

NATURAL PRODUCTS AND MICROBIAL RESOURCES

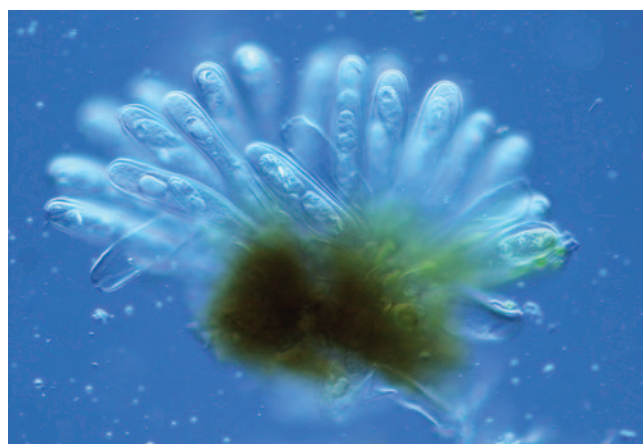
Fundación MEDINA writes about natural products and their potential for novel drugs and new product applications

The renovated interest in microbial natural products as sources of novel drugs and high valued biotechnology products is bringing the attention to the role of microbial collections in preserving this microbial diversity as well as untapped sources of potential new products.

Microbial natural products and industrial microbial collections

Historically, microbial natural products have been one of the most prolific sources of new leads in modern drug discovery, especially in the case of antibiotics, with more than one hundred new compounds including natural products or natural product-based compounds introduced in the market in the last three decades. The pharmaceutical industry devoted massive efforts in the search for novel compounds and generated, after decades of intensive screening, most of the existing industrial microbial collections with hundreds of thousands of talented microbial strains for the discovery of new bioactive molecules. The strains were distributed among selected groups of fungi, actinomycetes, myxobacteria, cyanobacteria and other bacteria isolated from the largest diversity of environments and geographies after intensive sourcing programs and collaboration with the countries of origin.

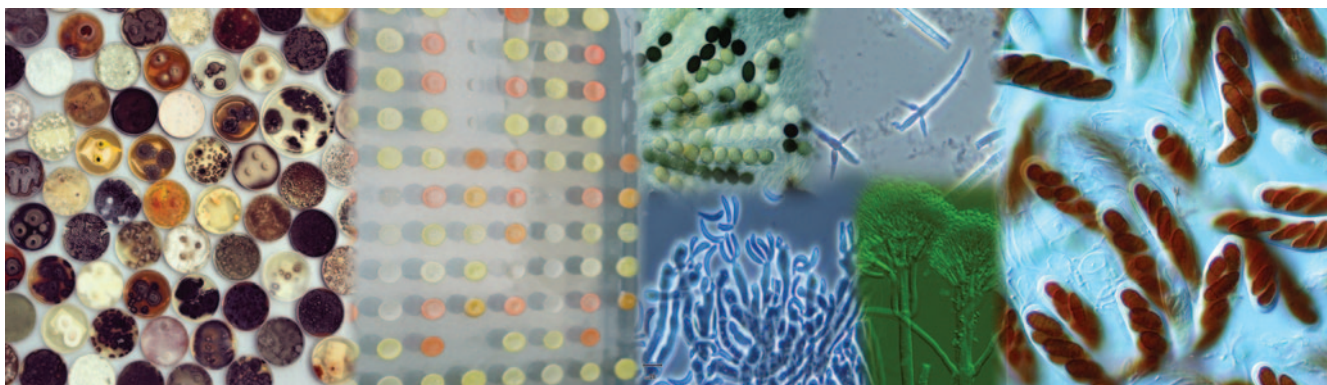
In this context the Convention of Biodiversity was developed in response to the need for a sustainable use of biological diversity, with fair and equitable sharing of future exploitation benefits, and defined a new paradigm in the way industry is required to address the access to biological resources in third countries, and in the way industrial microbial collections were going to be built. Despite two decades of efforts to clearly manage the access and



benefit sharing to these genetic resources, and the transfer of relevant technology, wrong expectations about the potential economic returns have been frequently observed. Emerging protective legislation in some countries, and the absence of clear authorities to grant access, have determined the introduction of voluntary guidelines to assist the efficient management of the exploitation of biological resources that were reinforced more recently with the implementation of the Nagoya protocol. Whereas this protocol aims at providing a legal framework for providers and users of genetic resources, including a proposed infrastructure to track materials and agreements, its conceptual and practical implementation is still a challenge in many countries and has set up the alarm for many users both in the academic and industry communities. These regulations did not prevent the continued interest in expanding the diversity of strains in public and industrial microbial collections.

With the decline of the natural products programmes in the pharma environment, these microbial collections that had shown to be extremely prolific in delivering novel compounds were sold, dispersed or transferred to more academic environments for future exploitation. These culture collections represent unique reservoirs of biodiversity today and continue to provide new opportunities for the discovery of potential novel molecules and novel high valued biotechnology products that have not yet been fully explored. These industrial strain collections clearly complement public academic culture collections that play a major role in conserving a referenced fraction of the biodiversity of micro-organisms in Nature.





Paralleling the consolidation of the new roles of microbial collections in biotechnology, we have seen that microbial genomes sequences in public databases increased exponentially in the last years, revealing the broad diversity of gene clusters involved in the biosynthesis of natural products, and the unnumbered cases of silent biosynthetic gene clusters potentially involved in the production of previously not detected novel natural products. The thousands of strains in industrial microbial collections remain untapped sources of metabolic diversity that are the objective of new screening programs, and intensive genome mining campaigns, from which novel gene sequences and novel pathways are being identified.

Disciplines such as synthetic biology and more specifically the metabolic engineering of biosynthetic pathways is overcoming the limitations of the structural complexity of natural products, and are helping to develop new ways to increase chemical diversity from strains in existing culture collections. These new synthetic biotechnology approaches are tackling former limitations and managing the efficient exploitation of these unique resources to express these new pathways in laboratory conditions.

Fundación MEDINA is a non-profit research organisation focused on drug discovery from microbial natural products and was established as a public private partnership between the Government of Andalucía, the University of Granada and Merck Sharp and Dohme de España, S.A. (MSD). MEDINA harbours one of the largest industrial microbial collections for the discovery of

novel natural products with more than 116,000 microbial strains of bacteria and fungi inherited from. The microbial collection was built from the broadest diversity of sources and it is widely accepted that the successful discovery of novel bioactive molecules is dependent on the chemical diversity of the NPs collections and the capacity of the selected strains to produce novel compounds. MEDINA is developing natural products research programmes leveraging more than five decades of natural products drug discovery expertise. In this context, the MEDINA microbial collection is being actively exploited in the research and development of new biotechnology products from microbial sources with applications in human and animal health, agriculture and other sectors of the bioeconomy. These programmes are included within the joint discovery efforts developed by MEDINA as part of its collaborative public private innovation models enabling the discovery of potential new products from its collections and libraries.

MEDINA is committed to the research of natural products and the exploitation of these microbial collections, and supports the renewed interest in fostering research and innovation in new natural product discovery and training support to ensure the future generation of scientists in the field.



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