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New Medicines Based On Traditional Knowledge: Indigenous and Intellectual Property Rights from an Ethnopharmacological Perspective

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8.1 Introduction

From the perspective of the wider public, the media and the scientific communities, potential new high-value medicines are the most widely recognised and high profile 'benefit' of ethnopharmacological research. This has been expressed very poignantly by Cox (2008):

> 'Ethnobotanical approaches are the oldest, but perhaps most successful, techniques in discovering new pharmaceuticals from biodiversity.'
>
> (p. 272)

Similarly, Schmidt *et al.* (2007) argued:

> 'Indeed, bioprospecting combined with the utilization of indigenous and traditional medical knowledge has been central to the history of the discovery of botanical therapeutics.'

Ethnopharmacology, First Edition. Edited by Michael Heinrich and Anna K. Jäger.

On the other hand, the use of indigenous and traditional knowledge in such projects has been criticised by a range of researchers, as exemplified by Isla (2007), who argues from what she calls an 'ecofeminist' perspective:

> 'This perspective understands the current triumphant neoliberal agenda as a continuation of a long history of capitalist, patriarchal, and racist colonization of women, peasants, indigenous peoples, land, and nature. So much of the accumulated capital was expropriated from these groups that a great deal of what counts as economic growth has been and continues today to be simply the transfer of local and communal wealth into external markets. Their subsistence production is both necessary to capital and necessary to their own survival and is taken through capitalist patriarchal violence.'

This critique has been embedded in a more fundamental critique of the legal and economic aspects of protecting intellectual property (e.g. Mgbeoji, 2006) as well as being based on a critique of the lack of respecting existing values recognized by local communities:

> 'The "decontextualization" of the "components" of biodiversity or culture results in the unauthorized extraction of inalienable information and materials. This ignores the "sacred balance" between all life, and violates the kinship relationships that indigenous and traditional peoples maintain with their "extended family" of all living things.'
>
> (Posey, 2002a)

In essence there is no way to reconcile such fundamentally diverging views and this chapter will not try to achieve this. Instead it will look at the direct responsibilities of researchers in the context of ethnopharmacological and bioprospecting work, and discuss examples of compounds or extracts that have been developed up to a clinical level. The focus of this brief overview is therefore on the researchers' responsibilities in a context as it has been outlined by many, including, for example, Shiva (2007), who also takes a critical view and offers what fundamental requirements need to be fulfilled:

> 'The bioprospecting paradigm needs to be examined in the context of equity, specifically its effect on the donor community, potential recipient communities, and bioprospecting corporations. Even though bioprospecting contracts are based on prior informed consent and compensation, unlike the case of biopiracy where no consent is taken and no compensation given, not all owners/carriers of an indigenous knowledge tradition are consulted or compensated. Not only does this lead to inequity and injustice but it also has the potential of pitting individual against individual within a community and community against community.'

8.2 The legal framework

Without doubt today's ethnobiological research and any other research involving the use of the biological resources of a country are based on agreements and permits, which in turn are based on international and bilateral treaties. The most important of these is the Convention of Rio or CBD, which provides a framework for research and development (R&D) based on biodiversity at an international level (Secretariat of the Convention on Biological Diversity, 2001):

> 'The objectives of this Convention, to be pursued in accordance with its relevant provisions, are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of the benefits arising out of the utilisation of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding.'
>
> (Secretariat of the Convention on Biological Diversity 2001)

This defines the rights of countries (i.e. internationally) and as such is directly relevant in the context of international R&D projects on biodiversity (including local and traditional knowledge). The rights of indigenous peoples and other keepers of local knowledge is clearly stated in article 8j:

> '(j) Subject to its national legislation, respect, preserve and maintain knowledge, innovations and practices of indigenous and local communities embodying traditional lifestyles relevant for the conservation and sustainable use of biological diversity and promote their wider application with the approval and involvement of the holders of such knowledge, innovations and practices and encourage the equitable sharing of the benefits arising from the utilization of such knowledge, innovations and practices.'
>
> (Secretariat of the Convention on Biological Diversity 2001)

This and the subsequent treaties significantly changed the basic conditions for ethnopharmacological and bioprospecting research. Countries that provide resources for natural product research and drug development have well-defined rights, which specifically include sharing benefits that may potentially arise from such research.

