

FRONTIERS

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Big pharma is in big trouble. Its future could lie in the developing world.

One billion people, mostly in developing countries, use natural products for medicinal purposes. The pharma industry has become increasingly interested in their health-care practices.

The modern pharmacopeia is well endowed with life-changing products that come from nature. Take reserpine. This extract, from the plant *Rauwolfia serpentina*, is used to control high blood pressure. Or vinblastine, an extract from *Catharanthus roseus* leaves, used in cancer treatments. Then there is rapamycin, an extract from the bacteria of the *Streptomyces* species, used as an immunosuppressant drug to prevent rejection in organ transplants.

Yet, in recent years, developed and developing countries have adopted different approaches to the relationship between natural products and modern research and development (R&D). In the developed world, despite well-known examples of its use in the treatment of deadly diseases, natural products R&D continues to focus more

on dietary and cosmetic products, and less on conventional healthcare. Supermarket shelves are loaded with examples, such as green tea, the appetite suppressant *Caralluma* cactus and the skin lotion *Aloe vera*.

In the developing world, in contrast, natural products are very much at the forefront of disease therapy. Despite the global success of modern health-care systems, those living in the world's poorest countries still rely on traditional medicine, which uses natural products almost exclusively.

It is true that many scientists are working in natural products research. Leading examples includes the National Botanical Institute at the University of Antananarivo in Madagascar, the Natural Products Research Group at the University of Natal in South Africa, my own International Centre for Chemical and Biological Sciences in Pakistan, and the Cosmetic and Natural Product Research Centre at Naresuan University in Thailand.

This sounds impressive (and in many ways it is). But the scale of the effort remains small in comparison to conventional pharmaceutical R&D. For example, GlaxoSmithKline (GSK) alone spends \$5 billion a year on R&D.

Yet, these are hard times for large pharmaceutical companies too. Many blockbuster drugs have come off-patent (such as GSK's Zantac, which is used to treat peptic ulcers). Others are about to do so. The product pipeline for GSK, Pfizer and others is smaller than it should be, and, as *Nature* reported in its 10 July 2008 issue, a series of mergers and acquisitions has led to costly disruptions in R&D, which means more delays for impending products and more time needed to build teams for future products.

A decade ago many industry leaders pinned hopes of revival on a technology known as combinatorial chemistry, in which powerful computers tried to mimic the effects of potential new drugs and produce a new class of synthetic compounds. But this has proved disappointing and companies are now more interested in exploring the potential for biotechnology in drug discovery.

In their search for new vistas, it is vital that companies do not completely sever their roots in natural products. Indeed, natural products still have a big role to play: it was only a decade ago that the anticancer drug taxol was isolated from the bark of the Pacific yew tree (*Taxus brevifolia*); discodermolide, currently in phase-I clinical trial for cancer, was extracted from the marine sponge *Discodermia dissolute*; and the antimalarial drug artemisinin was derived from the shrub *Artemisia annua*. These examples show that there is still significant scope in natural product R&D for the

treatment of life-threatening diseases.

But the main difference between then and now is the emergence of world-class laboratories in developing countries. Researchers in these laboratories can play an important role in the drug-discovery process. Thanks to the continued use of traditional medicines, there is an intimate knowledge of, literally, hundreds of thousands of products that traditional practitioners use in medical care on a daily basis.

At the same time, we now have the latest hardware and, more importantly, skilled and creative research chemists. Liquid chromatography, nuclear magnetic resonance, mass spectrometry and super-critical fluid chromatography are just four technologies that many researchers in developing countries have at their disposal to help them understand the chemistry of natural products. By partnering with colleagues from developed countries, we can help determine if our traditional medicines might be the blockbuster drugs of tomorrow.

Collaborations are already taking place, but on a relatively small scale. One such partnership, between P.J. Margo in India and W.R. Grace in the USA, led to Neem-based pesticides (*Azadirachta indica*). Chinese developers and Novartis in the USA are currently working together to develop the antimalarial drug coartemether (*Artemisia annua*).

But we need many more South-South and South-North partnerships — not only to conduct R&D, but also to build the capacity to assess the commercial potential of scientific findings and to devise effective business plans for the resulting products. Moreover, there is a need to broker an equitable international intellectual property rights regime that will not only promote collaboration among the various players (drug companies, university researchers and practitioners of traditional medicine), but also discourage biopiracy.

Technology is of course important in natural products research. But I would argue that nature is even more important. More than 80% of the biodiversity found in terrestrial and marine organisms, fungi, bacteria, plants and animals has yet to be described by modern science. Global collaboration is the only way that the world (both rich and poor) can fully benefit from Earth's vast treasure trove of natural products, traditional knowledge and scientific research. Given the growing environmental stress being experienced by our planet in terms of loss of habitat and biodiversity, there is not a minute to lose. ■

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