We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

15

Bioprospecting: Creating a Value for Biodiversity

Alan L. Harvey[1] and Nigel Gericke[2]
[1]*University of Strathclyde*
[2]*Niche Botanicals*
[1]*United Kingdom*
[2]*South Africa*

1. Introduction

Bioprospecting is the exploration of biological material for commercially valuable genetic and biochemical properties (Reid et al., 1993). This chapter will focus on the search for activities that could form the basis of new pharmaceuticals. Historically, most of the active ingredients in medicines have been natural products (Sneader, 1996), and natural products continue to form a productive source of new drugs (Newman and Cragg, 2007; Butler, 2008). Given that most drug discovery activity takes place in companies in the developed world and that most biodiversity is found in countries of the southern hemisphere, there needs to be a means whereby access to biodiversity is possible under terms and conditions that are mutually acceptable. After hundreds of years of unregulated collection of samples for many different purposes, the United Nations produced a framework for preserving the world's biodiversity while encouraging the sustainable use of biodiversity. This Convention on Biological Diversity has been widely accepted, and it is discussed in the following section. The chapter will continue with descriptions of various attempts to calculate an economic value for biodiversity, followed by an outline of current bioprospecting practices.

2. United Nations Convention on Biological Diversity

The United Nations Convention on Biological Diversity (CBD) (www.biodiv.org) was one of the major outcomes of the Earth Summit in Rio de Janeiro in June 1992. The CBD has three main goals:

- the conservation of biodiversity
- the sustainable use of the components of biodiversity
- 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 genetic and biological resources (i.e., biodiversity) within their boundaries, and agree to the conditions in the CBD for the preservation and sustainable use of biodiversity.

In relation to accessing natural products for drug discovery, the CBD has a number of Articles (see Appendix) that set the tone for future interactions between companies and research organisations with countries with desired biodiversity. Biodiverse-rich countries that have ratified the CBD have to facilitate access to their biological resources (Article 15.2).

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). Article 8(j) also commits signatories to preserving the traditional knowledge of indigenous and local communities and to promoting their involvement in developing wider applications of their knowledge; however, there is little guidance on how this might be achieved.

Since 1992, 192 countries and the European Union have signed or ratified the CBD, the notable exception being the USA. However, issues relating to access to biological resources have not been fully resolved. Only about 25 countries have introduced new regulations to facilitate access, and the vast majority of countries still have to formulate the appropriate laws.

To assist the implementation of bioprospecting under the CBD, the Conference of the Parties (the official CBD body) adopted the Bonn Guidelines on 'Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising out of their Utilization' (Secretariat, 2002). These are not legally binding, but they are intended to help all parties follow best practices in setting up bioprospecting agreements. Various professional bodies have responded to the Bonn Guidelines with their own recommendations. For example, the International Federation of Pharmaceutical Manufacturers and Associations has published its views on 'industry best practices' and the enabling steps that governments need to take with regard to regulating bioprospecting (IFPMA, 2007). The Biotechnology Industry Organisation of the USA has produced detailed guidelines for its members about engaging in bioprospecting (BIO-1, n.d.). These cover the general conduct of bioprospecting, sharing of financial benefits and of results of research, intellectual property rights, and conservation and sustainable use of biodiversity. The organisation has also published a model Material Transfer Agreement for use in bioprospecting operations (BIO-2, n.d.). There is a very useful resource published by the International Institute for Sustainable Development as an 'access and benefit-sharing management tool' and an accompanying handbook (IISD, 2007). This provides a step-by-step guide to obtaining prior informed consent, reaching mutually agreed terms, agreeing benefit-sharing arrangements, and dealing with issues relating to traditional knowledge and conservation.

The Bonn Guidelines are likely to be superseded by the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (Secretariat, 2011). This is a new treaty under the CBD that was adopted in Nagoya in October 2010. It will be operational once 50 countries ratify it (40 have done so by the end of July 2011). The aim of the Protocol is to provide greater legal certainty about all aspects of bioprospecting. In particular, it is intended to establish more predictable conditions for access to biodiversity and to ensure appropriate benefit-sharing. The Protocol deals more explicitly than previous documents with the use of traditional knowledge associated with genetic resources: contracting parties have to ensure that local communities have provided prior informed consent and that there is fair and equitable benefit-sharing with the relevant communities. The Nagoya Protocol also recognises that genetic resources are rarely confined to a single country and that traditional knowledge related to use of genetic resources is often shared by different communities. The Protocol demands involvement and cooperation of the relevant parties.

A major weakness in the implementation of the CBD with respect to bioprospecting has been the slow development of national systems for governing access to biodiversity. The

Nagoya Protocol is explicit about the responsibilities of signatories to create 'national focal points' and 'competent national authorities' to make available information on how to access genetic resources and traditional knowledge and to be responsible for granting access to biodiversity. In Africa, a diverse range of policies and laws relevant to access and benefit-sharing is in place in some countries, but these are most developed in South Africa through the National Environmental Management: Biodiversity Act (10 of 2004) ('the Biodiversity Act') and the regulations passed under this Act in 2008. The Biodiversity Act requires bioprospectors to obtain a permit from the Government for bioprospecting involving indigenous biological resources, and for the export of these resources. Prior informed consent is required with landowners and indigenous communities before a permit is issued. Benefit-sharing agreements must be entered into with indigenous communities who use the resource traditionally, or who have knowledge of its properties (Wynberg et al., 2009).

