



Bioprospecting – why is it so unrewarding?

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Abstract. Some economic analyses have placed high values on the chemical diversity residing in threatened habitats [Balick and Mendelsohn (1992), *Conservation Biology* 6: 128–130; Principe (1996), *In Biodiversity and its Importance to Human Health*, Columbia University Press, New York; Rausser and Small (2000), *Journal of Political Economy* 108: 173–206]. Consequently, bioprospecting (searching for new biologically active chemicals in organisms) is considered by some to be a way of funding the preservation of biodiversity, especially in the less developed countries. However, the large multinational pharmaceutical and agrochemical companies spend very little of their research effort on bioprospecting [Cordell (2000), *Phytochemistry* 55: 463–480]. Why is this? The answer lies in the fact that any chemical (whether a synthetic or a natural product) has a very low probability of possessing useful biological activity. The common belief that every natural product has been selected by its producer such that only biologically active natural products are made is not correct. Given that random collections of synthetic or natural products have a similar chance of containing a chemical with specific activity against any one target, and given that synthetic chemicals are nearly always much easier to synthesise on an industrial scale, it is predictable that major agrochemical and pharmaceutical companies will devote only a limited amount of their R & D budget to bioprospecting. Although Rausser and Small (2000) argued that scientific advances will make bioprospecting more cost-effective in future, an alternative scenario is presented where current biotechnological developments will further erode the value of bioprospecting. It is concluded that there should be no reliance on large-income streams being available from bioprospecting agreements to help fund the preservation of biodiversity.

Bioprospecting – the hope

Pharmaceutical drugs currently have annual sales exceeding \$200 billion. It has been estimated that over 25% of the drugs sold in the developed world and 75% in the less developed countries (LDCs) are based on chemicals made by organisms (Pearce and Puroshothamon 1995). These two facts have been given considerable emphasis by those seeking to put the case for conserving biodiversity. Noting that only a small fraction of the chemicals made by plants or microbes has been fully assessed for useful biological activity, it was argued that there was a real commercial value in retaining this unexplored biodiversity in order to preserve the valuable chemical diversity (Eisner 1989; Balick and Mendelsohn 1992; Principe 1996; Rausser and Small 2000). For example, Balick and Mendelsohn (1992), studying the harvesting of medicinal plants from a rain forest, estimated that annual revenues of \$16–61 per ha could be achieved by exploiting the pharmaceutical value of such plants. The general public readily picked up these ideas in a simpler form from the

popular press, which emphasised the possible miracle cancer cures that awaited discovery in rain forests, in coral reefs or in the deep ocean. It was argued that the preservation of these habitats, and the organisms they contain, was a matter of self-interest for the health-conscious wealthy nations. Pearce and Puroshothamon (1995) estimated that OECD countries might suffer an annual loss of £25 billion if 60000 threatened species were actually lost as a medicinal resource. The widely publicised agreement by Merck and Co. to enter into a bioprospecting agreement with the National Institute for Biodiversity (INBio) in Costa Rica in 1991 and a significant investment by Eli Lilly in Shaman Pharmaceuticals seemed to offer verification of the logic of bioprospecting. During the 1990s there was evidence of renewed interest in screening natural products (Reid et al. 1993; Garrity and Hunter-Cevera 1999; ten Kate and Laird 1999). The pharmaceutical companies were not alone in renewing their interest in screening chemicals from the natural world. The US National Cancer Institute (NCI) had screened 200000 extracts of organisms for anticancer activity in the period 1955–1980, with such limited success that they had turned their attention instead to ‘rational drug design’ (Aylward 1995). However, the introduction of improved screening methods (much higher throughputs, lower costs and targeting more specific biological targets) encouraged the NCI to begin screening biological samples again in 1986. By 1995 the NCI had produced 40000 extracts for screening and of the 18000 screened for anticancer activity about 1% showed some positive activity. This renewed interest in plant products as a source of pharmaceutical leads led optimists in the development community to identify an opportunity to build a revenue stream between the rich and the poor countries. The health-conscious, rich countries might be willing to pay the less developed countries for access to their biodiversity (Swanson 1995). Discussions about bioprospecting moved on to consider issues of equity. How could the poor, developing nations negotiate a good deal with the powerful drug multinationals? How could any income stream that was negotiated be targeted at the most appropriate groups within the developing country? Much has been written about these equity issues (ten Kate and Laird 1999; Svarstad and Dhillon 2000), but less about the scientific principles that underpin the basic premise. Are rain forests, coral reefs or pristine oceans a wonderful source of chemical diversity? More importantly, is this chemical diversity likely to contain the next generation of blockbuster drugs?

