Where are the new medicines? The case for terrestrial microorganisms

Many significant medicines are derived from natural sources. Tradition and curiosity drove early healers to experiment with vascular plants, and in the modern era organic chemists and pharmacologists have helped develop an understanding of these systems on a molecular level. The path to finding medicines from microbial sources has lagged behind those from plants, because it depends on the development of the sciences of microbiology and mycology, and although there are examples of traditional uses of microbes for medicinal use, red yeast rice being one, the breakthroughs have really been those created in the 1940s by Alexander Fleming and Selman Waxman, with the discovery of antibiotics from fungi and bacteria. Since then, there have been intense efforts in academic and industrial laboratories to discover and document biologically active metabolites from microbial sources.

However, it has become clear that a majority of microorganisms, even after decades of research, are still unknown to science, and exploration of the terrestrial and marine worlds will, without doubt, lead to the discovery of new microbes and novel compounds to add to the current catalog of metabolites used for medicine, agriculture, and animal health.

The wide chemical diversity shown by both bacterial and fungal metabolites is reflected in the pharmacological action associated with these compounds, which range from antibacterial to hallucinogenic.

The effect of penicillin was first noticed in 1928; after almost one hundred years of research since this discovery, and with increasing competition from synthetic chemistry, in all its forms, there are a number of observations that strongly favor continued and increased efforts in this field.

New medicines from microbial sources continue to be introduced to the clinic — one of the most recent is Istodax (Romidepsin), a cyclic peptide produced by the bacterium *Chromobacterium violaceum*, which was discovered by the Fujisawa Pharmaceutical Company in Japan, developed by Gloucester Pharmaceuticals and approved by the US FDA in November, 2009, as a treatment for cutaneous T-cell lymphoma.[1] Fingolimod, a product based on myriocin, a metabolite first reported from the fungus *Isaria sinclairii*, was quite recently approved for treating multiple sclerosis.[2]

A majority of terrestrial and marine microorganisms have yet to be isolated and investigated. For example, approximately 5% of the 1.5 million fungi predicted to exist have been described in the literature, and similar estimations have been made for prokaryotic organisms.

A recent study[3] from Japan has shown that, on an average, each microorganism from a particular industrial collection had the capacity to produce between two and three novel compounds; taken with the predicted number of organisms thought to exist, the fungal kingdom alone has the potential to provide a library of three to five million unique compounds.

Recent genomic analysis[4] has revealed that many organisms contain genetic information for potential secondary metabolites, which have yet to be reported. In the case of prokaryotic organisms, knowledge of the rules of polyketide synthases has enabled the prediction of structures from these so-called *Silent Biosynthetic Pathways* (SBP). In the case of fungi as many as 30 or more polyketide synthases (PKS) sequences have been detected in a single fungus, and in all cases of fungal sequencing reported so far, genes for PKS and non-ribosomal peptide synthases have been detected. Assuming that each fungal species contains these SBPs, then taken together with the prediction of there being 1.5 million species, this again supports the existence of a truly vast resource of potential new medicines.

Genetic engineering of new microbial products is in its infancy and has already shown its power with, for example, the development of the epothilones, originally isolated from myxobacteria,[5] and the bacterial Sirolimus (rapamycin), and related analogs, which have shown many new activities, including the potential for treating stroke victims.[6]

The future for microbial products should be strong; many major pharmaceutical companies have withdrawn almost

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totally from this area of research, especially in the USA, where the last large pharmaceutical company in-house microbial products department, at Wyeth, was acquired by Pfizer, which subsequently closed this group. It is now up to the academic groups and smaller independent research-driven companies to seize the opportunities, collaborating with interested microbiologists, chemists, and pharmacologists support to make new discoveries and their subsequent development, which will lead to novel medicines for the many neglected diseases and unmet needs of society.

It seems that India in particular, with a wide variety of ecosystems, from deserts to tropical forests, which are surely teeming with microbial diversity, coupled with a large number of very highly educated and experienced scientists, and critical neglected diseases and unmet medical needs, could make significant progress by exploring this area.

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REFERENCES

1. Vandermolen KM, McCulloch W, Pearce CJ, Oberlies NH. Romidepsin (Istodax, NSC 630176, FR901228, FK228, depsipeptide): A natural product recently approved for cutaneous T-cell lymphoma. J Antibiot (Tokyo) 2011;64:525-31.
2. Strader CR, Pearce CJ, Oberlies NH. Fingolimod (FTY720): A recently approved multiple sclerosis drug based on a fungal secondary metabolite. J Nat Prod 2011:74;900-7.
3. Ito T, Odake T, Katoh H, Yamaguchi Y, Aoki M. High-throughput profiling of microbial extracts. J Nat Prod 2011;74;983-8.
4. van den Berg MA, Albang R, Albermann K, Badger JH, Daran JM, Driessen AJ, *et al*. Genome sequencing and analysis of the filamentous fungus *Penicillium chrysogenum*. Nat Biotechnol 2008;26:1161-8.
5. Arslanian RL, Tang L, Blough S, Ma W, Qiu RG, Katz L, *et al*. A new cytotoxic epothilone from modified polyketide synthases heterologously expressed in myxococcus xanthus. J Nat Prod 2002;65:1061-4.
6. Ruan B, Pong K, Jow F, Bowlby M, Crozier RA, Liu D, *et al*. Binding of rapamycin analogs to calcium channels and FKBP52 contributes to their neuroprotective activities. Proc Natl Acad Sci U S A 2008;105:33-8.

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