3. Value of bioresources

A key issue in bioprospecting is benefit-sharing. However, much of the debate on this topic assumes that there are benefits to share. The historical successes in drug discovery based on natural products would suggest that there should be a continued appetite for accessing natural products for use in drug discovery programmes. Despite this, the pharmaceutical industry, in general, has reduced its use of natural products (Harvey, 2008), and there are few current examples of large-scale programmes designed to access a wide variety of natural products collected from their native environment. Moreover, advances in techniques for manipulating microbes to produce novels chemicals make the use of locally sourced bacterial samples more attractive to industry (Kingston, 2011). Never-the-less, it is reasonable to ask what an appropriate price might be for biodiversity, its conservation and its availability for bioprospecting. This is an area with much debate but little consensus (see, for example, Castree, 2003).

Future royalty streams from blockbuster drugs (drugs that generate $1 billion in sales per year) directly or indirectly derived from bioresources were anticipated to contribute significantly to the conservation of biodiversity in source countries, and to the development of indigenous knowledge holder communities. However the age of blockbuster drugs seems to largely be over, and the pharmaceutical sector, as it is currently structured, is unable to deliver enough new products to market to generate revenues sufficient to sustain its own growth. Nearly all major drug developers are critically examining current R&D practices and, in some cases, considering a radical overhaul of their R&D models (Kaitlin, 2010). Only 13 natural product–derived drugs were approved in the United States between 2005 and 2007 (Harvey, 2008), and FDA approvals of new drugs reached a 24-year low in 2007 (Li & Vederas, 2009). With the contraction and consolidation seen in the pharmaceutical industry, and with only 3 in 10 new products generating revenues equal to or greater than average pharmaceutical industry R&D costs (Kaitlin, 2010), it would seem that royalty streams from natural product-derived pharmaceuticals are too uncertain to be included in the valuation of biodiversity.

A pragmatic approach to valuation is to focus on the monetary value paid by end users. In the early 1990s, Merck & Co. entered an agreement with the National Biodiversity Institute of Costa Rica, INBio, that provided a defined amount of cash (reported as $1 million) for a certain number of samples; although this deal is frequently mentioned in articles on the pros and cons of bioprospecting, key elements of the financial terms are still confidential, notably the payment per sample. More recently, GlaxoSmith Kline had an arrangement with the biotechnology company Extracta in Brazil: at its reported value of $3.2 million for a collection

of 30,000 samples (Dias & da Costa, 2007), this does not seem like a high price - about $100 per sample. The Swiss company Novartis also had an agreement with a Brazilian organisation, Bioamazonia, reported to be $4 million for 10,000 samples of micro-organisms. It should be noted that political concerns in Brazil about inappropriate commercialisation of its biodiversity caused both interactions to be terminated, highlighting the need for clear national focal points and competent authorities, as called for in the Nagoya Protocol.

In a development from academic collaborations on natural products and drug discovery, the Strathclyde Institute for Drug Research, UK acted as a broker for natural product samples provided by its collaborators and offered samples under licence to companies for bioassay. Because each species could be used several times, the cumulative return on a single extract could be quite impressive, reaching $500-1,500 per gram. This can be compared with commodity prices obtained for a known herbal medicine that has proved active in double-blind clinical trials: raw material costs for *Hypericum perforatum* (St John's wort) are $8-10 per kg. However, there is currently little demand from companies for samples of natural product extracts, and the brokerage activity has stopped.

Another approach to valuation of biodiversity has argued that a value can be put on the potential contribution of an area of land to drug discovery (Simpson et al., 1996; Rausser & Small, 2000). Depending on the assumptions used, this varied from $21 per hectare (Simpson et al., 1996) to $9,177 per hectare (Rausser & Small, 2000). The latter valuation was thought to be sufficient to provide an economic reward to sustain biodiversity conservation. A later paper (Costello & Ward, 2003) sought to explain the very different valuations reached by the previous authors. They concluded that Rausser and Small's focus on species in biodiversity hotspots was largely responsible.

Another approach to valuation of biodiversity used the pharmaceutical industry figures for costs and rewards of drug discovery and development to formulate a discounted cash flow model that gave a Net Present Value for an extract in a screening programme (Artuso, 1997). This was $487 per extract. A similar approach was used to explore the impact of varying the balance between upfront payments for sample supply and long-term royalties from sales of commercialised products (Lesser & Krattinger, 2007). In theory, more value is attached to a deal with an emphasis on royalty payments, but the authors note that larger up-front fees may be more of an incentive for conservation of biodiversity. The same approach was used to explore the potential added value of traditional knowledge and of pre-screened extracts. On average, use of samples suggested by traditional knowledge was expected to double the value of the deal. However, it is unlikely that this approach, which is based on averaging the theoretical outcome of testing large collections of samples, is appropriate for use of samples from traditional medicinal uses. These are more likely to be commercialised (if at all) on an individual basis. In addition to the possibility of providing a source for new chemical entities or derivatives, traditional medicinal plants may be commercialised as standardised plant extracts developed into polymolecular botanical medicines, dietary supplements or functional foods. The value of a registered botanical medicine may be considerable. In December 2005, the German Federal Institute for Drugs and Medical Devices (BfArM, Bonn) approved a new licence for the use of a proprietary extract of the root of the South African plant *Pelargonium sidoides*, (EPs® 7630), known as Umckaloabo, as a drug (Conrad et al., 2007). This registered liquid herbal medicine has been reported to have an annual turnover in Germany alone in 2006 of €80,000,000 (Brendler & van Wyk, 2008).

In-country fractionation and screening could also, potentially, raise the value of a collection of natural product extracts on the basis of reducing the risk of failure to the commercial

development partner. However, there has to be the necessary infrastructure and expertise to allow the screening, and the preliminary tests have to be relevant to the commercial partner (Lesser & Krattinger, 2007).