Bioprospecting – the reality

Drug development is more than drug discovery

Scientific drug discovery is essentially a reductionist extension of herbalism but with one crucial difference. Humans can make chemicals to supplement those that occur naturally. Drug discovery at its initial phase is thus composed of two parts:

- obtaining chemical samples,
- testing the samples for a useful biological effect (often called ‘screening’).

However, the discovery of a potentially useful biological activity by screening is only the first step of a lengthy, expensive process. Each of the following questions must be addressed:

- Will the drug be safe to use? (e.g. are there adverse side effects due to the chemical having more than one effect?)
- Is the drug clinically useful? (e.g. does the effect found in the test tube translate into a positive outcome for the patient?)
- Can the chemical be extracted, synthesised or produced by fermentation on an industrial scale economically?
- Can the drug and its derivatives be adequately protected by patents?
- Is the market big enough to repay the typical >\$500 million development costs for the drug?

Bioprospecting must thus be seen not as an independent process but as a contributor to a larger activity. The fact that so many large, successful pharmaceutical and agrochemical companies spend much more on making and screening synthetic chemicals than they do on isolating and testing natural products suggests that bioprospecting must bring with it disadvantages as well as advantages. The extent of this neglect of bioprospecting is brought into sharp focus when it is appreciated that the much publicised \$1 million bioprospecting investment by Merck and Co. in INBio in 1991 was less than 0.1% of that company's R & D budget for that year. Although evidence has been presented (ten Kate and Laird 1999) as to the extent and value of natural product screening programmes to some pharmaceutical companies, it is sometimes overlooked that the total expenditure on such projects remains at best a very small fraction of the R & D budget of the major companies. Indeed, several major pharmaceutical companies have totally eliminated or scaled down their natural product screening programmes (Cordell 2000). A recent survey of companies involved in bioprospecting concluded that no major pharmaceutical company had found investment in bioprospecting especially rewarding (Macilwain 1998). However, a recent sophisticated economic analysis (Rausser and Small 2000) has suggested that technological advances could increase the success of bioprospecting. Unfortunately, that analysis ignored some fundamental scientific considerations and it is only by appreciating these factors that a realistic evaluation of the potential for bioprospecting can be achieved.

Bioprospecting – the science

Why do some organisms make the kind of chemicals that humans sometimes find useful as drugs?

There are known to be hundreds of thousands of chemicals made by plants and microbes. Every species of plant or the microbe makes its own unique mix of such chemicals. This rich chemical diversity is apparent in the foods we eat daily. It is these secondary metabolites or natural products that produce the tastes and smells

that determine individual food preferences. Apples and pears have different tastes. Bananas and onions have different odours. Why do these plants make different chemicals? The last half of the 20th century saw a consensus emerge as to the answer to this question. It was widely accepted that secondary metabolites or natural products were being made because they possessed a biological activity that enhanced the fitness of the producer (Fraenkel 1959; Chadwick and Whelan 1992; Demain 1995). For example, a soil microbe making an antibiotic could have more exclusive access to resources for its growth if it could inhibit competing bacteria. Likewise, a plant making an insecticide could outperform its competitors if it was less susceptible to insect attack. The appealing concept of a 'chemical arms race' between organisms became the dominant paradigm. It followed from this concept that every plant or microbe would contain some potent biologically active substances. Consequently, plants and microbes should be excellent sources of potent biologically active substances that could have great value to humans (Fellows and Scofield 1995). However, this paradigm is now being undermined by data that ironically come from the pharmaceutical and agrochemical industries.

