabolite yield. This approach was applied in our study on the improved production of the anticancer drug actinomycin D (Fig. 1), isolated from a *Streptomyces* sp. strain collected in a Saharan region in Algeria.

From the 50 secondary metabolites belonging to different chemical classes reported from Actinobacteria collected in Algerian habitats, 17 new molecules were obtained exhibiting interesting bioactivities. An example is represented by the isolation of nigericin and related polyethers from *Streptomyces youssoufiensis* collected in an Algerian semi-arid soil, which showed to affect significantly the glioblastoma stem cells proliferation, and therefore of promising interest in the development of a potential drug to treat this aggressive brain cancer. A further case study is given by a new polyketide, which represents the lacking member in the series of phaeochromycins, from an endophytic *Streptomyces* strain isolated from a brown alga *Fucus* sp. The compound exhibited a selective and potent bacteriostatic activity against methicillin-resistant *Staphylococcus aureus* (MRSA), the most commonly occurred antibiotic resistant bacterium responsible for human infections. This is relevant in the light of an increasing incidence of antibiotic-resistant bacterial pathogens like those of the ESKAPE group.

***Ibtissem Djinni*^{1,2}, *Andrea Defant*², *Mouloud Kecha*¹, *Ines Mancini*²**

¹*Laboratoire de Microbiologie Appliquée, Département de Microbiologie, Faculté des Sciences de la Nature et de la Vie, Université de Bejaia 06000- Bejaia, Algeria*

²*Laboratory of Bioorganic Chemistry, Department of Physics, University of Trento, Sommarive 14, 38123 Povo Trento, Italy*

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Ibtissem Djinni, Andrea Defant, Mouloud Kecha, Ines Mancini

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