The discussion above has only considered direct monetary benefits. However, both the Bonn Guidelines and the Nagoya Protocol list possible non-monetary benefits in addition to the monetary ones (Table 1). The non-monetary benefits need to be looked at seriously because technology transfer and improvements in capacity may contribute to sustainable development in biodiversity-rich countries, although that assumption has been questioned (Castree, 2003).

1.	Monetary benefits may include, but not be limited to:
a.	Access fees/fee per sample collected or otherwise acquired;
b.	Up-front payments;
c.	Milestone payments;
d.	Payment of royalties;
e.	Licence fees in case of commercialization;
f.	Special fees to be paid to trust funds supporting conservation and sustainable use of biodiversity;
g.	Salaries and preferential terms where mutually agreed;
h.	Research funding;
i.	Joint ventures;
j.	Joint ownership of relevant intellectual property rights.
2.	Non-monetary benefits may include, but not be limited to:
a.	Sharing of research and development results;
b.	Collaboration, cooperation and contribution in scientific research and development programmes, particularly biotechnological research activities, where possible in the Party providing genetic resources;
c.	Participation in product development;
d.	Collaboration, cooperation and contribution in education and training;
e.	Admittance to ex situ facilities of genetic resources and to databases;
f.	Transfer to the provider of the genetic resources of knowledge and technology under fair and most favourable terms, including on concessional and preferential terms where agreed, in particular, knowledge and technology that make use of genetic resources, including biotechnology, or that are relevant to the conservation and sustainable utilization of biological diversity;
g.	Strengthening capacities for technology transfer;
h.	Institutional capacity-building;
i.	Human and material resources to strengthen the capacities for the administration and enforcement of access regulations;
j.	Training related to genetic resources with the full participation of countries providing genetic resources, and where possible, in such countries;
k.	Access to scientific information relevant to conservation and sustainable use of biological diversity, including biological inventories and taxonomic studies;
l.	Contributions to the local economy;
m.	Research directed towards priority needs, such as health and food security, taking into account domestic uses of genetic resources in the Party providing genetic resources;
n.	Institutional and professional relationships that can arise from an access and benefit-sharing agreement and subsequent collaborative activities;
o.	Food and livelihood security benefits;
p.	Social recognition;
q.	Joint ownership of relevant intellectual property rights.

Table 1. Monetary and non-monetary benefits to be considered in bioprospecting agreements (from the Nagoya Protocol)

Under the CBD, there is a clear need to reach agreement with the source of biodiversity on appropriate sharing of benefits arising from any commercialisation. There is also a commitment in the CBD to recognise and protect indigenous knowledge about uses of biodiversity. When it comes to benefit-sharing from commercial developments from such traditional knowledge, agreements can be hard to reach (see Boyd, 1996; Mays & Mazan, 1996). In part, this can be because of a cultural clash, e.g. where traditional knowledge is regarded as communal and not capable of being owned in a Western sense (see Cotton, 1997; Prathapan & Rajan, 2011). There can certainly be arguments over inventorship when the natural products in question are in widespread use, and there are frequent disputes about what constitutes appropriate benefits. In some cultures, monetary returns may have little meaning, and various attempts have been made to set up, for example, charitable foundations to distribute benefits in other ways (Mulholland & Wilman, 2003).
Various access and benefit-sharing agreements have been analysed (Castree, 2003; Mulholland & Wilman, 2003; Medaglia, 2004; Laird & Wynberg, 2008). Clear criteria for success, in either economic or conservation terms, are missing so that it is difficult to reach objective conclusions. It seems to be extremely unlikely that bioprospecting will be a sufficient economic driver to support conservation of biodiversity. Indeed, the case of paclitaxel has been cited to show that a bioprospecting success can lead to negative consequences (Frisvold & Day-Rubenstein, 2008). Bioprospecting should perhaps be examined as an activity with some opportunities for local benefits and one that has to be regulated to make sure that it does not endanger biodiversity or deny fair and equitable benefits to indigenous knowledge-holders.

4. Historical successes in pharmaceutical bioprospecting

Bioprospecting (in terms of seeking leads for new drugs from natural products) can follow two main approaches: use of leads from traditional medical uses (i.e., from "ethnopharmacology"), and use of natural products as a highly diverse set of chemicals for random screening.

4.1 Traditional medicines

Historically, nature was the origin of all medicines (Sneader, 1996), and ethnopharmacology has provided some very notable past successes, including morphine (isolated in 1804), quinine (isolated in 1820), digitoxin (isolated in 1841), ephedrine (isolated in 1897), and tubocurarine (isolated in 1935). These compounds, or their analogues and derivatives, are still in widespread use. A further 50 examples are given by Cox (1994). More recent developments with an association with traditional uses include artemisinin and derivatives for malaria and prostratin as an anti-viral (see, e.g., Kingston, 2011).
The development of a pharmaceutical product (as an appetite suppressant) from the traditionally used South African plants in the *Hoodia* genus was stopped, although the plant moved into development as a food supplement (Laird & Wynberg, 2008; van Heerden, 2008). Unfortunately, the early promise was not upheld and the commercial development rights have reverted to CSIR in South Africa. The approach to the commercial development of Hoodia was a case with inappropriate agreements between the South African research organisation CSIR and commercial development partners: the original agreements did not include the holders of the traditional knowledge, the San people. The absence of any

benefits accruing to the San was subsequently successfully challenged by the South African San Council, and a mutually acceptable agreement was finally reached between the CSIR and the South African San Council after 18 months of negotiations (Wynberg et al., 2009). The more recent efforts to develop a medicinal or dietary supplement product from another plant (*Sceletium tortuosum*) originally used by the San may be instructive: the company involved, HG&H Pharmaceuticals (Pty) Ltd, successfully concluded a prior informed consent benefit-sharing agreement with the South African San Council and was also awarded the first bioprospecting and export permit to be issued by the South African Government (see http://www.zembrin.com/).