Screening programmes

After the discovery of penicillin, hundreds of thousands of microbial cultures were screened for their ability to produce antibiotics – the first era of large-scale bioprospecting had begun. The ready availability of soil samples, the ease of culturing at least some microbes from each sample and the simplicity of testing for antibiotic activity made such a large-scale screening viable, despite the very low success rate in finding useful biological activity. However, this huge effort yielded rather fewer antibiotics than predicted by the chemical arms race model (Nisbet 1992). Likewise, the experience of the agrochemical industry was that powerful insecticides and fungicides were not as commonly found in plant extracts as might have been expected – the only major class of agrochemicals that can trace their origin to a natural product are the synthetic pyrethroids. Indeed, the general experience of both pharmaceutical and agrochemical industries was that the very low probability of finding a useful compound among a random collection of chemicals was similar in either collections of man-made or naturally made chemicals. The very low frequency (<1 in 1000) of any chemical possessing potent, specific biological activity is actually predicted by the current understanding of the way in which individual chemicals interact with individual proteins at a molecular level. In order for a chemical in solution at a very low concentration to interact with a protein there must be a very precise three-dimensional (3D) match between the charge distribution on the chemical and that on the surface of the protein (Firn and Jones 2000). The probability of any chemical having the appropriate structure to provide that precise match is very low. Recognising that this fundamental molecular characteristic must have been a serious constraint in the evolution of chemicals possessing biological activity, it was predicted that plants and microbes would have evolved mechanisms to generate and retain chemical diversity (Jones and Firn 1991). Individuals that possessed an ability, after any mutational event, to generate

the greatest sustainable chemical diversity would be favoured. It was also postulated that in order to retain a capacity to generate new chemical diversity, it would be necessary to tolerate the retention of chemicals that possess no current useful biological activity, chemicals that could not play an immediate role in increasing the fitness of the producer (Jones and Firn 1991). A consequence of this model for the evolution of secondary metabolism is that plants and microbes will contain a very large number of chemicals with very weak biological activity. The rich chemical diversity that resides in plants and microbes is not of chemicals selected for potent biological activity, but of chemicals being screened over evolutionary time for a value that very few will have. Organisms that contain a rich diversity of chemicals are not necessarily organisms that will contain a richness of biologically active molecules. Only by appreciating this fact the true potential of bioprospecting can be appreciated.

Enzymes versus chemical reagents – the crucial difference

If one compares the structures of a collection of chemicals made by organisms with structures of chemicals that have been made by humans, the most striking difference is that of structural complexity. Humans, late starters in the art of chemical synthesis, have tended to make huge numbers of chemicals that are relatively simple in structure. Most of the chemical diversity that has been made by humans (80000 different chemicals have been synthesised industrially) comes from making small alterations or additions to fairly simple chemical structures. Humans have only a limited number of chemical tricks (reacting chemical X with chemical Y). The ingenuity of the successful chemist is to combine the right tricks, in the right order, to generate the desired chemical from an available simple starting material. However, as the molecule built by the chemist becomes more complex, it becomes harder to find reagents that are sufficiently selective to bring about only the desired change. Consequently, a very large incentive is needed to embark on a programme of synthesising structurally very complex molecules. Very complex structures are rarely elaborated by humans just on the off chance that they might be biologically active. Indeed, such an ambitious synthetic programme usually only begins after a need has already been established (for example, when it was desired to make more light-stable analogues of the natural insecticide pyrethrin). In contrast to the chemists, organisms use enzymes instead of chemical reagents to bring about chemical transformations. The crucial advantage of using enzymes in biosynthetic sequences is that enzymes can bring about specific structural changes to very specific sites in a complex molecule. This facility of microbes and plants to make structurally complex molecules with relative ease means that humans inevitably find it hard to manufacture natural products. This difference in the chemical complexity between synthetic chemicals and natural products, stemming from a fundamental difference in the methods used to make the chemicals, is crucial to understanding one of the major disadvantages of bioprospecting. When the rare potent, biologically derived chemical is found, it is often so chemically complex that it is hard or