Numerous other agreements (including most recently the Nagoya Protocol of 2010, http://www.cbd.int/abs/about/, which aims to ascertain the 'fair and equitable sharing of benefits arising out of the utilization of genetic resources (Article 1)' or trade-related aspects of intellectual property rights (TRIPS), World Trade Organization (WTO) agreements, cf. www.wto.org) now form a complex framework of regulations and it is the general consensus in major academic circles that their implementation is an essential foundation of any form of ethnopharmacological and related research.

The debate about access rights and benefit sharing dates back to well before these international conventions and several learned societies played a crucial role in its development and later implementation. As pointed out many times, 'there is an inextricable link between cultural and biological diversity'. This principle was first formulated at the First International Congress on Ethnobiology in Belem in 1988. No generally agreed on standards have so far been accepted, but the importance of obtaining the informants' prior informed consent and ascertaining appropriate benefit-sharing agreements has been stressed by numerous authors (e.g. Posey, 2002b), even though the exact requirements of such arrangements sometimes remain contentious.

8.3 Industrial research in an ethnopharmacological context

While there is a fundamental academic consensus on the ethical foundations of research, research in the context of commercial development is both complex and driven by a wide range of stakeholders and factors. Firstly, while this chapter and the entire book focuses on the academic field of ethnopharmacology, the borderline to what is called 'bioprospecting' is blurred. Traditionally ethnopharmaoclogy is defined as a scientific approach that focuses on the 'exchange of information and understandings about people's use of plants, fungi, animals, microorganisms and minerals and their biological and pharmacological effects based on the principles established through international conventions' (*Journal of Ethnopharmacology* 2014). The goal is often seen to evaluate traditional and local medicines with the idea to contribute to a more evidence-based use of such medicines in the context of the respective cultures of origin (Verpoorte, 2012). On the other hand, the 'transformation of traditional medicines into modern drugs' (Corson and Crews, 2007) and into other higher

value products directly targeted to the rich markets is a reality in an ever-increasing number of countries, including in Europe, North America, Australia/New Zealand and more recently in fast-growing markets in Asia, South America and Africa. While a lot of attention has been paid to new medicines, there also is a rising demand for new healthcare products like nutraceuticals, cosmetics and high-value foods.

Industrial R&D generally works on fundamentally different principles in terms of the key criteria used to develop a new product. The specific criteria vary in the various sectors of industry and between companies, but there is a set of common principles relevant in the industry that are used as decision points to decide whether a project (e.g. on a specific species) should be taken forward or not (so-called go/no go decisions):

- First and foremost, industrial R&D will always focus on projects that avoid any form of obstacles that may result in problems with the development of a product into a commodity. These problems range from problems with the long-term and large-scale supply of material (a common problem with natural products and less often of concern with synthetic compounds) and possible concerns about toxicity and other risks, to concerns about the acceptability of the final product. The supply problem may, for example, be due to problems associated with securing sufficient quantities of the starting material, but also pre-existing claims, for example based on local or traditional use.
- The protection of the intellectual property (IP) for the company is, of course, a central requirement for any industrial R&D project. Ideally this IP should be a new chemical entity with a new biological–pharmacological activity, but there are also weaker patent claims a company may want to consider (see chapter 9, A. Hesketh).
- An industrial drug or nutraceutical development is a unidirectional process, which, for example in case of medicine development, goes from early preclinical research to advanced studies focusing on safety and formulation science, and then into the various stages of clinical development (and is because of its unidirectionality often called a 'pipeline').
- Ideally such a new product should offer a unique selling point to the company which allows them to position themselves in a key market (see below).
- From an industrial perspective the demands of key markets result in a very different set of diseases, which are of primary relevance. In general terms chronic, degenerative conditions and diseases are more important than the acute diseases often at the centre of ethnopharmacological research.
- Any R&D activity for a product will have to fit into the wider strategy of a company for developing a certain sector of a market, therefore very potent pharmacological effects not relevant to the core economic areas of a company may well result in the ending of a project.
- Importantly, a specific local or traditional use of a species is generally *not* central to a company's strategy, aside from possibly at a later stage, for marketing purposes, especially in case of supplements and cosmetics (with a few exceptions of companies that consciously want to develop products based on local and traditional uses).