There have also been leads from traditional medicines used as the starting point for the development of analogues that become the active ingredients of the final medicinal product. An example is podophyllotoxin, a compound isolated from *Podophyllum peltatum*, a plant used traditionally in North America for treating warts: this stimulated the work that led to the anti-cancer agent etoposide. Other examples can be found in the review by Newman and Cragg (2007), and more details and examples of ethnopharmacological investigations can be found in the books by Chadwick and Marsh (1994) and Cotton (1997). As discussed in the preceding section, accessing natural products used as traditional medicines can lead to many challenges - relating to ownership of intellectual property and benefit-sharing. It is also not necessarily a successful strategy for developing pharmaceutical products, as evidenced by the failure to date of either Shaman Pharmaceuticals or Phytopharm to commercialise new drugs or botanical medicines from traditional medicines.

4.2 Lucky finds

Random screening of natural products does not presuppose the existence of particular biological activities in any set of natural products: it relies on the assay to detect the activity. The key to success is likely to be having the most chemically diverse collection of natural products, and this can be approached by using collections from diverse genetic sources.

Notable successes include the development of cyclosporine A from a fungus (*Tolypocladium inflatum*) collected in Norway, and the development of rapamycin from a microbe (*Streptomyces hygroscopicus*) from Easter Island. The anti-cancer agent paclitaxel was discovered as a result of the National Cancer Institute's large-scale screening of plant extracts (Frisvold & Day-Rubenstein, 2008).

Conservationists have highlighted the fact that 70% of the world's plant species and more than 60% of the world's vertebrate species are found on 1.4% of the land area of the world, and that some of the regions containing the greatest biodiversity are being threatened by development (Mittermeir *et al.,* 1999). The richest regions have been defined as 25 mega diverse "hotspots" on the basis of the number of species found there and the high proportion of endemic species, i.e. those that occur naturally only in that region. The hotspots are shown in Table 2 along with the number of plant species they contain. Collections from areas with high endemism would be expected to yield many unusual compounds. However, apart from INBio's efforts in Costa Rica, there have been no systematic and widespread collections of samples from the biodiversity hotspots for bioprospecting.

Seventy percent of the earth's surface is covered by sea, and the marine environment contains examples of most types of organisms. There may be more than 10 million species of marine macro fauna (Poore and Wilson, 1993) and many more species of marine micro-organisms. There are few marine-based collections for bioprospecting: possibly, those of

Magellan BioScience (www.magellanbioscience.com) in USA and MarBank in Norway. There has been relatively little work on bioprospecting such marine biodiversity, although salinosporamide from a marine bacteria is in early-stage clinical trials and ecteinascidin 743 (trabectedin) from a marine tunicate has been approved in Europe for the treatment of some cancers.

Hotspot	**Plant species**	**Endemic species**
Tropical Andes	45,000	20,000
Penisular Malaysia and Western Indonesia	25,000	15,000
Mediterranean basin	25,000	13,000
Mesoamerica	24,000	5,000
Atlantic Forest, Brazil	20,000	6,000
Indo-Burma	13,500	7,000
Madagascar and Indian Ocean Islands	12,000	9,700
Caribbean	12,000	7,000
Mountains of south-central China	12,000	3,500
Brazilian cerrado	10,000	4,400
Wallacea (Indonesia)	10,000	1,500
Choco-Darien-Western Ecuador	9,000	2,250
Guinean forest, West Africa	9,000	2,250
Cape floristic province, South Africa	8,200	5,700
Philippines	7,620	5,800
Polynesia/Micronesia	6,500	3,300
Caucasus	6,300	1,600
South-west Australia	5,500	4,300
Succulent Karoo, South Africa	4,800	1,860
Western Ghats and Sri Lanka	4,780	2,180
Californian floristic province	4,400	2,125
Eastern arc mountains, Tanzania and Kenya	4,000	1,400
Central Chile	3,400	1,600
New Caledonia	3,320	2,500
New Zealand	2,300	1,865

Table 2. The megadiverse hotspots and their vascular plants. Adapted from the information given by Mittermeier et al. (1999).

New and unusual biodiversity is still being discovered as unusual habitats are being sampled (Harvey 2007). Since this biodiversity has never been available for biological testing, it can be predicted that novel chemicals with potential as drug leads will be discovered if such biodiversity can be accessed for screening. However, this is largely driven by small-scale

academic endeavours. Few companies are currently involved in providing access to biodiversity samples. Table 3 lists companies cited in 2001 as being active in this area (Harvey, 2002). Apart from Albany Molecular Research (AMRI), all have gone out of business or changed strategy. Analyticon still provides screening samples, but these are prepared as synthetic modifications of natural product scaffolds rather than purified natural products.

