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Review article

THE CONTINUING VALUE OF NATURAL PRODUCTS FOR DRUG DISCOVERY

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ABSTRACT: **Natural products are the most consistently successful source of drug leads, both historically and currently. Despite this, the use of natural products in industrial drug discovery has fallen out of favour. Natural products are likely to continue to be sources of new commercially viable drug leads because the chemical novelty associated with natural products is higher than that of any other source: this is particularly important when searching for lead molecules against newly discovered targets for which there are no known small molecule leads. Despite the commonly held assumptions, natural products can be a more economical source of chemical diversity compared with synthesis of equivalent numbers of diverse chemicals. Additionally, natural products that are found to be biologically active in assays are generally small molecules with drug-like properties. That is, they are capable of being absorbed and metabolised by the body. Hence, development costs to produce orally active medicines are likely to be much lower than with biotechnological products or with most compounds produced to date from combinatorial chemistry. Since less than 10% of the world's biodiversity is reckoned to have been tested for biological activity, many more useful lead compounds are waiting to be discovered from natural products. The challenge is how to access this natural chemical diversity. Several different strategies are emerging, as will be described in this review.**

(Key words: drug discovery; natural products; high throughput screening; convention on biological diversity

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EL VALOR DE LOS PRODUCTOS NATURALES EN EL DESCUBRIMIENTO DE NUEVOS MEDICAMENTOS

RESUMEN **Los productos naturales son las fuentes más exitosas y consistentes de los fármacos líderes tanto históricamente como en la actualidad. A pesar de esta característica y la novedad química que poseen generalmente superior a fármacos de otros orígenes, el empleo de estos en la industria del descubrimiento de nuevos medicamentos no ha sido favorecido. La novedad química es particularmente importante cuando se investiga en la búsqueda de moléculas líderes que actúan sobre dianas recién descubiertas para las cuales no se dispone de pequeñas moléculas líderes. Contrariamente a los criterios comúnmente establecidos, los productos naturales pueden ser una fuente más económica de diversidad química si se compara con la síntesis de un número equivalente de químicos diversos. Además de lo anteriormente señalado los productos que son activos en los ensayos biológicos son generalmente pequeñas moléculas con propiedades similares a los medicamentos, capaces de ser absorbidos y metabolizados por el organismo. Como consecuencia de lo antes expresado los costos para el desarrollo y producción de medicamentos activos por vía oral son mas bajos que los obtenidos por la vía biotecnológica o productos combinados con compuestos obtenidos hasta la fecha mediante la química combinatoria. Se calcula que menos del 10% de la biodiversidad del mundo se le ha probado la actividad biológica, muchos más compuestos líderes de fuentes naturales están esperando ser descubiertos. El reto está en como acceder a toda esta diversidad química natural. Algunas nuevas estrategias diferentes están emergiendo y de ello trataremos en esta revisión.**

(Palabras clave: descubrimiento de nuevos medicamentos; productos naturales; pesquisajes para alto rendimiento; convención de diversidad biológica)

INTRODUCTION

Drug discovery involves finding chemicals that have activity on a biological system that is relevant to the target disease. While many successful drugs have been developed from traditionally used medicines (1) or from chance observations of effects of compounds on administration to humans (2), most drug discovery activity currently involves random testing of chemicals on biological assays. With advances in molecular biology, robotics and computer power, it is possible to screen millions of compounds rapidly. However, the successes in terms of new medicines reaching the market have not increased with the application of such technologies.

With increased throughput, why is drug discovery productivity not improving?

The scale of high throughput screening (HTS) for drug discovery has increased tremendously in recent years, but there has been no corresponding growth in the numbers of early-stage projects moving from discovery to preclinical development.

Why might this be?

To be successful, HTS needs appropriate therapeutic targets and collections of drug-like compounds that are highly diverse in their three-dimensional shapes. The assay targets are probably becoming better chosen as a result of insights into diseases from genomics and application of molecular biological techniques such as transgenic animals. What can be said about the chemical collections used in HTS?

Large numbers of compounds are commercially available, and most pharmaceutical companies have their own in-house collections from previous projects. There are also several approaches to rapid synthesis of libraries of compounds using combinatorial chemistry. It should not be difficult for a company to obtain a screening library of one to two million compounds. However, perhaps such collections do not contain sufficient variety in the shapes of molecules.