impossible to synthesise economically¹. In contrast, if a synthetic chemical is found to be potentially useful, the chances are good that an economically viable manufacturing process for that chemical, or another biologically active analogue, can be devised. Evidence in support of this logic can be found in the case of the most important naturally derived biologically active compounds that humans utilise – the polyketide antibiotics, including penicillin, streptomycin, etc. These chemically complex molecules are made economically viable because the micro-organisms that make them can be cultured easily under factory conditions and the organisms can be highly selected to increase the yield of desired product. The enzymes produced by the microbes can carry out a synthesis which would be impossible or very expensive using chemical reagents. Thus, bioprospecting in plants or microbes tends to give lead chemicals that have been made using methodologies that are not easily duplicated by humans. The failure to recognise and to account for this severe limitation to bioprospecting undermines the recent economic analysis of bioprospecting (Rausser and Small 2000). In Rausser and Small's analysis the cost of obtaining a chemical to screen was considered to be independent of subsequent development costs, yet it is clear that natural products often bring with them higher manufacturing costs.

A summary of the key fundamental scientific principles underpinning bioprospecting

The majority of natural products found in plants and microbes are unlikely to possess potent biological activity. Such organisms are even less likely to contain specific, potent biological activity that could be usefully exploited for pharmaceutical use. Furthermore, even when a naturally derived chemical is found to give a good lead, the chemical complexity so characteristic of natural products may make commercial production expensive or impossible. A lead compound produced by a microbe offers the best opportunity for the economic production of a natural product

¹ Taxol is an excellent example of a natural product that has great value as a drug, yet is so chemically complex that factory synthesis is not yet economically feasible. Taxol was discovered over 30 years ago in the bark of Pacific Yew trees (*Taxus brevifolia*) where it occurs at only 0.02%. When Taxol was found to be a useful treatment of certain forms of cancer, initially the only source was the bark and removal of the bark, for extraction, killed the tree. The bark from 3000 trees produces only 1 kg of Taxol. To treat ovarian cancer with Taxol in the USA alone would require the destruction of 75000 trees per year. Conservationists rightly worried about harvesting trees on such a scale – the Spotted Owl was considered to be at risk if such harvesting continued. The exploration of other *Taxus* species identified the needles of the ornamental shrub *T. baccata* as a source of a related chemical that could act as a precursor for a close relative of Taxol, hence pressure on the Pacific Yew has decreased. Although synthetic routes to Taxol have been reported, none have been successfully brought into commercial production despite considerable effort. Likewise attempts to grow *Taxus* cells in culture have not yielded an alternative commercial source of the chemical. It is clear that a natural source of a very important drug is not always good news for conservation (Dhillon and Amundsen 2000). Taxol also holds another interesting lesson for us. It is unlikely that Taxol was evolved because of its anticancer properties. The cancers found in animals are not common causes of death or disease in plants. Thus ethnobotanical knowledge could not be a reliable indicator of where to seek such compounds.

because the fermentation industry has extensive experience of optimising the production of fermentation products. Despite considerable effort, plant tissue or cell cultures have yet to prove a commercially viable way of making natural products. Hence, the commercial exploitation of complex plant-derived compounds may be severely limited by high extraction or production costs.

Bioprospecting – is there a future?

Will ecological and ethnobotanical knowledge come to the rescue?

Rausser and Small (2000) propose that the success of bioprospecting will increase as ecological and ethnobotanical knowledge directs the screening effort. Such optimism may be unjustified. Firstly, the chemical interactions between organisms are usually very specific and while a generalised model of such interactions may be constructed, such a model can make no predictions as to which chemicals may be utilised or in which way. The very specificity that has evolved makes generalised exploitation of the knowledge very hard. Secondly, the links between some aspect of ecological knowledge and human health will often be very limited. For example, knowing that plant A is not eaten by insect B hardly helps the making of a judgement as to whether plant A might contain a chemical that could help treat HIV. Even ethnobotanical knowledge can only be of limited help, because the diseases that are common in one society will be uncommon in another – communities with a rich ethnobotanical knowledge might be expected to have a very different age structure, diet and gene pool from the rich, older patients in the developed world. The major pharmaceutical companies seek products that can be sold to the rich; hence ethnobotanical knowledge, of great relevance to the poor, is not always a useful guide when seeking commercially valuable products. Although it has been shown that ethnobotanical knowledge can be used to enhance the success rate of screening natural products in some specific cases (Sheldon and Balick 1995), the mismatch between the health needs of rich and poor countries may leave much ethnobotanical knowledge under-exploited.