Company	**Type of natural product**	**Description**	**Current status**
Drug Discovery Ltd, UK	Plant extracts	Worldwide sources 87% of plant families 6,500 species	Not active
MicroBotanica, USA	Plant extracts	Peruvian Amazon 12,000 samples	Not active
BioProspect, Australia	Plant extracts	Western Australian 3,000 samples Untested species	Focusing on product development
Molecular Nature, UK	Plant compounds	Unusual compounds from relatively common plants	Not active
AnalytiCon Discovery, Germany	Compounds	Made to order libraries	Synthetic modifications of natural product scaffolds
bioLeads, Germany	Microbial extracts	45,000 actinomycetes and other microorganisms	Taken over by BioFrontera; now a dermatological company
InterLink Biotechnologies, USA	Microbial samples	33,000 samples	Assets sold; no longer active in bioprospecting
Albany Molecular Research, USA	Microbial extracts	Ex-PanLabs collection of 25,000 microbial species	Now AMRI; expanded to 300,000 samples including marine and plant species
Exalpha, USA	Microalgae compounds	Prefractionated	Now lab test company
Phytera	Marine and plant extracts	Neptune library and ExPAND tissue culture-derived samples	Taken over; no longer active in bioprospecting
Diversa, USA	Microbial gene products	Small molecules from unique gene expression pathways	Now Verenium Corporation; changed to product development based on enzymes
Cubist, USA	Microbial extracts	54,000 partially characterised extracts of fungi and actinomycetes	Focus on clinical development of antibiotics

Table 3. Companies previously active (in 2001) in providing access to biodiversity for drug discovery purposes and their current status.

5. Current practices in bioprospecting

Most bioprospecting is currently performed on a small scale by numerous academic groups throughout the world. There are some larger programmes based on multi-group collaborations. These include the various International Cooperative Biodiversity Groups (ICBG) funded by the NIH in the USA and efforts coordinated by individual universities such as Rutgers in New Jersey and Strathclyde in Scotland. ICBG programmes involve US institutions and commercial companies with overseas participants in Costa Rica, Fiji, Indonesia, Madagascar, Panama, Papua New Guinea, the Philippines, and Vietnam and Laos (Cao & Kingston, 2009; Kingston, 2011). Rutgers University hosts a relatively new initiative: the Global Institute for BioExploration, GIBEX. This is an international network that aims to promote successful drug discovery from biodiversity through developing pharmacological screening methods that can be readily transferred to groups in partner countries (see http://www.gibex.org/). The University of Strathclyde has a long history of research in phytochemistry in collaboration with research groups in institutes overseas. This formed the basis for the creation of a worldwide network for drug discovery based on natural products. A highly diverse collection of plant extracts was assembled (covering more than 90% of the world's plant families) and used in drug discovery screening assays, either with a commercial partner or through collaborations between members of the network (see http://www.sidr.org/).

Very few large pharmaceutical companies have maintained a strong presence in natural product-based drug discovery. Novartis has developed extensive collaborations with a few academic centres in the Far East, notably in China and Thailand. AstraZeneca had a long connection with a group based at Griffith University in Queensland. This continues within the Eskitis Institute (see http://www.griffith.edu.au/science-aviation/eskitis-institute-cell-molecular-therapies). There are smaller specialist companies involved in bioprospecting. These include MerLion Pharmaceuticals in Singapore (http://www.merlionpharma.com/) and Sequoia Sciences in St Louis, Missouri (http://www.sequoiasciences.com/).

A different approach has been developed to make use of the structural diversity of isolated natural products: *in silico* drug discovery or virtual screening. In this, the chemical structures and physico-chemical properties of compounds are gathered in a computerised database that can be searched to find matches either to complement the three-dimensional structure of a drug target or the chemical features of a compound with the desired activity. This has been used at the University of Strathclyde in its Drug Discovery Portal (www.ddp.strath.ac.uk). Chemists can submit structures to the Portal's database and biologists can propose therapeutic targets. Compounds are screened *in silico* by computational chemists within the Portal against the targets and the relevant chemists and biologists are notified of any predicted hits. The chemists then supply compounds to the biologists for testing on real assays against the target. Because chemists can only enter compounds into the Portal's database if they can guarantee that they can supply the compounds and because biologists can only suggest targets if they have relevant assays available, the reduction to practice can be very rapid after the initial *in silico* screening. The unique chemical database is rapidly expanding (currently over 14,500 compounds), with academic scientists from 21 institutions in five continents contributing, and the compounds have been shown to be highly diverse but still generally drug-like in their properties (Clark et al., 2010; Harvey et al., 2010; Schuster & Wolber, 2010). Another approach to using natural products and virtual screening has been developed at the University of

Innsbruck, Austria. Several databases of natural products have been created: a large general natural product database ("NPD") including over 110,000 compounds of molecular weights between 150 and 700, a small database of about 10,000 constituents from medicinal plants mentioned by Dioscorides ("DIOS" database) and a TCM database of about 10,000 compounds known from plants used in Traditional Chinese Medicine (Rollinger et al., 2004; 2009). The assumed advantage of using compounds from known medicinal plants is that they may be less likely to be toxic than randomly sampled constituents.

6. Future prospects

Bioprospecting has been proposed as a potential means to encourage the conservation and sustainable use of biodiversity. The legal framework under the auspices of the United Nations is slowly being implemented by biodiversity-rich countries, but much still needs to be done if there is to be a genuine facilitation of bioprospecting. Perhaps the implementation of the Nagoya Protocol will provide the necessary impetus.