Relatively little is known about a specific industrial project prior to reaching the level of wider commercialisation. Commercial secrets generally cover all aspects relating to specific arrangements for benefit sharing and commercial development. This situation is made more complex by the fact that many of the R&D projects are managed or driven by small enterprises, which often are very reluctant to share information. The best approach is therefore to assess examples of natural products that either were brought to the market or got close to getting a full marketing authorisation.

8.4 Some case studies

Several examples of pure chemical entities (prostratine, peplin, galanthamine) and mixtures (Sangre de drago or *Croton lechleri* Müll.Arg. and Hoodia) are discussed in this section. The most famous example, artemisinin, obtained from Chinese *Artemisia annua* L., shows what can be achieved and this development has been reviewed and discussed widely (e.g. Hsu, 2006, 2010). Its development predates the CBD and is therefore not discussed here. This discussion is not about success in scientific and R&D terms, but the way indigenous and local intellectual rights were taken into account or not. Consequently, the focus is on:

- the evidence for links between local/traditional knowledge and drug development
- the mechanisms put in place to ascertain benefit sharing (if any)
- the benefits for local communities arising from it
- the problems and challenges.

Excluded are substances that were discovered as a part of a larger screening effort which did not incorporate an ethnopharmacological element, and drugs that were developed well before the implementation of the CBD. Consequently, there are only limited examples that can be used to analyse the success of ethnopharmacologically driven drug developments.

8.4.1 Pure natural products as drug leads

A promising lead derived from *Homalanthus nutans* (G.Forst.) Guill. (Euphorbiaceae), a small rainforest tree used by Samoan healers to treat hepatitis, is currently considered for clinical development in the treatment of HIV/AIDS. Its extracts exhibited potent *in vitro* anti-HIV activity. It yielded a unique non-tumor-promoting protein kinase C (PKC) activator, prostratin, a 12-deoxyphorbol ester, which showed strong anti-HIV-1 effects (Figure 8.1). The compound was first isolated and its structure reported in 1992 at the time of the implementation of the CBD. Prostratin effectively activates HIV gene expression in latently infected Jurkat cells and acts by stimulating IκB kinase (IKK)-dependent phosphorylation and degradation of IκBα, leading to the rapid nuclear translocation of NF-κB and activation of the HIV-1 long terminal repeat. Ultimately, it has been postulated that prostratin induces the HIV virus to leave cells and thus makes a silent virus accessible to other medication. Prostratin has been licensed to the NCI as a candidate drug for treating AIDS/HIV. The inventors made the commitment that

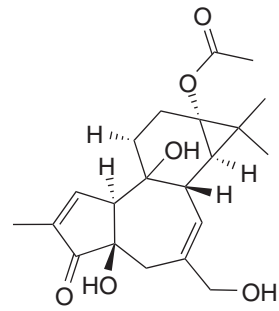


Figure 8.1 Structure of prostatin.

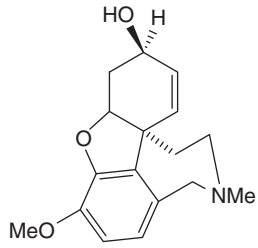
20% of the potential license income shall be returned to the Samoan people if a product based on this compound reaches the market. Prior to such a marketing authorization funds were also made available to the community in order to support schools, medical clinics, water supplies, trails, an aerial rainforest canopy walkway and an endowment for the rainforest. However, the exact amount that became available in the region of origin is unknown and since the product has not reached the market it is likely to be low (Cox, 2001, 2008; Heinrich, 2013). To date no clinically used product has been developed and, therefore, no socioeconomic benefits have been derived from prostatin.