Combinatorial chemistry vs. bioprospecting

The low probability of finding a biologically active molecule in any screening trial has prompted two major developments in the pharmaceutical and agrochemical industries. Firstly, chemists have developed quicker and cheaper ways of making diverse collections of chemicals. Combinatorial chemistry recognises that the old goal of a chemist, to devise a synthetic route that led to the maximum yield of one pure product, was not strictly rational if one was seeking to discover any new biologically active chemical. In the initial phases of a screening programme, instead of devising an elegant way of producing a single pure chemical (which has a very low probability of possessing useful biological activity), the combinatorial chemist devises ways of generating as much chemical diversity as possible in the hope that

one of the many compounds generated might be biologically active. The analogy could be the use of the shotgun rather than the rifle in unskilled hands to hit a partly hidden target.

Combinatorial biochemistry

It has been noted by Firn and Jones (1998) that combinatorial chemists are only following the route taken by plants and microbes millions of years earlier when evolution proved the benefits of generating chemical diversity. However, plants and microbes use combinatorial biochemistry because these organisms possess the enzymic abilities discussed previously. There is increasing evidence that some of the enzymes involved in the biosynthesis of the secondary products in microbes and plants can transform a range of substrates into multiple products (Firn and Jones 2000). Consequently, it should be possible to enhance the generation of chemical diversity of an organism by adding to that organism a gene coding for an alien enzymic activity. It does not matter where that gene comes from. It could be derived from a plant, from a microbe or even a mammal (there are non-specific enzymes involved in transformations of substances in the liver, for example). Consequently, bioprospecting can be carried out on laboratory-generated organisms. This laboratory-based bioprospecting on genetically enhanced organisms will have added advantages. It will be possible to use organisms that can be grown easily in the laboratory and which can later be grown economically on a large scale. This strategy for bioprospecting takes into account at the start of the programme the later needs to scale up the synthesis should a useful compound be found. This approach also opens up the huge untapped potential that lies in micro-organisms that currently cannot be grown in the laboratory (Handelsman et al. 1998). Judging microbial diversity in the soil by DNA diversity, there is evidence that 90% of soil microbes have never been grown in culture due to their unknown nutrition needs not being met. However, the DNA of such organisms is now accessible; hence their biochemical capacity to make novel secondary chemicals can be explored by incorporating parts of their DNA into other organisms that can be cultured (Wells 1998). This is bioprospecting in a new guise and one that is based on a random choice of genes rather than a random screen of chemicals (Firn and Jones 1998). The genes that give the useful product are just as likely to be found in an insignificant microbe that will never be identified, let alone grown in culture, as in the most beautiful tropical tree. Furthermore, as our knowledge of the way in which DNA sequences influence protein structure and function increases, it will be possible to engineer the biosynthetic ability of organisms to change their spectrum of biosynthetic capabilities, hence the products they can make.

Conclusions

Prospecting has always tended to enrich the dreams and build up the hopes of some sectors of the community. There is no doubt that there are many exciting, very

valuable chemicals awaiting discovery in organisms but they lie hidden among a much larger number of chemicals that are currently of little human value. The developing understanding of secondary metabolite production suggests that combinatorial (bio)chemistry was evolved by organisms to enhance the chances of finding the rare, potent, biologically active molecule that enhanced the fitness of the producer. Given that humans often have quite different needs to those of other organisms in terms of the types of biological activity that could be beneficial, it is rational for humans to develop and utilise their own high throughput screening programmes to find the biological activity they seek. Once such a screen is operating, the most efficient method of proceeding is to test the widest range of chemical compounds that can be obtained most cheaply, preferably using chemicals that can be made economically on a large scale. It is easier to identify ways by which human knowledge can be used to improve combinatorial chemistry or combinatorial biochemistry in the laboratory than it is to see how knowledge can be used to improve the success rate of bioprospecting in the field.

The scientific realities discussed in this paper underpin the previous economic analyses (Barbier and Aylward 1996; Simpson et al. 1996; Simpson 1997), which suggested that the economic potential for bioprospecting is, and is likely to remain, very limited.

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