However, the appetite for bioprospecting by pharmaceutical development companies has clearly diminished since the Rio Earth Summit in 1992, partly because of the complexities relating to access and benefit-sharing, often in the absence of adequate national regulatory clarity and institutional capacity. Despite the continuing appearance of successful drug development projects based on natural products, there is a sentiment that this approach may be too old-fashioned to be considered seriously: screening of natural products for new leads. Various technical problems undoubtedly exist with the screening and isolation of natural products, but the rewards for overcoming them would seem to justify the effort required, and technical solutions are being described in the literature. For example, purification and identification of natural products are believed to be difficult and slow: high throughput separation methods coupled with sensitive analytical techniques can resolve this (Bugni et al, 2008; Hu et al, 2008). Natural products are chemically complex: comparisons of the chemical properties of collections of natural products show that they more closely match the "chemical space" of successful drugs than collections of synthetic chemicals (Grabowski and Schneider 2007; Ganesan 2008). Natural products are reputed to give too many false positives on modern screening assays, but phenotypic assays are becoming more and more popular and it has been suggested that natural products, with their drug-like properties, are well-matched to such cell-based approaches, and extracts of natural products can be processed to remove reactive compounds or even convert them into novel drug-like structures (Rishton 2008). Natural products may only be available in small amounts: techniques for direct synthesis (Sunazuka et al, 2008) or production by molecular biology (Kennedy 2008) have been rapidly developing.

While there is certainly no single "best" way to conduct drug discovery, just as there is not a single panacea for all ailments, it is surely time for a fresh look at the relatively unexplored opportunities provided by modern approaches to applying natural products in drug discovery. Perhaps the lead will have to be provided by the numerous academic groups active in bioprospecting. However, these groups would stand more chance of success if they could pool resources and work towards finding validated lead compounds that are likely to be suitable for development into medicines for unmet therapeutic needs. The growth of translational research and the establishment of centres of translational research will enable academic groups to become essential partners in pharmaceutical innovation.

7. Appendix

7.1 Articles 15 and 16 from the United Nations Convention on biological diversity

Article 15. Access to Genetic Resources

1. Recognizing the sovereign rights of States over their natural resources, the authority to determine access to genetic resources rests with the national governments and is subject to national legislation.
2. Each Contracting Party shall endeavour to create conditions to facilitate access to genetic resources for environmentally sound uses by other Contracting Parties and not to impose restrictions that run counter to the objectives of this Convention.
3. For the purpose of this Convention, the genetic resources being provided by a Contracting Party, as referred to in this Article and Articles 16 and 19, are only those that are provided by Contracting Parties that are countries of origin of such resources or by the Parties that have acquired the genetic resources in accordance with this Convention.
4. Access, where granted, shall be on mutually agreed terms and subject to the provisions of this Article.
5. Access to genetic resources shall be subject to prior informed consent of the Contracting Party providing such resources, unless otherwise determined by that Party.
6. Each Contracting Party shall endeavour to develop and carry out scientific research based on genetic resources provided by other Contracting Parties with the full participation of, and where possible in, such Contracting Parties.
7. Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, and in accordance with Articles 16 and 19 and, where necessary, through the financial mechanism established by Articles 20 and 21 with the aim of sharing in a fair and equitable way the results of research and development and the benefits arising from the commercial and other utilization of genetic resources with the Contracting Party providing such resources. Such sharing shall be upon mutually agreed terms.

Article 16. Access to and Transfer of Technology

1. Each Contracting Party, recognizing that technology includes biotechnology, and that both access to and transfer of technology among Contracting Parties are essential elements for the attainment of the objectives of this Convention, undertakes subject to the provisions of this Article to provide and/or facilitate access for and transfer to other Contracting Parties of technologies that are relevant to the conservation and sustainable use of biological diversity or make use of genetic resources and do not cause significant damage to the environment.
2. Access to and transfer of technology referred to in paragraph 1 above to developing countries shall be provided and/or facilitated under fair and most favourable terms, including on concessional and preferential terms where mutually agreed, and, where necessary, in accordance with the financial mechanism established by Articles 20 and 21. In the case of technology subject to patents and other intellectual property rights, such access and transfer shall be provided on terms which recognize and are consistent with the adequate and effective protection of intellectual property rights. The application of this paragraph shall be consistent with paragraphs 3, 4 and 5 below.
3. Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, with the aim that Contracting Parties, in particular those that are developing countries, which provide genetic resources are provided access to and

transfer of technology which makes use of those resources, on mutually agreed terms, including technology protected by patents and other intellectual property rights, where necessary, through the provisions of Articles 20 and 21 and in accordance with international law and consistent with paragraphs 4 and 5 below.

4. Each Contracting Party shall take legislative, administrative or policy measures, as appropriate, with the aim that the private sector facilitates access to, joint development and transfer of technology referred to in paragraph 1 above for the benefit of both governmental institutions and the private sector of developing countries and in this regard shall abide by the obligations included in paragraphs 1, 2 and 3 above.
5. The Contracting Parties, recognizing that patents and other intellectual property rights may have an influence on the implementation of this Convention, shall cooperate in this regard subject to national legislation and international law in order to ensure that such rights are supportive of and do not run counter to its objectives.

8. References

Artuso, A. (1997). *Drugs of Natural Origin: Economic and Policy Aspects of Discovery, Development, and Marketing*. Haworth Press, Binghamton, New York.

BIO-1 (n.d.). Guidelines for BIO Members Engaging in Bioprospecting. Accessed 1 May 2011, Available from http://www.bio.org/ip/international/200507guide.asp

BIO-2 (n.d.). Suggested Model Material Transfer Agreement. Accessed 1 May 2011, Available from http://www.bio.org/ip/international/BIO_Model_MTA.pdf

Boyd, M.R. (1996). The position of intellectual property rights in drug discovery and development from natural products. J. Ethnopharmacol. 51, 17-27, ISSN: 0378-8741.

Brendler, T. & van Wyk, B.-E. (2008). A historical, scientific and commercial perspective on the medicinal use of *Pelargonium sidoides* (Geraniaceae). J. Ethnopharmacol. 119, 420-433, ISSN: 0378-8741.