The second example offers fascinating insights into the complexity of ethnopharmacology-based drug discovery. In 2012, a gel containing 0.015% or 0.05% peplin or ingenol mebutate (Picato®), an unusual diterpene ester, isolated from *Euphorbia peplus* L., petty spurge (Euphorbiaceae), was licensed for use in actinic keratoses on the face, scalp, trunk and extremities. Clinical research into other cancers (bladder, intravesicular; leukemia, systemically) are ongoing. The research was started by an Australian company in Brisbane (Peplin Ltd), which in 2009 was bought by the Danish pharmaceutical company LeoPharma.

E. peplus is a weedy species native to Europe, where it is widely distributed and particularly common in gardens and other disturbed environments. As part of European migration it became a common weed in many temperate to warmer regions of the world. Local and traditional uses of the species in Europe, most notably in the treatment of warts and other skin conditions, have been well documented and span many centuries. In fact the species is included in many of the classical early 16th century herbals. However, the discovery of its medicinal potential goes back to uses of the species saps in the Brisbane region of Australia. During the 1970s and 1980s, members of the Australian public used the sap from *E. peplus* to treat skin cancers and solar keratosis (Green and Beardmore, 1988; Wheeton and Chick, 1976). This is based on only eight use reports from a total of 2095 respondents who returned the survey. However, this made *E. peplus* the second most popular plant within this survey with *Aloe vera* having 35 reports (Green and Beardmore, 1988) and a total of 164 persons indicating self-treating/ment of skin cancers and solar keratoses. Although this is a relatively small number, it clearly served as a starting point to investigate the species' medical effects (Ogbourne *et al.*, 2007), proving that this R&D project was clearly ethnopharmacologically driven. *In vitro* and *in vivo* evidence led to the establishment of a well-defined mechanism of action and clinical trials proved its effectiveness (Lebwohl *et al.*, 2012). Interestingly, in this case questions relating to the CBD and to benefit sharing were never raised and the author is not aware of any claims relating to the use of this species in the development of a medicine.

A third example, Galanthamine (syn. galantamine), is an anti-Alzheimer's drug developed in the 1990s and initially isolated from *Galanthus* and *Leucojum* species as well as other members of the Amaryllidaceae (Figure 8.2). Its history has been reviewed in detail (cf. Heinrich and Teoh 2004; Heinrich 2010). The initial idea for developing a medicine (in this case in the treatment of poliomyelitis) firstly from *Galanthus woronowii* Losinsk. seems to be based on the local use in far Eastern Europe. According to unconfirmed reports, in the 1950s the common snowdrop growing in the wild was used to ease nerve pain by rubbing it on the forehead, but without more ethnobotanical data these claims are impossible to assess.

The early development of galanthamine in Eastern Europe for use in the treatment of poliomyelitis started with the alkaloid's isolation from the garden snowdrop (*Galanthus* spp., most notably *G. woronowii*), but today the compound is obtained from other members of the same plant family, such as the daffodil (*Narcissus* spp.) and the snowflake (*Leucojum* spp., esp. *L. aestivum L.*), as well as, most importantly, being made synthetically.



6 Galanthamine

Figure 8.2 Structure of galanthamine.

Based on unconfirmed reports, in the Caucasian mountains region snowdrops were used to treat poliomyelitis but no reference is made to the traditional use of snowdrop in the Caucasian region by the Russian authors who published the initial papers on this topic (Heinrich, 2010). However, all this is based on very few secondhand reports on the use of snowdrops prior to the development of galanthamine as a licensed medicine. Despite the lack of precise data on local and traditional uses of this species it is highly likely that this development process for a new antipoliomylitis drug is based on such information. It is therefore an example of the successful ethnobotany-driven development of a natural product into a clinically important drug. At the same time it throws a spotlight on the difficulties of establishing the link between local and traditional uses and drug development. The initial commercial R&D (in the 1950s in the Soviet Union and other Eastern Block countries) is focused on the drug's effect on the peripheral nervous system, while later research targeted similar enzymes in the CNS (acetylcholine esterase, AchE). Interestingly, local and traditional use gave an essential initial idea, but at this point the evidence for where the initial ethnobotanical information came from remains scanty, pointing to the need not only to fully record such knowledge, but also to make this information publicly available.

8.4.2 Extracts and partially purified preparations as drug leads

Most drug development programmes focus on pure compounds and the following examples highlight some of the specific challenges of industrial projects based on ethnopharmacological data. In 2012 a product based on *Croton lechleri* Muell. Arg., Sangre de drago (Euphorbiaceae), a Peruvian rainforest plant commonly used in its region of origin for a variety of diseases, including for the treatment of diarrhoea, was licensed as a medicine to treat HIV/AIDS-associated diarrhoea. In the Amazon this species is well known for treating gastrointestinal problems. A semi-purified proanthocyanidin oligomer mixture from *C. lechlerii* was initially shown to have broad activity against a variety of RNA and DNA viruses (Ubillas *et al.*, 1994). Later on it was shown to modulate chloride and fluid secretion in the gastrointestinal tract (Gabriel *et al.*, 1999; Cottreau *et al.*, 2010; Tradtrantip *et al.*, 2010). In terms of the R&D, there can be no doubt that the development of this medicine was based on local and traditional knowledge. Its development was initiated by Shaman Pharmaceuticals, a California-based small company dedicated to developing new medicines based on the principles of benefit sharing not only once a product is on the market but also during its development (Wells, 1998). The company was active from 1989 until 1999, when it stopped

R&D on new pharmaceutical entities and was taken over by Napo Pharmaceuticals, which in 2005 and 2008, respectively, licensed it to Glenmark Pharmaceuticals (India) and Salix Pharmaceuticals (USA) for exclusive commercialisation in in different countries. It remains unclear whether benefits are currently being paid to the countries or regions of origin.

A now classical example of a failure to develop a new high-value product is the Southern African species *Hoodia gordonii* (Masson) Sweet ex Decne (Apocynaceae), from which two hunger-suppressing pregnane glycosides were isolated and that was patented in 1998 (for details see Heinrich, 2013) (Figure 8.3). The appetite-suppressant effect of the plants extracts had already been established in 1983. At least since the 19th century it was known that this desert plant quenches thirst, e.g. as recorded for the Khoi-San people, but it seems to have been known also in other groups.

This research was initiated and driven by the Council for Scientific and Industrial Research (CSIR) of South Africa. A small British company (Phytopharm) obtained the rights and the extracts were investigated for hunger-suppressant and later antidiabetic effects. In 1998 clinical studies for treating obesity were started and the extract was licensed to Pfizer, with the goal of developing a fully licensed medicine on the basis of a characterized extract with a defined amount of the active metabolites for the treatment of obesity. After a considerable investment in clinical and preclinical research, in July 2003 Pfizer unexpectedly returned the license to Phytopharm. In late 2004, Unilever stepped in with the strategic goal of developing a slimming food but in 2008 this R&D was stopped, too. An important element in this decision