One reviewer (3) concluded that "the notion that combinatorial synthesis acting *alone* will accelerate drug discovery research has not been borne out by experience over this first decade (of use of combinatorial libraries). The ideology of a single universal library as a source of leads against a plethora of molecular targets, purported by some, is not credible." This seems to be the case because an analysis of the origins of all of the new drugs introduced between 1981 and 2002 did not find one that originated from combinatorial chemistry (4), and a more recent analysis (5) concluded that only one product had its origins in screening of combinatorial chemistry libraries.

Given this background, natural products, with their higher structural diversity (6, 7), can be considered as a ready complement to combinatorial libraries: natural product screening could provide the initial leads, while combinatorial chemistry could accelerate the optimisation of those leads.

Natural products: then and now

It has been commented that all of drug discovery to date has used less than 500 molecular targets (8) and the "druggable" genome is not much bigger (9, 10). What is less commonly appreciated is that drug development has relied on a similarly small number of molecular scaffolds to produce our medicines: only 244 prototypic chemical structures have been used up to 1995 (1). Overwhelmingly, these chemical scaffolds have come from natural sources: 83% from animal, plant, microbial and mineral origin, with the remaining 17% from serendipitous observations of activity of compounds or from chemical synthesis. Thus, natural products have, historically, been the single most successful source of new medicines.

More recent drug introductions have also been heavily dependent on use of natural products. In their review of the sources of new drugs introduced in the period 1981 to 2007, Newman and Cragg (5) found that around half of the drugs introduced since 1994 were either natural products or derived from natural products. They also pointed out that many other drugs were derived from use of natural products during the discovery process.

The successes of natural products are commercially important. Of the 20 best selling non-protein drugs in 2000, nine were either derived from, or developed as the result of leads generated by natural products. Their combined annual sales were over US$16 billion. Many new developments from natural products are in the pipeline (10, 11).

For HTS and drug discovery, the key advantage of natural products over synthetic chemistry collections is their structural diversity. In a comparison of published databases of natural products and synthetic chemicals, Henkel and colleagues from Bayer revealed that 40% of the chemical skeletons in natural products were not found in the libraries of synthetic chemicals (6). Therefore, screening for new leads is more likely to be successful if a diverse set of natural products is included.

Natural products: what's the problem?

Despite the known structural diversity of natural products and their tremendous value in previous drug discovery efforts, pharmaceutical companies currently are reluctant to make large-scale use of natural products in HTS.

Why should this be? It seems to relate to several real and perceived limitations of natural products:

- their chemical complexity;
- the difficulty of screening mixtures of compounds in natural product extracts;
- the time-consuming nature of natural products chemistry;
- the belief that screening of natural products gives rise to large numbers of artefacts;
- the supposedly common occurrence of synergistic actions between different components in an extract;
- the fear of poor reproducibility between different batches of extracts, possibly from seasonal effects on plant secondary metabolism;
- the uncertainty of being able to obtain resupplies of an interesting extract in large quantities; and
- the general political problems of access to biodiversity and the implications of the United Nations Convention on Biological Diversity.

The more technical issues will be discussed in the next section, while the political ones will be addressed here. The United Nations Convention on Biological Diversity (CBD) (www.biodiv.org) has three main goals: the conservation of biodiversity, the sustainable use of the components of biodiversity, and the sharing of benefits arising from the commercial and other utilization of genetic resources in a fair and equitable way. Signatories to the CBD recognise that countries have sovereign rights over their biological resources within their boundaries, and they agree to the conditions in the CBD for the preservation and sustainable use of biodiversity – almost all countries of the world have ratified the Convention.

In relation to accessing natural products for drug discovery, the CBD has several Articles that impact on future interactions between companies and research organisations and countries with desired biodiversity. Biodiverse-rich countries that have ratified the CBD must facilitate access to their biological resources (Article 15.2), and such access must be in accordance with appropriate legislation (Article 15.1), and be on mutually agreed terms (Article 15.4) involving prior informed consent (Article 15.5). The source country is expected to be involved in collaborative research and development projects relating to its biodiversity (Article 15.6) and the source country should benefit from technology transfer (Article 16.2), from the results of research (Article 15.7) and from sharing of commercial benefits resulting from use of its biodiversity (Article 15.7).

Companies wishing to access the broadest range of biodiversity will almost certainly have to consider sources outside of their own countries. The companies are faced with the daunting task of making CBD-compatible agreements with groups or agencies in each source country, involving politically delicate issues of benefit-sharing and technology transfer. However, such issues can be resolved simply by working with a reliable network such as operated by SIDR. This natural product network is based on legally-binding and CBD-compatible agreements with legitimate groups in several biodiversity-rich countries throughout the world. Companies accessing the natural product collection make one contract, which then takes care of benefit-sharing and other obligations. Currently, the natural product collection based on plants is the most biodiverse available for screening. As it covers 90% of the world's plant families, it has exceptionally high genetic diversity that will provide correspondingly high diversity of small molecules for screening. The network also provides reliable resupplies of materials, if required for larger scale experimental work.

Ways forward with natural products and drug discovery

Chemical complexity? Natural products are generally perceived as being considerably more complex than synthetic ones. However, this is not necessarily so as revealed in the comparison of synthetic collections with natural products (6, 7). For example, a natural product lead with interesting anti-obesity properties has molecular weight below 200 (13). Another natural compound with anti-proliferative properties is structurally more complex, but it is capable of being synthesised in commercial quantities (14). Other screening efforts using a collection of plant extracts have several examples in which the natural product "hits" provided enough chemical information to enable the construction of a theoretical pharmacophore followed by synthesis of analogues with improved activity (15).

Difficult mixtures? The traditional way to use natural products has been to screen mixtures in the form of relatively crude extracts. However, the trend is away from use of complex mixtures in HTS. Perhaps

the most desired format for HTS assays is to have single pure compounds in each well. However, this is technically and economically challenging to achieve for any great number of samples of natural products, but reports of successful approaches have been published (16, 17; for reviews, see 18, 19). Never-the-less, it seems more cost-effective to take a different approach that involves initial screening with cleaned-up extracts followed by rapid confirmation of real hits by a combination of preliminary fractionation and back-up bioassays.

Time-consuming processing? The many advances in separation chemistry and in techniques for analysis and structural elucidation of natural products make it much easier than before to work with natural products (20-22). Therefore, following up initial hits made with extracts should not take any longer or be more difficult than scaling up and reconfirming hits made from a combinatorial library. Additionally, the higher resolution of current techniques means that structures can be obtained from much smaller quantities of natural products than before, opening the way to early production of synthetic material and of analogues for optimisation studies. When working with microbial broths, Singh and colleagues (23) concluded that pure compounds could be isolated in less than two weeks and that most chemical structures could be elucidated in a similar period.

Prone to artefacts? With extracts, some relatively simple and inexpensive pre-processing goes a long way towards reducing the possibility of false positive results in assays. For example, with plant extracts, polyphenolic tannins and chlorophylls can easily be removed. Reactive molecules have been cited as a general problem during HTS (24), and there are techniques to remove these from natural product extracts. Personal experience of screening against a variety of targets indicates that collections of synthetic molecules, whether randomly assembled or "pharmacophore-enriched", generate at least as many false positives in screening campaigns as collections of plant extracts.

Synergistic effects? The traditional approach with natural product mixtures is bioassay-guided fractionation in an attempt to isolate a pure active substance. Undoubtedly, some attempts fail, with biological activity apparently being lost at one stage of fractionation. There is a tendency to assume that such a result is because two or more components are required to be present simultaneously to cause the biological effect or that several components act synergistically to create a detectable effect that is lost when the components are separated. Since the amount of material in each fraction generally gets smaller with each stage of separation, the loss of activity is possibly due to the decrease in amount of compound such that it is below the limits of detection of the bioassay: the problem is one of scale, rather than of synergism. Very few examples of synergistic effects have been published, and they may still represent new leads for biological activity.

CONCLUSION

All-in-all, the structural varieties of small molecules derived from natural products offer continuing promise for drug discovery campaigns (see also 25). Many of the traditional difficulties associated with natural products have been overcome or sidestepped. If the technical and political hurdles are still too daunting for pharmaceutical companies, specialist groups can fill the gap.

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