Bugni, T.S. *et al.* (2008). Marine natural product libraries for high-throughput screening and rapid drug discovery. J. Nat. Prod. 71, 1095-1098, ISSN: 0163-3864.

Butler, M.S. (2008). Natural products to drugs: natural product-derived compounds in clinical trials. Nat. Prod. Rep. 25, 475-516, ISSN 0265-0568.

Cao, S. & Kingston, D.G.I. (2009). Biodiversity conservation and drug discovery: can they be combined? The Suriname and Madagascar experiences. Pharm. Biol. 47, 809-823, ISSN: 1388-0209.

Castree, N. (2003). Bioprospecting: from theory to practice (and back again). Trans. Inst. Br. Geogr. 28, 35-55, ISSN:0020-2754.

Chadwick, D. & Marsh, J. (Eds.). (1994). *Ethnobotany and the Search for New Drugs*. Wiley, Chichester, UK.

Clark, R.L., Johnston, B.F., Mackay, S.P., Breslin, C.J., Robertson, M.N., Harvey, A.L. (2010). The Drug Discovery Portal: a resource to enhance drug discovery from academia. Drug Discovery Today 15, 679-683, ISSN 1359-6446.

Conrad, A., Kolodziej, H., Schulz, V. (2007). *Pelargonium sidoides* extract (EPs® 7630): registration confirms efficacy and safety. Wiener Medizinische Wochenschrift 157, 331-336, ISSN: 0043-5325.

Costello, C. & Ward, M. (2006). Search, bioprospecting, and biodiversity conservation: comment. J. Envir. Econ. Mgmt. 52, 616-625, ISSN: 0095-0696.

Cotton, C.M. (1997). *Ethnobotany. Principles and Applications.* Wiley, Chichester, UK.

Cox, P.A. (1994). The ethnopharmacological approach to drug discovery: strengths and limitations. In: Chadwick, D. & Marsh, J. (Eds.). *Ethnobotany and the Search for New Drugs*. Pp. 25-36. Wiley, Chichester, UK.

Dias, C.C. & da Costa, M.C. (2007). International Cooperation and Bioprospecting in Brazil and Peru. RECIIS - Electronic Journal of Communication, Information & Innovation in Health 1, 121-125 DOI: 10.3395/reciis.v1i1.33en, ISSN: 19816278.

Frisvold, G. & Day-Rubenstein, K. (2008). Bioprospecting and biodiversity: what happens when discoveries are made? Arizona Law Rev. 50, 545-576, ISSN 0004–153x.

Ganesan, A. (2008). The impact of natural products upon modern drug discovery. Curr. Opin. Chem. Biol. 12, 306-317, ISSN: 1367-5931.

Grabowski, K. & Schneider, G. (2007). Properties and architecture of drugs and natural products revisited. Curr. Chemical Biol. 1, 115-127, ISSN: 1872-3136.

Harvey, A.L. (2002) *Natural Product Pharmaceuticals: a Diverse Approach to Drug Discovery*, PJB Publications, Richmond, Surrey.

Harvey, A.L. (2007). Natural products as a screening resource. Curr. Opin. Chem. Biol. **11,** 480-484, ISSN: 1367-5931.

Harvey, A.L. (2008). Natural products and drug discovery. Drug Discovery Today 13, 894-901, ISSN 1359-6446.

Harvey, A.L., Clark, R.L., Mackay, S.P., Johnston, B.F. (2010) Current strategies for drug discovery through natural products. Expert Opin. Drug Discovery 5, 559-568, ISSN 1746-0441.

Hu, J.F., Eldridge, G.R., Yu, Y.H., O'Neil-Johnson, M. (2008). High-throughput natural product chemistry methods and the application of the capillary NMR probe. Progr. Chem. 20, 429-440, ISSN: 1005-281X.

IFPMA (2007). Guidelines for IFPMA Members on Access to Genetic Resources and Equitable Sharing of Benefits Arising out of their Utilization. Accessed 1 May 2011, Available from http://www.ifpma.org/Issues/fileadmin/templates/ifpmaissues/pdfs/2008_05_22_Guidelines_Genetic_Resources_EN.pdf

IISD (2007). ABS-Management Tool. Best Practice Standard. Accessed 1 May 2011, Available from http://www.iisd.org/pdf/2007/abs_mt_standard.pdf

Kaitlin, K.I. (2010). Deconstructing the drug development process: the new face of innovation. Clin. Pharmacol. Ther. 87, 356–361, ISSN: 0009-9236.

Kennedy, J. (2008). Mutasynthesis, chemobiosynthesis, and back to semi-synthesis: combining synthetic chemistry and biosynthetic engineering for diversifying natural products. Nat. Prod. Rep. 25, 25-34, ISSN 0265-0568.

Kingston, D.G.I. (2011). Modern natural products drug discovery and its relevance to biodiversity conservation. J. Nat. Prod. 74, 496-511, ISSN: 0163-3864.

Laird, S. & Wynberg, R. (2008). *Access and Benefit-Sharing in Practice: trends in Partnerships across Sectors*. CBD Technical Series no. 38, Secretariat of the Convention on Biological Diversity, Montreal, Canada.

Lesser, W.H. & Krattiger, A. (2007). Valuation of bioprospecting samples: approaches, calculations, and implications for policy-makers. In *Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices* (eds. A Krattiger, RT Mahoney, L Nelsen, et al.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A. Accessed 1 May 2011, Available online at www.ipHandbook.org.