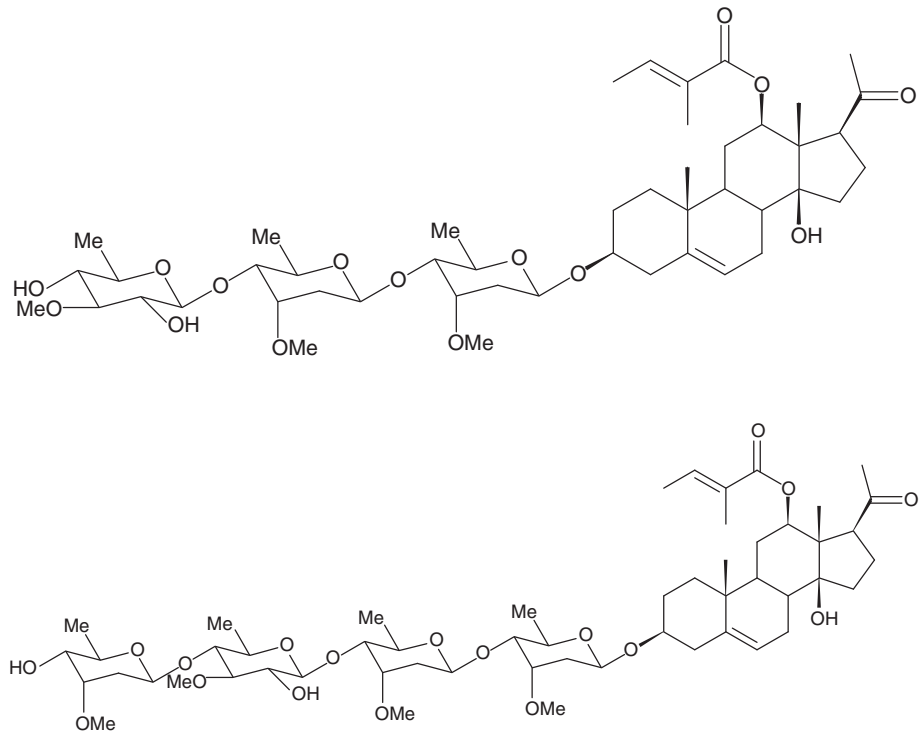


Figure 8.3 Structures of the two hunger-suppressing pregnane glycosides isolated from *Hoodia gordonii* (Masson) Sweet ex Decne (Apocynaceae).

were concerns about the product's safety. Today only unlicensed products of very doubtful composition and quality are on the market. This is linked to the non-existent regulatory basis of these products, but also to problems with the supply of a wild-harvested slow-growing desert species.

Without doubt this development was driven by ethnpharmacological considerations, and, interestingly and worryingly, the IP had been patented and developed without the prior consent of the Khoi-San people. Only in 2004 was a benefit-sharing agreement signed between the Khoi-San and CSIR. This is one of the first benefit-sharing agreements and it would have given the Khoi-San a share of royalties derived from the sale of products containing the patented extract if a product would have been developed on the basis of this knowledge (see Heinrich, 2013).

8.5 Conclusions

While there certainly is a wide recognition that drug development based on ethnopharmacological studies possesses considerable potential, as in all other drug discovery programmes the chances for developing a new product that ultimately makes it to the market are very slim indeed (Amirkia and Heinrich, 2015). This is not only linked to the intrinsic challenges of the drug discovery process, but also to some very specific aspects of natural product and ethnopharmacological research:

- The supply of the starting material and the sustainable extraction of a compound depends on a multitude of factors and most successful programmes are focused on either widely distributed plants (weeds) or compounds for which an economically viable synthesis was developed.
- There is not necessarily a direct link between local/traditional uses and the key targets in drug discovery. It is well known that local/traditional medicines are commonly used for acute and often infectious conditions, while most of the commercial drug development activities are focused on diseases like diverse cancers or chronic, aging-related conditions.
- The multidisciplinary expertise required for such ethnopharmacology-driven drug development programmes and the willingness in the relevant industries to support commercial projects with an uncertain supply chain is lacking
- The advent of 'biologicals', i.e. pharmaceuticals derived from research in molecular biology and pharmacological biochemistry, offers an attractive alternative to such a 'classical' approach.

Ethnopharmacologically driven research generally has much more non-commercial, scientific and social benefits (Heinrich *et al.*, 2014) and these should be at the centre of attention. Not discussed in this context are food supplements and other healthcare products, which are developed under very different frameworks, especially in poorly regulated markets. Here concerns continue both about the products' quality and the risks of non-sustainable, often short-term product cycles. This chapter has focused on the period since about 1992 and highlighted that industrial development offers unique opportunities for ethically based drug development. It also shows that major debates continue about the benefits of such an approach. Clearly, in the long run the development of new medicines that is conducted in a highly regulated environment offers some opportunities for achieving sustainable partnerships and for improving health care.

Note

The development of new medicines has been an ongoing interest of mine and the ideas presented here have developed over many years. Some were discussed in more detail previously (especially in Heinrich, 2013; Heinrich and Teoh, 2004) and this work presents a new synthesis of these concepts.

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