Novel drugs from botanical sources

'Natural products offer a diverse range of structures, beyond the rational synthetic strategies of combinatorial chemistry'

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The diverse range of biosynthetic pathways in plants, fungi and bacteria has provided an array of lead structures that have been used in drug development. Approximately 40% of the new drugs developed in North America during the period 1983–1994, were derived from natural compounds [1].

Despite this success, many large pharmaceutical companies have now stopped screening natural resource collections because they are not thought to fit into modern HTS strategies and because of concerns about the ownership of leads from natural resources. Extract screening and the isolation and characterization of active compounds have, therefore, been passed onto smaller companies or academics. However, these companies do not have the funds and expertise to take leads through clinical trials and to the market place, and hence leads will still have to be sold or licensed to larger companies for product development. In theory the involvement of small companies in the early stages of development sounds feasible, but the collapse of a high number of these natural product companies indicates that, in practice, it is not an ideal approach; when a small company collapses, the drugs in development are usually dropped. Therefore, unless changes are made, the number of natural-product-derived drugs reaching the market will decline, despite the increased interest in natural cures shown by society.

History shows that those natural compounds that make it to the market place have a 'champion', often someone working in industry or with colleagues in pharmaceutical companies. One such champion was Monroe Wall, who died last year; in the 1950s, Wall and his team started work on the Chinese medicinal plant *Camptotheca acuminate*, resulting in the isolation of the anticancer compound, camptothecin, which led to the currently used derivatives, irinotecan and topotecan. We seldom see such champions today, despite the fact that the natural-product-derived leads in this example, along with the taxols (paclitaxel), vinca alkaloids (vinblastine and vincristine), mitomycins and doxorubicin, are now mainstream anticancer agents. These leads, together with the increasing evidence that the plant content of our diet influences our susceptibility to cancer, suggest that further research should be undertaken on plant-derived compounds, not only as drugs but also as chemopreventive agents.

Selecting natural resources for screening

Natural products offer a diverse range of structures, beyond the rational synthetic strategies of combinatorial chemistry but although combinatorial chemistry has failed to provide leads for some areas of medicine, especially multidrug-resistant bacteria, companies are investing more in the development of combinatorial chemistry than in natural products.

A rational strategy

To date, most antibiotics have been discovered through the screening of microbial collections but a case can be made for a move from such random screening to a more rational strategy that exploits the ability of natural selection pressures to select for biochemical pathways that produce biologically active molecules. The metabolites in plants and microbes have evolved, via selection, to physiologically or ecologically affect the fitness of the organism. For example, plant roots have to protect themselves from invasion by microbes as well as insects and nematodes and the success of the plant often depends on the ability of the roots to capture nutrients and to kill roots and seeds from other plants and invasive organisms.

A successful plant is likely to be one that has evolved compounds to combat the detoxification strategy of the predator or microbe efficiently. Thus it is highly likely that a study of root–microbe interactions would identify compounds with antibiotic activity. The range of organisms involved in these interactions is large and, hence, the range of compounds is also likely to be large and could differ between plant families. Advances in analytical and screening techniques mean that these types of studies are now

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possible because they require minimal amounts of extracts and compounds. Furthermore, once an active metabolite has been identified, molecular biology can provide the tools to study and manipulate the biosynthetic pathways in plants to produce more of that metabolite.

Identifying roles

Interestingly, in countries such as China, many traditional antibacterial medicines comprise roots rather than leaves or fruits and, in many cases, the active compounds in these roots are still unknown.

Understanding the function of molecules in the survival systems of animals has already assisted in the design of drugs. For example, blood-feeding insects, leeches and bats have had to evolve effective anti-coagulants; peptides from their saliva have been isolated and some are now in clinical trials as treatments for circulatory disorders [2]. Other examples include the use of toxins from snakes, bees and scorpions as tools in the study of diseases of the CNS. However, there are concerns about the use of these drugs because there are no antidotes as yet, but certain plants are traditionally used to treat blood loss from leech wounds and snake bites, and a phytochemical study of these plants might identify antidotes.

Ownership of genetic resources

The medicinal properties of plants and fungi have fascinated scientists for centuries. In the past, active ingredients were isolated from plants and developed as drugs with little regard for the rights of indigenous communities with respect to information about the use of the plant or for the rights of the source country regarding the use of the genetic resource. The Convention on Biological Diversity (CBD) treaty (http://www.biodiv.org), that formed part of the 1992 Rio de Janeiro Earth Summit, highlighted the need to ensure that biodiversity was not exploited without benefit for source countries [3]. The CBD recognizes the sovereign rights of states over their genetic resources and advocates the facilitation of access to these resources for environmentally sound uses but provides no guidelines as to how this is to be achieved.

The implementation of the CBD has worried many multinational pharmaceutical companies [4]: how do they ensure that indigenous communities and other stake-holders' share in the benefits of the use and exploitation of genetic resources? These companies do not want to be labelled 'biopirates' and, thus, it is easier for them to research synthetically derived compounds than those from natural sources.

Conclusions

If the health of our society is to benefit from the diversity of compounds that have evolved in our flora and microbes, we need to maximize the chances of finding lead compounds: rational design of plant selection strategies, and cooperation between natural product chemists and those involved in drug development will help to achieve this. Interaction with government representatives to develop clear systems to access genetic resources will also be key. The sixth Conference of the Parties (http://unfccc.int/cop6) in April 2002 outlined voluntary guidelines required for the implementation of the CBD, including requirements for obtaining informed consent for access to biodiversity and the mechanisms of sharing benefits with indigenous and local communities.

This will help to clarify the processes by which scientists and companies can gain access to genetic resources and share the benefits, allowing the full potential of new plant-derived drugs to be realized. In the meantime, however, we need to continue our exploration of the potential in our own gardens.

References

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