Li, J.W.-H. & Vederas, J.C. (2009). Drug discovery and natural products: end of an era or an endless frontier? Science 325, 161-165, ISSN: 0036-8075.

Mays, T.D. & Mazan, K.D. (1996). Legal issues in sharing the benefits of bioprospecting. J. Ethnopharmacol. 51, 93-102, ISSN: 0378-8741.

Medaglia, J.C. (2004). Biodiversity for (bio)technology under the Convention on Biological Diversity: bioprospecting partnership in practice. Accessed 1 May 2011, Available online at http://cmsdata.iucn.org/downloads/cel10_medaglia_1.pdf

Mittermeier, R.A., N. Myers, P. Robles-Gil, & C.G. Mittermeier (Eds.). (1999). *Hotspots. Earth's Biologically Richest and Most Endangered Terrestrial Ecoregions*. CEMEX/Agrupación Sierra Madre, Mexico City.

Mulholland, D.M. & Wilman, E.A. (2003). Bioprospecting and biodiversity contracts. Environ. Develop. Econ. 8, 417-435, ISSN: 1355-770X.

Newman, D.J. & Cragg, G.M. (2007). Natural products as sources of new drugs over the last 25 years. J. Nat. Prod. 70, 461-477, ISSN: 0163-3864.

Prathapan, K.D. & Rajan, P.D. (2011). Biodiversity access and benefit-sharing: weaving a rope of sand. Curr. Sci. 100, 290-293, ISSN**:** 0011-3891.

Poore, G.C.B. & Wilson, G.D.F. (1993). Marine species richness. Nature 361, 597-598, ISSN**:** 0028-0836**.**

Rausser, G.C. & Small, A.A. (2000). Valuing Research Leads: Bioprospecting and the Conservation of Genetic Resources. J. Polit. Econ. 108, 173-206, ISSN: 0022-3808.

Reid, W.V., Laird, S.A., Meyer, C.A., Gomez, R., Sittenfeld, A., Janzen, D.H., Gollin, M.A. & Juma, C. (Eds.) (1993). *Biodiversity Prospecting: Using Genetic Resources for Sustainable Development.* World Resources Institute, Washington, DC; Instituto Nacional de Biodiversidad, Santo Domingo de Heredia, Costa Rica; Rainforest Alliance, New York; African Centre for Technology Studies, Nairobi, Kenya.

Rishton, G.M. (2008). Natural products as a robust source of new drugs and drug leads: past successes and present day issues. Am. J. Cardiol. 101 (Suppl.), 43D-49D, ISSN**:** 0002-9149.

Rollinger, J.M., Haupt, S., Stuppner, H., Langer, T. (2004). Combining ethnopharmacology and virtual screening for lead structure discovery: COX-inhibitors as application example. J. Chem. Inf. Comput. Sci. 44, 480-488, ISSN: 0095-2338.

Rollinger, J.M., Schuster, D., Danzl, B., Schwaiger, S., Markt, P., Schmidtke, M., Gertsch, J., Raduner, S., Wolber, G., Langer, T. & Stuppner, H. (2009). *In silico* target fishing for rationalized ligand discovery exemplified on constituents of *Ruta graveolens*. Planta Med. 75, 195-204, ISSN: 00320943.

Schuster, D. & Wolber, G. (2010). Identification of bioactive natural products by pharmacophore-based virtual screening. Curr. Pharm. Des. 16, 1666-1681, ISSN: 1381-6128.

Secretariat of the Convention on Biological Diversity (2002). Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising out of their Utilization. Montreal: Secretariat of the Convention on Biological Diversity.

Secretariat of the Convention on Biological Diversity (2011). Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity. Montreal: Secretariat of the Convention on Biological Diversity.

Simpson, D., Sedjo, R. & Reid, J. (1996). Valuing biodiversity for use in pharmaceutical research. J. Polit. Econ. 104, 163–185, ISSN: 0022-3808.

Sneader, W. (1996). *Drug Prototypes and their Exploitation*. Wiley, Chichester, UK.

Sunazuka, T., Hirose, T. & Omura, S. (2008). Efficient total synthesis of novel bioactive microbial metabolites. Acc. Chem. Res. 41, 302-314, ISSN: 0001-4842.

Van Heered, F.R. (2008). *Hoodia gordonii*: a natural appetite suppressant. J. Ethnopharmacol. 119, 434-437, ISSN: 0378-8741.

Wynberg, R., Schroeder, D. & Chennels, R. (Eds.) (2009). *Indigenous Peoples, Consent and Benefit Sharing. Lessons from the San-Hoodia Case*. Springer, Heidelberg, Germany.

Research in Biodiversity - Models and Applications

Edited by Dr. Igor Pavlinov

ISBN 978-953-307-794-9
Hard cover, 364 pages
Publisher InTech
Published online 12, October, 2011
Published in print edition October, 2011

The book covers several topics of biodiversity researches and uses, containing 17 chapters grouped into 5 sections. It begins with an interesting chapter considering the ways in which the very biodiversity could be thought about. Noteworthy is the chapter expounding pretty original "creativity theory of ecosystem". There are several chapters concerning models describing relation between ecological niches and diversity maintenance, the factors underlying avian species imperilment, and diversity turnover rate of a local beetle group. Of special importance is the chapter outlining a theoretical model for morphological disparity in its most widened treatment. Several chapters consider regional aspects of biodiversity in Europe, Asia, Central and South America, among them an approach for monitoring conservation of the regional tropical phytodiversity in India is of special importance. Of interest is also a chapter considering the history of the very idea of biodiversity emergence in ecological researches.

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen