Frog tales – on poison dart frogs, epibatidine, and the sharing of biodiversity

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Abstract

Epibatidine is an alkaloid originally extracted in the 1970s from the skin secretions of a tiny poison frog from Ecuador. Today it is a major research tool in the development of analgesics, and several epibatidine derivatives are promising drug leads. Unsurprisingly, the relationships between the Ecuadorian state and local communities on the one hand and the drug companies on the other have been contested for several years, owing to claims of traditional use concerning the frogs' poison. Although this case can hardly be considered biopiracy, it presents great difficulties in determining whether traditional knowledge has been used, as well as the problems involved in applying the access and benefit-sharing regulations of the Convention on Biological Diversity. This article highlights that research objects tend to be unstable, compared with the rather static assumptions of

intellectual property rights and other legal frameworks concerning the use of biodiversity.

Keywords

- bioprospecting,
- drug discovery,
- epibatidine,
- traditional knowledge,
- access and benefit-sharing

Introduction

With “sweat and serendipity” – and several hundred poison-frog skins from Ecuador – John Daly and his colleagues opened up an entirely new area of research in the development of analgesics, according to the title of Gillis's homage to “frog man” John Daly (Gillis 2002). The relationship between Ecuadorian frogs and drug discovery stems from Daly's bioprospecting activities in the 1970s, which ultimately led to the development of epibatidine, an alkaloid with enormous potential as an analgesic. Although the idea of using nicotine as a painkiller dates back at least to 1932 (Davis *et al*. 1932), there had been hardly any research on analgesic compounds like epibatidine – antagonized by nicotinic rather than opioid receptors, contrary to the majority of available painkillers – before Daly and Myers collected about 750 frog skins in southern Ecuador in 1976. They extracted a highly toxic alkaloid from the poison in the skins and eventually determined the chemical structure of the alkaloid, then named epibatidine,2 in 1991 (Daly *et al*. 2000; McCurdy and Scully 2005). Whereas the sweat evoked by Gillis alludes to images of heroic explorers looking for unknown treasures in the most remote regions of the planet, serendipity seems to be at the very heart of Daly's and Myers’ endeavor. To begin with, the researchers did not find a species that *always* secretes highly bioactive alkaloids – the frogs they collected actually belong to a population of *Epipedobates anthonyi*, which happens to be able to secrete poison accumulated from a dietary source whose identity remains uncertain, although probably an arthropod species (Darst *et al*. 2005; Daly 1998). Furthermore, Daly and Myers managed to store their small and irreplaceable sample of the alkaloid for almost 15 years before elucidation of its chemical structure finally became possible owing to improved instrumentation. Nonetheless, accounts emphasizing the scientists’ serendipity and the tremendous impact of epibatidine and its derivatives on drug development notoriously neglect issues concerning the contested origin of epibatidine and its implications for the regulation

of the use of biodiversity, especially regarding the feasibility of access and benefit-sharing (ABS) regimes. Quite often, for example, there are claims that traditional use of the frogs' secretions as a dart poison pre-dates Daly and Myers's discovery (Martinez-Alier 2002), although it is almost impossible to prove that traditional knowledge[3] guided their efforts. In light of these contentious issues surrounding the collected frogs, their poison, its uses in drug discovery and the arising benefits, this article attempts to analyze what the epibatidine case can tell us about the investigation and use of biodiversity, and about what it means to use or access so-called "traditional knowledge". After presenting a brief chronology of the epibatidine case, the present paper highlights some delays and "speed-ups" in the process of transforming the alkaloid into a drug lead, particularly with regard to their consequences for the regulation of the uses of biodiversity – technologically enabled, nonlinear, "suspended" transactions (Parry 2004a) that enormously complicate any effort to regulate, control and monitor the "fate" of collected biological materials (Parry 2000). Additionally, this study discusses the local variations of biodiversity on a subspecies level that played a decisive role for the development of epibatidine, before finally analyzing the significance of traditional knowledge for the development of epibatidine. As has been mentioned above, it will be shown that it is extremely difficult to measure precisely the impact of traditional knowledge in this case, a point that probably has generalized validity for many cases of bioprospecting. Since the collection of the frogs in Ecuador took place in the 1970s, a long time before the Convention on Biological Diversity (CBD) was negotiated and ratified, *de jure* one cannot expect compliance with the ABS framework established by the CBD in this case. However, it might be interesting to take a closer look at the epibatidine case with regard to benefit-sharing policies since, even if the frogs were hypothetically collected today (and not brought to the United States, a country that has signed but never ratified the CBD and thus does not have any ABS obligations under the CBD[4]), it would be extremely difficult to assure robust benefit-sharing agreements. This is mainly because epibatidine is more a research tool than a substance of direct commercial value, and the status of derivatives remains unclear even after the recent adoption of the "Protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization" at the tenth conference of the parties of the CBD at Nagoya, Japan (Secretariat of the Convention on Biological Diversity 2011). Finally, the several changes and ambiguities in the frogs' taxonomy during the last 20 years will show that research objects tend to be unstable and subject to continuous modifications, thus undermining the rather static assumptions of legal regimes like the CBD or intellectual property rights, and complicating their application in the regulation of the uses of biodiversity. This study analyzes the epibatidine case by reviewing the relevant literature (especially natural product and drug discovery journals) and using results of some field work undertaken in Ecuador.

The discovery and development of epibatidine – a brief chronology

Daly and Myers were among the pioneering scientists in the research field of analyzing biological activity of alkaloids in frog skin after several field trips to western Colombia in the 1970s, which led, among other results, to the discovery of batrachotoxin alkaloids from poison-dart frogs like the dangerously toxic *Phyllobates terribilis*, the most toxic vertebrate species worldwide (Myers *et al*. 1978; Daly *et al*. 2000). They went on an initial exploratory field trip to southwestern Ecuador in 1974, and the trace frog skin alkaloid they managed to extract from skins of *E*. *anthonyi* proved to be so promising that they decided to return for a further collection in order to obtain more extracts required for isolation and structure elucidation – the analgesic potency of the trace alkaloid had turned out to be 200-fold greater than morphine! They also assessed the *in vivo* effects of the alkaloid by injecting it in mice, which were observed to arch their tails over their backs, an effect known as "Straub tail reaction" and typical for opioid alkaloids. So when they returned to Ecuador in 1976 for more of the so-called "Straub tail alkaloid", they hoped to detect a novel and very potent opioid structure in the frog poison. However, the frogs at one of the previous lowland collection sites had disappeared and the skin secretions of a population of the same species at a banana plantation contained no alkaloids. At a highland collection site, on the other hand, they were able to obtain skin extracts from 750 frogs, which yielded 60 mg of a mixture of alkaloids upon their return to Daly′s laboratory at the National Institutes of Health (NIH). Yet from this alkaloid cocktail no more than 500 µg of relatively pure "Straub tail alkaloid" could be obtained. Surprisingly, the analgesic activity of the alkaloid was not due to agonist activity at opioid receptors. Indeed, the exact mechanism of action could not be detected since the sensitivity of nuclear magnetic resonance (NMR) spectrometers at that time did not suffice to allow structure elucidation with the very small available trace sample – Daly and Myers had to return once again to Ecuador for more frog skin extracts. On subsequent field trips in 1979 and 1982, however, they were not as lucky as before and only found frogs with insignificant amounts of alkaloids in their secretions, whereas frogs raised in captivity were completely alkaloid-free, thus reinforcing quite early the hypothesis of a somewhat rare dietary source as the origin of the alkaloid. Apparently, the frogs do not produce the alkaloid by themselves but rather accumulate it from a dietary source only available at certain sites (Daly *et al*. 2000). Furthermore, in 1984 all frogs from the *Dendrobatidae* family (to which *E*. *anthonyi*

belongs) were listed in Appendix II of the Convention on International Trade in Endangered Species (CITES), thus putting an end to any further major collection that would be required to obtain enough raw material to define the molecular structure of the highly potent alkaloid Daly and Myers had discovered (Daly 1998). In the end, their alkaloid sample had turned out to be as promising as it was irreplaceable and, above all, not suitable for further research until structure elucidation could be accomplished or more frog skins obtained. Their only option was to store the sample and to contest the restrictions imposed by the CITES that "have greatly hindered further research on alkaloids from such brightly colored frogs" (Daly *et al*. 2000, p. 132) "even though such frogs are often incredibly abundant" (Daly 1998, p. 169).

In 1990, however, things started to change: the sensitivity and power of NMR spectrometers had advanced to such an extent that Daly and his colleagues dared to convert the unique sample of the alkaloid into a solution and to subject it to NMR analysis. The wagered analysis finally provided the molecular structure of the alkaloid now called "epibatidine"; the structure elucidation was reported in 1992 (Spande *et al*. 1992), and on 3 March, more or less at the same time, a patent on "Epibatidine and derivatives, compositions and methods of treating pain" was filed by Daly *et al*. (1994). Soon afterwards, several syntheses of the alkaloid were reported (Olivo and Hemenway 2002) and epibatidine's mechanism of action was determined – the analgetic activity is blocked by mecamylamine, a nicotinic antagonist (Badio and Daly 1994), not by opioid antagonists as in the majority of other analgesics, thus potentially reducing the risk of dependency and other undesirable side-effects of opioid analgesics. In spite of being too toxic for use in humans, epibatidine "has had a tremendous impact on research on nicotinic receptors and function" (Daly 2003, p. 447). It opened up an entire area of drug research that had been relatively unexplored before, and several epibatidine derivatives are promising drug leads, even though none of them has reached the prescription drug market yet (McCurdy and Scully 2005). One synthetic epibatidine-derivative, ABT-594, developed by Abbot, even generated some media excitement after the initial report in *Science* (Bannon 1998): TV crews asked for permission to shoot videos of the frogs at Abbott and were disappointed to learn that the pharmaceutical company did not have a frog colony but had actually developed a derivative of a synthesized version of an alkaloid extracted by Daly and Myers from frog poison years ago (Daly *et al*. 2000). Clinical trials of ABT-594 as an analgesic have been discontinued after completing phase II clinical tests, owing to gastrointestinal side effects (Cassels *et al*. 2005), but there is still "hope for the development of a "next generation" of drugs based on the epibatidine pharmacophore" (Jones *et al*. 2006, p. 257).

Delays, breakthroughs and suspended transactions

This brief chronology illustrates that the history of epibatidine has been full of delays and "suspended transactions", a concept Parry (2004a) introduces in her analysis of the trade in bio-information and plant genetic resources. At first, the amount of the extracted alkaloid was not enough to determine its chemical structure and its mechanism of action. Further collections were not successful because the alkaloid could only be found in certain frog populations, depending on their local dietary sources, and accessing the frogs turned out to be impossible since the frogs had become listed under the CITES. Then, more than 15 years later, improved instrumentation made the isolation and synthesis of the alkaloid possible: a sudden breakthrough in standardization after a long delay that finally made any return to the source of the alkaloid unnecessary and a new research tool available wherever synthesis of epibatidine could be accomplished, at least as long as the patents on the new substances and methods did not interfere. No radically new instruments could render a return to the source – always complicated and risky – ultimately unnecessary; the only improvements were in the sensitivity of spectrometers. In Daly's own words: "The Straub-tail alkaloid also represents a striking example of how technical advances in instrumentation have made possible what was impossible 15 years ago" (Daly 1998, p. 168). Improved instrumentation was the key to structure elucidation basically owing to the lack of a sufficient amount of frog-skin extract; had Daly and Myers been able to obtain more raw material, waiting for more sensitive spectrometers would have been unnecessary and the structure of epibatidine presumably could have been determined 15 years earlier. Therefore, finally, the delays and breakthroughs in investigating and using biodiversity in this case seem to have depended as much on the availability of adequate raw material as on advanced instrumentation.

Availability, however, does not only hinge on ecological conditions like the abundance (or the lack) of alkaloid-containing frogs at a certain site but also on political and legal questions. In the epibatidine case, for example, the listing of the frogs under the CITES made further collection impossible, whereas nowadays decisions under the CBD and national legislations often complicate bioprospecting efforts, as well as increased media and public attention on cases of perceived or actual biopiracy. In the Ecuadorian case, at least, the widespread distrust in any collection of biological material among local and particularly indigenous communities has become so pervasive today that an interviewed ethnobiologist spoke of a kind of "bioparanoia" which, in her opinion, compromised even the most harmless taxonomical investigations.5 However, complaints about

restrictive granting of permits to research or collect *in situ* seem to be neither very new nor exclusive to Ecuador. Daly, for example, complains a lot about the difficulty of obtaining collection permits in several of his articles and even suggests a way of dealing with this obstacle – going somewhere else:

The research has been hindered by difficulties in obtaining permits to collect any amphibians for scientific investigation, especially in neotropical countries of Central and South America, where the alkaloid-containing dendrobatid frogs are found. For this reason, in the past decade our research has shifted to bufonid frogs of Argentina and to mantellid frogs of Madagascar. (Daly 2003, p. 449)

Whereas Daly seems to forget that the polemics about the legitimacy of his original collections in the epibatidine case might have contributed to this difficulty of obtaining permits, at present strategies to avoid regulation perceived as excessive by doing research on less regulated subjects or in less regulated areas seem to be quite common. This might be one of the reasons – besides merely pharmacological reasons which cannot be assessed here – why sources of natural products other than the traditionally exploited plant extracts have become quite popular during the last few years, above all marine, microbial and insect sources (Harvey 2000; Gullo and Hughes 2005): all these tend to be less contentious, less restricted to so-called "biodiversity hot spots" and much less in the focus of media and public attention than spectacularly coloured frogs or traditional medicinal plants. Furthermore, bioprospecting unexplored or little-explored sources helps to avoid problems with previously existing intellectual property rights. Marine sources, in particular, are also likely to be even more difficult to monitor and control than terrestrial natural products, owing to their, quite literally, mobile and "fluid" nature, with ownership claims almost impossible to circumscribe, and no property or access issues at all outside of exclusive economic zones, in international waters (Pottage 2006).6

The technologically enabled delays and breakthroughs that occurred during the development of epibatidine and derived substances contributed to a dilemma that appears to be quite frequent in bioprospecting: relatively small and mobile resources like biochemical or genetic material have become rather easy to preserve for an almost unlimited time (especially after the development of cryopreservation) – compared with previous centuries when seed or seedlings had to be kept in a germinable state – but are extremely difficult to trace and control. Arguably, material transfer agreements as those suggested in Appendix I of the "Bonn Guidelines on Access to Genetic Resources and Fair and Equitable Sharing of the Benefits Arising Out of Their Utilization" (Secretariat of the Convention on Biological Diversity 2002) tend to be unable to provide efficient monitoring of the circulation of biological material (Parry 2004b), in spite of being part of "an increasingly baroque regulatory framework" (Parry 2004b, p. 254).7 In the epibatidine case, a

single collection in 19768 allowed the development of potentially highly valuable drug leads derived from the collected resources more than 15 years later – the delay between the first part of the transaction (access and collection) and the next part of it (isolation, structure elucidation and synthesis) did not put an end to the usability of the small and irreplaceable sample of frog alkaloid, even though the frog skins could no longer be collected. For this reason, Parry has serious doubts about whether existing legal regimes "are capable of regulating transactions that are 'suspended'" (2004a, p. 43). In the epibatidine case, at least, it is no longer possible to reconstruct or prove whether the frog skins had been collected and exported legally. Whereas Daly *et al*. (2000) insist that in the mid-1970s there was no regulatory agency in Ecuador and thus the collected samples were legally (or, at least, not illegally) exported with the appropriate US Fish and Wildlife import documentation, other sources do assume that in 1976 there was an Ecuadorian regulatory agency and an applicable law in force (*Ley de protección de la fauna silvestre y de los recursos ictiológicos* from November 1970), but admit there are no longer any archives at the then responsible *Ministerio de la Producción* (Werning 1999). Eventually, the technologically enabled delay between access and use rendered any proof of the legitimacy or illegitimacy of the original access to the frog skins impossible, since today it is not feasible to document the granting or rejection of the collection permits. Unfortunately, there seems to be no reason to conclude that the aforementioned dilemma has disappeared nowadays, after adoption of the CBD: suspended transactions continue to be a typical feature of the investigation and use of biodiversity, maybe even more than ever before, and they remain extremely difficult to trace and control – and without an efficient monitoring of the circulation of biological material, probably no ABS framework will ever work reliably. The Nagoya Protocol, on the other hand, does not constitute a real breakthrough as far as monitoring and compliance mechanisms are concerned. It establishes an international Access and Benefit-sharing Clearing-House (Art. 14), but mainly recommends national measures like focal points (Art. 13), checkpoints (Art. 17, 1) and certificates of compliance (Art. 17, 3 and 4; Secretariat of the Convention on Biological Diversity 2011). It remains an open question whether these rather vaguely defined (and, in part, nonobligatory) measures will indeed be able to monitor efficiently the circulation of biological materials that tend to be quite elusive and hard to grasp, as the epibatidine case has shown.

Biodiversity below the species level

Without the long-standing interest of Daly and Myers in frog alkaloids and their potential pharmacological activities, it is highly unlikely that epibatidine and its potent analgesic properties and the subsequent determination of its mechanism of action would have ever occurred. While there was considerable interest in both the academic and industrial communities in efforts to synthesize epibatidine as documented above, it was not until the mechanism of action of epibatidine was determined by Badio and Daly that the value of this novel frog alkaloid was fully appreciated. (Daly *et al*. 2000, p. 134)

This statement by Daly *et al*. is true, without any doubt. Their research in arthropod alkaloids extracted from frog skin was pioneering and yielded totally unexpected results. However, the researchers seem to forget that all their efforts would have been fruitless without the unique properties of the only very locally available frogs they had collected. So, when Daly states that "in the mid-1980s, we had what had become an irreplaceable sample of epibatidine" (Daly 1998, p. 169), his assertion might be even more literally correct than he intended. Thus, Daly admits in another article that the alkaloid profiles of various populations belonging to the same species "can differ remarkably even for populations close together on a single island" (Daly 2003, p. 449) and may also "change markedly over the years probably because of alteration of ecosystems by human inroads" (ibid., p. 450).9 Daly and his group struggled with this change over time first-hand when they were unable to collect frogs that produced more than only trace amounts of epibatidine on field trips in 1979 and 1982 at exactly the same site of their original collection from 1976 (Daly *et al*. 2000). Ultimately it seems to be no coincidence that, in spite of their several field trips during almost 10 years, Daly and his colleagues detected significant amounts of epibatidine only in two populations, in 1974 and 1976.10 The variation in alkaloid profiles between distinct frog populations or even individuals is so remarkable that there is only a weak correlation between alkaloid secretions and species (Cipriani and Rivera 2009; Darst *et al*. 2005) and the ideal unit of analysis would be *individual* alkaloid profiles, as an interviewed Ecuadorian biologist told me. Since the frogs do not synthesize the alkaloid by themselves but accumulate it from dietary sources, the highly local variation of biodiversity below the species level in this case depends on an ultimate source whose identity remains uncertain, probably an ant species. In any case, the dietary source of epibatidine "was neither abundant nor widely distributed" (Daly *et al*. 2000, p. 132), so it is striking that for the discovery of epibatidine the diversity below the species level and the technologically

enabled preservation of these locally specific traces were decisive. In a way, even the frogs themselves can be seen as a kind of screening or bioprospecting device: only the frogs know the precise source of epibatidine, as Daly himself admits, according to Gillis (2002): “The frogs are much better bioprospectors than I am […]. They're the ones that found the chemicals in the arthropods”. So, if medicinal plants tend to be “considered ‘living laboratories’ yet ones that are notoriously inconsistent in the production of active ingredients” (Wahlberg 2008, p. 40), the same might be true of poison dart frogs. Thus, the discovery and development of epibatidine – totally unexpected, and yet highly influential for the previously almost nonexistent area of research on nicotinic analgesics (McCurdy and Scully 2005) – owes a lot to a single population of tiny poison frogs that lived more than 30 years ago in Ecuador. Finally, it should be clear that biodiversity is much more than just diversity between different species: as the epibatidine case illustrates, variations between populations belonging to the same species (in this case, owing to unknown dietary sources only available at specific sites) can be as important as differences between species. Hence, focusing mainly on the species level is not an efficient approach either to biodiversity conservation or to bioprospecting.

What does it mean to use traditional knowledge?

Was there *only serendipity* in the choice of the adequate frog population and the subsequent discovery of epibatidine by Daly and his colleagues? Or did so-called traditional knowledge guide them, besides the obvious experience and knowledge the researchers themselves had acquired with regard to poisonous frogs? For a number of reasons it is rather difficult to determine whether in the epibatidine case traditional knowledge was used. This is due in part to the fact that what it means to access or use traditional knowledge is less evident than one may expect. So it is not merely an open question as to whether there was a traditional use of the poison of *E. anthonyi* – even if certainty in this regard could be achieved, the relevance of a traditional use of the frog poison for the subsequent development of drug leads derived from the extracted alkaloid would be difficult to assess.

During the field work I undertook in Ecuador in 2008, some interviewees stated a traditional use of the secretions of *E. anthonyi* as a source of dart poison, whereas others denied it, amongst them an herpetologist who claimed that other related species were traditionally used for the preparation of dart poison but not *E. anthonyi*. In his opinion, the general knowledge of the traditional use of

poison obtained from frogs belonging to the dedrobatid family may have served as a hint that there might be some potentially interesting frog poison to investigate, but does not amount to an actual use of traditional knowledge. Daly *et al*. explicitly deny any local tradition concerning the frog poison they had obtained: "Despite recent statements in the media, there was no tradition in Ecuadorian folklore that the skin of *Epipedobates tricolor* had analgesic or other medicinal properties, and, in fact, the frog was considered locally as an unimportant part of the fauna" (2000, p. 132). On the other hand, Martinez-Alier states that "[i]nterest in the frog arose because the physiological effects were known locally" (2002, p. 133); however, does "arising interest" amount to an explicit use of local knowledge? In 1998 Ecuador filed an official claim that Abbot should share any benefits generated by epibatidine and its derivatives with the Ecuadorian state.11 In order to support this claim, Ecuador alleged that indigenous knowledge had been instrumental for the development of epibatidine and that any potential benefits were derived from this knowledge (Ribadeneira 2007). Given the lack of legal instruments to enforce the benefit-sharing, the Ecuadorian claim failed. Furthermore, "Abbot Laboratories said that it owes nothing to Ecuador because it merely got the inspiration for its drug by reading a scientific paper about the frog chemical" (Martinez-Alier 2002, p. 134). Immediately after this statement, Martinez-Alier asks: "But why and where were the frogs' skin secretions investigated to start with?" (ibid.) His obvious intention is to criticize Abbot's refusal to share benefits, but there is more about this question than the author himself might have intended since it is rather difficult to determine a precise "degree zero" from which the investigation of the frog skins' properties started. Abbot seems to consider mainly the research undertaken by Daly's group as relevant *prior art* and apparently had never worked directly with the frogs or their secretions (Daly *et al*. 2000), whereas Daly never mentions traditional knowledge or support by locals in his publications, not even in the acknowledgment section. Without relevant sources, it is obviously impossible to reconstruct the events that occurred in the mid-1970s when the frogs from which epibatidine was extracted were collected – we simply do not know if Daly and Myers were supported by locals or even used their knowledge.12

According to Gillis's homage, the researchers chose a – quite literally – trial-and-error method in order to discern which frogs to collect: "Once in the field, the two had a simple test to decide whether to take a particular frog. 'It involved touching the frog, then sampling it on the tongue. If you got a burning sensation, then you knew this was a frog you ought to collect', says Daly" (Gillis 2002). So *if there was* local knowledge with regard to certain frog species, it might have cautioned them against sampling the most toxic frog poisons on their tongues, and potentially even have saved their lives – but does this amount to a "use of traditional knowledge" in terms of *prior art* relevant for the subsequent development of a product derived from the frog poison? In a strictly legal sense,

the answer probably would be “no” since the traditional and the new use would need to be closely related in order to affirm the charge; but how should the required degree of relatedness of forms of usage (and whether these must refer to the same family, species or even population) be determined without arbitrariness? In the epibatidine case, a traditional use as dart poison (if it could be proved) arguably would be closely enough related to an analgesic use; however, if epibatidine analogs are employed as imaging agents owing to their affinity to cholinergic receptors (Dukat and Glennon 2003), the relationship seems to be rather distant. Yet, where exactly should the line that divides related and unrelated forms of usage be drawn? And how directly, systematically and consciously must local knowledge be used in order to count as relevant *prior art*?13 Again, the epibatidine case raises more questions than answers – it is not possible anymore to establish whether Daly and Myers used traditional knowledge during their search for poison dart frogs, and in general it is not always obvious what it means to use traditional knowledge in bioprospecting.

Sharing the benefits of derivatives?

Even if a traditional use of the poison of *E. anthonyi* could be established beyond any doubt (and even if it were a case happening today, after the adoption of the relevant CBD protocols), epibatidine basically is a research tool that has opened up an entirely new area of research on nicotinic analgesics but it cannot be used directly by humans – it is much too toxic – and apparently “there have been no efforts to develop epibatidine for clinical use” (Daly *et al*. 2000, p. 134). So, on the one hand the impact of epibatidine in drug discovery and development can hardly be overestimated,14 but one the other there are no *direct* benefits generated through epibatidine that could be shared with any local community or source country – without benefits, there can be no benefit-sharing. It might sound slightly absurd to state that there may not have been any benefits obtained from epibatidine: owing to epibatidine, an entire area of research has been opened up, and there are several patents granted on epibaditine and derivatives.15 Yet “derivative” is the key word here since the role of derivatives in the ABS framework established by the CBD and subsequent protocols has never stopped being fiercely debated at various conferences of the parties. Even in the recently adopted and much celebrated *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization*, no consensus in this regard could be achieved (Secretariat of the Convention on Biological Diversity 2011). Since at Nagoya the majority of biodiversity-rich developing countries were pushing for an explicit recognition that

the scope of the protocol also includes derivatives of accessed genetic resources, a ruling that most industrialized countries wanted to avoid at any cost, the question of the role of derivatives in the protocol was simply omitted – otherwise, the adoption of the whole protocol probably would have failed (Régnier 2010). Further clarification of this polemic aspect was left for lawyers, courts and the subsequent conferences of the parties, although the question of derivatives presumably belongs to the key issues that have to be resolved in order to obtain a robust and enforceable ABS framework.

It seems to be anything but easy to determine the adequate scope of derivatives to be included into an ABS agreement. If one does not decide to establish compulsory benefit-sharing for *any* derivative of a genetic resource (the new Ecuadorian constitution from 2008 goes even further – in article 402 it prohibits the granting of intellectual property rights on any derivatives "obtained from the collective knowledge associated with the national biodiversity", a legal measure probably incompatible with the TRIPS agreement that does not allow exceptions for traditional knowledge-related products, and furthermore only applicable to intellectual property rights (IPR) applications filed in Ecuador; *Constitución Del Ecuador*, 2008), a certain arbitrariness in establishing the degree of derivation under which benefits have to be shared may be unavoidable, as the epibatidine case shows. Epibatidine derivatives like epiboxidine or tebanicline (ABT-594) arguably would not have been developed without the isolation of epibatidine from *E. anthonyi*, but it is difficult to assess (for patent attorneys, for law-makers and for anyone else) if these molecules owe more to the inventiveness of drug companies or to their parent compound epibatidine. Notwithstanding the rather rhetorical and *en passage* references to the original extraction of epibatidine from poison frogs at the beginning of most scientific articles on epibatidine derivatives, the majority of researchers working on nicotinic analgesics actually have never seen the Ecuadorian poison dart frogs and just do their "normal" work inside the laboratory with synthesized alkaloids. For them, these compounds may stem from the pioneering research undertaken by Daly's group and be known owing to the relevant publications, but not from any (remote, and long dead) frog population. Furthermore, when patent offices decide over the granting of patents on derivatives of natural products, one might often perceive what legal scholar James Boyle calls a "romantic bias" – a systematic overestimation of the inventor's contribution and an underestimation of the biological (or cultural) "raw materials" he summarizes with the maxim: "Authorship devalues sources" (Boyle 1996, p. 107). Sunder highlights this point, too, by stating that "the line between what law considers 'raw material' versus 'intellectual property' is less stable and more fraught with bias than the binary approach would acknowledge" (2007, p. 101). In the patent on the epibatidine-derivative ABT-594, for example, this underestimation of the compound's material sources is striking, since there is

absolutely no mention of either the frog poison or of epibatidine (Caruso 2000). On the one hand, this lack of disclosure of the material sources from which the compound was derived is probably rather normal in patent applications, which tend to give "internalist" accounts and cut the links to any possible *prior art* or material source that may interfere with the patent claims (Bowker 1992). On the other hand, this lack of disclosure of origin in the specific case of natural product derivatives implies that a lot of derivatives presumably remain unnoticed and thus totally avoid any issues with IPR counterclaims or ABS compliance (and, again, the Nagoya protocol does not establish strong and compulsory certificates of origin that could, for example, invalidate patent claims if not complied with). Additionally, for competitive reasons secrecy is a major factor in the pharmaceutical industry, so, presumably, rather often than not the precise origin of compounds remains undisclosed. Finally it is not only difficult to decide whether the benefits of derivatives *should be shared* with countries or communities of origin; furthermore, it is rather arduous *to detect* the derivatives of biological materials if these are not disclosed voluntarily – a major problem if one considers that natural product derivatives and "mimics" are among the principal sources of new chemical entities, as the often-cited study by Newman and Cragg (2007) shows. Thus, it is certain neither whether the indirect benefits generated by compounds like epibatidine and the direct benefits possibly generated by their derivatives must be shared with the provider of the source material nor how this might be accomplished. As long as it is not clearly established what constitutes a benefit according to the CBD and how these benefits might be measured, any ABS framework will be very hard to enforce, in particular in cases like epibatidine that provide important research tools but hardly any direct monetary benefit.

"The frog formerly known as *Epipedobates tricolor*" – the unstable identity of research objects

Practically all articles on epibatidine assume that the alkaloid was extracted from skins of the Ecuadorian poison dart frog *Epipedobates tricolor*. However, recent studies show that apparently Daly and his group mixed up *E. tricolor* with another related and similar looking species, *Epipedobates anthonyi*; the alkaloid profile of *E. tricolor* has not been assessed so far (Darst *et al.* 2005). Only very recently have preliminary investigations on this species started (Cipriani and Rivera 2009). In an earlier article Daly *et al.* (1980) even designate the species to which an

extracted alkaloid (not the one that later became known as epibatidine) is attributed as *Dendrobates tricolor*. If the name and the taxonomy of the same frog have changed twice over the last 30 years, what does this "species trouble" imply for bioprospecting and its regulation? There seems to be another point in common between the epibatidine case and bioprospecting in general – the dynamic nature of biodiversity and knowledge on biodiversity, a dynamic arguably rather difficult to handle in legal frameworks on ABS or IPR. So, if taxonomies or species names change, it becomes an open question as to which species or even to which population a corpus of traditional knowledge must be related to in order to constitute relevant *prior art* for rejecting IPR claims by foreigners or for establishing ABS agreements.16 Could changing taxonomic classifications or species names *retrospectively* invalidate (or, respectively, justify) benefit-sharing or IPR-claims? If, for example, the existence of traditional knowledge relating to *E. tricolor* could have been proved, what would be the consequences arising from the fact that epibatidine apparently was extracted from another species (even though the researchers assumed it was from *E. tricolor*)? Furthermore, *E. tricolor* and *E. anthonyi* are quite hard to distinguish; does this imply that traditional knowledge must be validated by genome analysis in order to assure that it relates to the correct species? What should be done about so-called "cryptical biodiversity" – species that morphologically cannot be distinguished at all? After all, taxonomies tend to be unstable and in more or less constant change. Populations and species are often especially difficult to distinguish, as the epibatidine case illustrates. Furthermore, the species level is not necessarily decisive (see above on biodiversity below the species level), and there is not even a universally accepted notion of what constitutes a species in the biological sciences. However, if stability and absolutely clear-cut distinction cannot always be presupposed in taxonomy, on which system of classification and denomination should the regulation of biodiversity be based – and on *whose* classification systems? Since in the majority of cases indigenous or local classifications of flora and fauna arguably do not coincide with formal bio-scientific taxonomies, there would be a certain degree of arbitrariness in ruling out local classifications in advance and establishing "Western" scientific taxonomies as the only valid distinction criteria to determine if there is traditional knowledge in a specific case or not. Finally, both (indigenous *and* nonindigenous) knowledge and biodiversity tend to be rather fluid and undermine clear-cut distinction – habitats of species and populations overlap and change as well as knowledge and classifications.

Nevertheless, the existing legal frameworks on ABS or IPR require certain reliable distinctions in order to operate efficiently and differentiate classified entities from each other. Thus, their assumptions presumably are more static than the dynamic and rather unstable nature of research objects in general and biodiversity in particular. From a more general perspective, understanding

what it means for an object to change might be helpful. Actor–network theory, for example, "proposes that *objects are an effect of stable arrays or networks of relations*. The suggestion is that objects hold together so long as those relations also hold together and do not change their shape" (Law 2002, p. 91). Therefore, epibatidine changed from an irreplaceable sample of undefined, but highly promising "Straub-tail alkaloid" into a precisely defined and synthesized research tool, and over the years it was associated with three differently named frog species – several changes in the network of relations, although these did not end up losing their shape completely. ABS and IPR frameworks, however, typically fail to recognize this fluidity in the constitution of objects in their intent to recognize and fix the precise contribution of raw materials and various types of knowledge to a certain product or process. Actually it is rather difficult to imagine how they may *not fail* in distinguishing dynamic objects like frog species and traditional knowledge as long as the predominant mode of ABS are contracts that provide remuneration only if specific biodiversity-based products turn out to be successfully sold. A *pay-per-access*-model which requires – relatively low – payments irrespective of the final outcome might do more justice to the dynamic nature of knowledge and of biodiversity as a research object, at least with regard to ABS-frameworks.17

Conclusion

An interviewed Ecuadorian biologist told me that, when they were on a field trip looking for poison dart frogs, locals recommended that they "just had to look for that guy who sells frogs to the *gringos*". However, they were unable to check the veracity of this rumor or information, so it remains an open question if there actually is someone selling frogs without authorization to foreigners (and if so, whether the frogs are sold for bioprospecting or for merely decorative purposes as pets). This anecdote illustrates a dilemma of many analyses of bioprospecting (that must be faced in the epibatidine case, too): it is hard to gather robust data, so that to a certain extent some speculation is unavoidable, whereas at the same time, the risk of biopiracy remains latent "out there", difficult to verify. Beyond this difficulty in obtaining reliable information, many cases of bioprospecting seem to have a lot in common with the epibatidine case. In particular, a problem shared by a relevant number of instances of bioprospecting is that the ABS framework envisioned by the CBD does not appear consonant with the everyday realities and practices of the investigation and use of biodiversity. So, for example, nonlinear, suspended transactions that seriously compromise any monitoring of the circulation of biological materials owing to the delay between

access and use tend to be quite frequent, just like in the epibatidine case. Since many drug leads are derivatives of biological materials rather than unmodified natural products, the question of ABS in the case of derivatives also remains an issue yet to be resolved. Furthermore, it often turns out to be difficult to prove whether traditional knowledge was used in the development of a product, as the case of epibatidine and the frogs' possible local uses highlights.

Of course, the adoption of the Nagoya protocol on ABS represents a major breakthrough for the regulation of the investigation and use of biodiversity, and of course I hope the rather pessimistic outlook this article offers with regard to the sharing of the benefits arising from the utilization of biological materials turns out to be completely wrong. Certainly, with the Nagoya protocol adopted the world seems to be better off than without it. Still, this article poses several questions that the Nagoya protocol (or any other possible ABS agreement) has yet to address and that seriously undermine its enforceability, basically because the ABS regulation as envisioned by the CBD presupposes a number of clear-cut distinctions and attributions that are rather difficult to handle: where exactly do certain biological materials come from? Were they accessed and exported in a licit way (maybe a long time ago)? Was traditional knowledge used, and if so, whose knowledge? Was this knowledge relevant *prior art* for a subsequent invention? Is a certain product derived from biological materials, and if so, must potential benefits be shared? Given the lack of reliable answers to these and other questions, and in the light of the ambiguities of the scientific and commercial practices highlighted by the epibatidine case, the stakes and the risk implied in bioprospecting remain rather high for many stakeholders, in particular local communities in developing countries. Ultimately, whereas today the investigation and use of biodiversity involves much more regulation and bureaucracy than before, it still requires a lot of sweat and serendipity, and there still is a lot to gain and maybe even more to lose: biodiversity, money, new drugs, social justice, cultural diversity and knowledge.

Notes

1. This article is related to the ongoing research for my PhD thesis on the investigation, the uses and the transformations of collected biological materials in intermediary institutions in Europe, especially in biotech-companies and botanical gardens. I would like to thank Andrea von Braun Stiftung for providing the funding for my PhD project. I also would like to thank Michael K. Dorsey for providing me his unpublished dissertation on "Commercialization of biodiversity: processes, actors, and contestation in Ecuador, 1536–2001". In this dissertation, Dorsey briefly analyzes the epibatidine case, too (Dorsey 2005, 2006).

Furthermore, I would like to thank the anonymous reviewer for providing several helpful suggestions and comments. Of course, I also would like to thank all the people who shared their knowledge and information so generously with me during my field work in Ecuador.

2. The name "epibatidine" was chosen because the alkaloid was extracted from frogs belonging to the species *Epipedobates anthonyi* (Dentrobatidae family), a species endemic to central and southern Ecuador. Usually the alkaloid is said to have been extracted from *Epipedobates tricolor* but recent investigations show that these two closely related species were mixed up by Daly and subsequently by all the authors referring to him, i.e. more or less the whole drug discovery literature (Cipriani and Rivera 2009). I will return to this point and its implications for the regulation of the use of biodiversity later in this article. In a previous article I also mixed the two species up and included an image of *E. anthonyi* wrongly labeled as one of *E. tricolor* (Angerer 2009).

3. The quite fiercely disputed notion of "traditional" or "local" knowledge – "a battlefield littered with academic landmines" (Oguamanam 2008, p. 35) – cannot be analyzed thoroughly here; for a further discussion see for example Agrawal (1995) and Sunder (2007). Hence "traditional knowledge" as used in this articles refers to nothing more than the knowledge and knowledge practices concerning locally known flora and fauna, particularly in indigenous, afroecuadorian or other local communities, without any further assumptions about the characteristics of these forms of knowledge and without presupposing any kind of homogeneity in these communities or a sharp divide between various forms of knowledge.

4. I would like to thank the anonymous reviewer for pointing me to the role of the United States as a crucial contributor to the discussions under the CBD. However, as far as the obligations to share the benefits of the uses of biological materials are concerned, the "failure of the US to ratify the CBD has serious ramifications for benefit sharing inasmuch as US-based firms have no mandate to comply with the letter and spirit of the CBD" (Vogel 2000, p. 6). Thus, as Vogel highlights (ibid.), bringing biological materials to the United States or bioprospecting resources taken to the United States previously, might be a way to circumvent ABS regulations established in other countries.

5. All interview sources mentioned in this article refer to a series of audiotaped interviews

undertaken during my fieldwork in Ecuador (April and May 2008, and August 2010).

6. It might be no coincidence that one of the most emblematic and systematic (and polemic) efforts of prospecting and screening marine biodiversity has been conducted by Craig Venter, a researcher with a good sense for new scientific and commercial trends, to say the least; Venter's *Sorcerer II* expedition has been analyzed by Pottage (2006) and Delfanti *et al*. (2009), amongst many others.

7. In Parry's opinion, the failure of ABS agreements under the CBD "did not occur because such agreements have not been well intentioned but rather because changes in the way biological materials are rendered and utilized have combined to make the task of monitoring and compensating for their use extremely difficult" (Parry 2004b, p. 255). Parry also emphasizes that the distinction between basic and applied science, respectively commercial and noncommercial uses of collected materials is seriously compromised by the ability to preserve biological substances for an almost unlimited time since even materials collected without any commercial intention might be re-used for profit one day.

8. Daly *et al*. (2000) stress this point by emphasizing that after 1980 they did not work with frogs at their NIH laboratory.

9. The following quotation may help to illustrate the scope of this enormous variation in alkaloid levels: "At one site, epibatidine was present at about 1 µg per skin, while at a nearby riparian site it was present at only 100 ng per skin" (Daly 2003, p. 448).

10. Recent investigations by Cipriani and Rivera (2009) render similar findings – they detected (unspecified amounts of) epibatidine-related alkaloids only in two out of four populations of *E. anthonyi* but found several previously unknown alkaloids, one of them similar to epibatidine.

11. Unfortunately it is not possible to discuss here the tensions between states (which legally assume ownership over genetic resources) and local communities (whose knowledge may have been used for choosing certain biological materials) that might arise from claims like this one by the Ecuadorian state.

12. In a previous field trip to the Columbian Chocó region, however, Daly and Myers extensively recorded local knowledge and practices among the Emberá indigenous; almost one-half of their article consists of an ethnographic description of practices of dart poisoning, blow gun fabrication and dart fabrication (Myers *et al*. 1978). Given that the dart poison was obtained from *Phyllobates terribilis*, a frog that contains enough poison to kill a dozen people and was new to science at that time (the species' holotype was collected by Daly and Myers during that field trip), paying attention to the way locals treated the frogs might not have been unimportant for the researchers. However, this does not tell us a lot about the epibatidine case, beyond the fact that Daly and Myers *sometimes did access* traditional knowledge; after all, epibatidine was extracted from a different species in another country during another field trip and even belongs to a different class of alkaloid than the batrachotoxin from *P. Terribilis*.

13. According to Gillis (2002), Daly and Myers also used expedition reports dating from the nineteenth century in order to detect potentially interesting sites for field trips; in that way, they might have indirectly used local knowledge gathered much earlier by other researchers. Today such an indirect access to local knowledge is relatively easy to accomplish owing to the existence of huge databases of natural products and their ethnobiological uses; one of the most important among these sources for what could be called "digital bioprospecting" is the NAPRALERT database that includes data from more than 200,000 scientific papers on upward of 60,000 species and more than 90,000 reports of ethnomedical use (http://napralert.org/, accessed 2 February 2011) (Graham and Farnsworth 2010).

14. According to a review from 2003, "few other nicotinic agents have had as profound an impact on nACh receptor research as has epibatidine. According to MEDLINE, >300 papers have been published on epibatidine since its structure was initially disclosed a decade ago […]. […] This quickly led to an entire issue of *Medicinal Chemistry Research* (Issue 7/8) being devoted to epibatidine. […] Prior to the discovery of epibatidine, it appeared that there existed an affinity barrier or ceiling beyond which it was almost impossible to venture" (Dukat and Glennon 2003, p. 365). Later on, the authors speak of the research on nicotinic receptors having been "revolutionized" by epibatidine and conclude by asking that one "can only wonder where nicotinic cholinergic receptor research would be today without the advent of epibatidine" (p. 375).

15. Epibatidine even turned out to be a surprisingly adaptable molecule, as Dukat and Glennon (2003) stress: “epibatidine motivated the development of numerous novel agents. The structural diversity of these agents and the amount of structural change that is tolerated by epibatidine without loss of affinity, is striking” (p. 375).

16. The Global Biodiversity Information Facility (GBIF) has started to implement a system of Persistent Identifiers for primary biodiversity data in order to allow for an unambiguous and permanent identification and classification of biological specimens. This might help to avoid some of the difficulties associated with determining to which collected sample a corpus of traditional knowledge (or a derived compound) is related, but obviously cannot be applied retrospectively to biological materials collected years ago, like the poison frog skins from which epibatidine was derived (http://www.gbif.org/communications/news-and-events/showsingle/article/a-beginners-guide-to-persistent-identifiers-published/; accessed 22 March 2011). I would like to thank the anonymous reviewer for pointing me to this interesting initiative undertaken by the GBIF. For a more general perspective on biodiversity data and its classification, see Bowker (2000).

17. For a similar proposal see the last chapter (“Back to the future”) of Parry's *Trading the genome* (2004b): she suggests that “we abandon the task of attempting to trace all the myriad uses that are made of collected genetic and biochemical materials and information and concentrate instead on working to secure a voluntary, global agreement from the pharmaceutical industry that they will add a sum of between 3 and 5 percent of their profit ratio to *all those products that they currently have in the marketplace that are based on collected natural materials*” (p. 261). However, the problems of any voluntary agreement are rather obvious, as well as the difficulties a “superfund” for distributing those benefits (like the fund proposed by Parry) would have to face.

References

- **1.** Agrawal, A. 1995. Dismantling the divide between indigenous and scientific knowledge. *Development and change*, 26(3): 413–439. [CrossRef], [Web of Science ®], [CSA]
- **2.** Angerer, K. 2009. Die Natur der Bioprospektion: Die Welt als biochemisches Labor. *Zeitschrift für Kulturwissenschaften*, 2: 91–102.

- **3.** Badio, B. and Daly, J.W. 1994. Epibatidine, a potent analgetic and nicotinic agonist. *Molecular pharmacology*, 45(4): 563–569. [PubMed], [Web of Science ®], [CSA]
- **4.** Bannon, A.W. 1998. Broad-spectrum, non-opioid analgesic activity by selective modulation of neuronal nicotinic acetylcholine receptors. *Science*, 279(5347): 77–80. [CrossRef], [PubMed], [Web of Science ®], [CSA]
- **5.** Bowker, G.C. 1992. "What's in a patent?". In *Shaping technology/building society. Studies in sociotechnological change*, Edited by: Bijker, W.E. and Law, J. 53–74. Cambridge, MA: MIT Press.
- **6.** Bowker, G.C. 2000. Biodiversity datadiversity. *Social studies of science*, 30(5): 643–683. [CrossRef], [Web of Science ®], [CSA]
- **7.** Boyle, J. 1996. *Shamans, software, and spleens: law and the construction of the information society*, Cambridge, MA: Harvard University Press.
- **8.** Caruso, F.S., 2000. *Analgesic composition and method for alleviating pain*. United States Patent 6054451. Available from: http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=2&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=68&f=G&l=50&co1=AND&d=PTXT&s1=ABT-594&OS=ABT-594&RS=ABT-594 [Accessed 23 January 2011].
- **9.** Cassels, B.K. 2005. From ligand design to therapeutic efficacy : the challenge for nicotinic receptor research. *Drug discovery today*, 10(23/24): 1657–1665. [CrossRef], [PubMed], [Web of Science ®]
- **10.** Cipriani, I. and Rivera, M. 2009. Detección de alcaloides en la piel de cuatro especies de anfibios ecuatorianos (Anura: Dentrobatidae). *Revista ecuatoriana de medicina y ciencias biológicas*, 30(1–2): 42–49.
- **11.** *Constitución Del Ecuador.* 2008. Available from: http://www.asambleanacional.gov.ec/documentos/constitucion_de_bolsillo.pdf [Accessed 31 January 2011] .
- **12.** Daly, J.W. 1998. Thirty years of discovering arthropod alkaloids in amphibian skin. *Journal of natural products*, 61(1): 162–172. [CrossRef], [PubMed], [Web of Science ®], [CSA]
- **13.** Daly, J.W. 2003. Ernest Guenther award in chemistry of natural products. Amphibian skin: a remarkable source of biologically active arthropod alkaloids. *Journal of medicinal chemistry*, 46(4): 445–452. [CrossRef], [PubMed], [Web of Science ®], [CSA]
- **14.** Daly, J.W. 1980. A new class of indolizidine alkaloids from the poison frog, Dendrobates

tricolor. X-ray analysis of 8-hydroxy-8-methyl-6-(2'-methylhexylidene)-1-azabicyclo[4.3.0]nonane. *Journal of the American Chemical Society*, 102(2): 830–836. [CrossRef], [Web of Science ®]

- **15.** Daly, J.W., Spande, T.F., and Garraffo, H.M., 1994. *Epibatidine and derivatives, compositions and methods of treating pain*. United States Patent 5314899. Available from: http://patft.uspto.gov/netacgi/nph-Parser?Sect1=PTO2&Sect2=HITOFF&p=1&u=%2Fnetahtml%2FPTO%2Fsearch-bool.html&r=7&f=G&l=50&co1=AND&d=PTXT&s1=epibatidine.TI.&OS=TTL/epibatidine&RS=TTL/epibatidine [Accessed 23 January 2011].
- **16.** Daly, J.W. 2000. Alkaloids from frog skin: the discovery of epibatidine and the potential for developing novel non-opioid analgesics. *Natural product reports*, 17(2): 131–135. [CrossRef], [PubMed], [Web of Science ®]
- **17.** Darst, C.R. 2005. Evolution of dietary specialization and chemical defense in poison frogs (Dendrobatidae): a comparative analysis. *The American naturalist*, 165(1): 56–69. [CrossRef], [PubMed], [Web of Science ®]
- **18.** Davis, L., Pollock, L. and Stone, T. 1932. Visceral pain. *Surgical gynecology and obstetrics*, 55(4): 418–426.
- **19.** Delfanti, A., Castelfranchi, Y. and Pitrelli, N. 2009. "What Dr Venter did on his holidays": exploration, hacking, entrepreneurship in the narratives of the Sorcerer II expedition. *New genetics and society*, 28(4): 415–430. [Taylor & Francis Online], [Web of Science ®]
- **20.** Dorsey, M.K. 2005. *Commercialization of biodiversity: processes, actors, and contestation in Ecuador, 1536–2001*, Unpublished thesis. University of Michigan.
- **21.** Dorsey, M.K. 2006. Future markets in biology: life after bioprospecting. *NACLA report on the Americas*, 39(5): 31–34.
- **22.** Dukat, M. and Glennon, R.A. 2003. Epibatidine: impact on nicotinic receptor research. *Cellular and molecular neurobiology*, 23(3): 365–78. [CrossRef], [PubMed], [Web of Science ®], [CSA]
- **23.** Gillis , A.M. , 2002 . Serendipity and sweat in science. "Frog Man" Daly follows curiosity to ends of the Earth. *The NIH record*, 44(18). Available from: http://nihrecord.od.nih.gov/newsletters/09_03_2002/story01.htm [Accessed 21 January 2011].
- **24.** Graham, J.G. and Farnsworth, N.R. 2010. "The NAPRALERT database as an aid for

discovery of novel bioactive compounds". In *Comprehensive natural products II: chemistry and biology. Vol. 3: Development and modification of bioactivity*, Edited by: Mander, L. and Hung-Wen, L. 81–94. Amsterdam: Elsevier.

- **25.** Gullo, V. and Hughes, D. 2005. Exploiting new approaches for natural product drug discovery in the biotechnology industry. *Drug discovery today: technologies*, 2(3): 281–286. [CrossRef]
- **26.** Harvey, A. 2000. Strategies for discovering drugs from previously unexplored natural products. *Drug discovery today*, 5(7): 294–300. [CrossRef], [PubMed], [Web of Science ®], [CSA]
- **27.** Jones, W.P., Chin, Y. and Kinghorn, A.D. 2006. The role of pharmacognosy in modern medicine and pharmacy. *Current drug targets*, 7(3): 247–264. [CrossRef], [PubMed], [Web of Science ®]
- **28.** Law, J. 2002. Objects and spaces. *Theory, culture and society*, 19(5–6): 91–105. [CrossRef], [Web of Science ®], [CSA]
- **29.** Martinez-Alier, J. 2002. *The environmentalism of the poor: a study of ecological conflicts and valuation*, Cheltenham: Edward Elgar.
- **30.** McCurdy, C.R. and Scully, S.S. 2005. Analgesic substances derived from natural products (natureceuticals). *Life sciences*, 78(5): 476–84. [CrossRef], [PubMed], [Web of Science ®]
- **31.** Myers, C.W., Daly, J.W. and Malkin, B. 1978. A dangerously toxic new frog (phyllobates) used by Emberá indians of western Colombia, with discussion of blowgun fabrication and dart poisoning. *Bulletin of the American Museum of Natural History*, 161(2): 307–366.
- **32.** Newman, D.J. and Cragg, G.M. 2007. Natural products as sources of new drugs over the last 25 years. *Journal of natural products*, 70(3): 461–477. [CrossRef], [PubMed], [Web of Science ®]
- **33.** Oguamanam, C. 2008. Local knowledge as trapped knowledge: intellectual property, culture, power and politics. *The journal of world intellectual property*, 11(1): 29–57. [CrossRef]
- **34.** Olivo, H. and Hemenway, M. 2002. Recent syntheses of epibatidine. A review. *Organic preparations and procedures international*, 34(1): 1–25. [Taylor & Francis Online], [Web of Science ®]
- **35.** Parry, B. 2000. "The fate of the collections: social justice and the annexation of plant

genetic resources". In *People, plants, and justice: the politics of nature conservation*, Edited by: Zerner, C. 374–402. New York: Columbia University Press.

- **36.** Parry, B. 2004a. "Bodily transactions: regulating a new space of flows in "bio-information". In *Property in question: value transformation in the global economy*, Edited by: Verdery, K. and Humphrey, C. 29–48. Oxford: Berg.
- **37.** Parry, B. 2004b. *Trading the genome: investigating the commodification of bio-information*, New York: Columbia University Press.
- **38.** Pottage, A. 2006. Too much ownership: bio-prospecting in the age of synthetic biology. *BioSocieties*, 1(2): 137–158. [CrossRef]
- **39.** Régnier, M. 2010. *Fortschritte bei der Artenvielfalt. E+Z*, 51(12): 482
- **40.** Ribadeneira, M. 2007. *La biopiratería, el desafío de construir un camino entre una acusación política y una categoría legal*, Unpublished manuscript.
- **41.** 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. Available from: http://www.cbd.int/doc/publications/cbd-bonn-gdls-en.pdf [Accessed 21 March 2011].
- **42.** Secretariat of the Convention on Biological Diversity, 2011. *Nagoya protocol on access to genetic resources and the fair and equitable sharing of benefits rising from their utilization to the Convention on Biological Diversity*. Montreal: Secretariat of the Convention on Biological Diversity. Available from: http://www.cbd.int/abs/doc/protocol/nagoya-protocol-en.pdf [Accessed 21 March 2011].
- **43.** Spande, T.F. 1992. Epibatidine: a novel (chloropyridyl) azabicycloheptane with potent analgesic activity from an Ecuadoran poison frog. *Journal of the American Chemical Society*, 114(9): 3475–3478. [CrossRef], [Web of Science ®]
- **44.** Sunder, M. 2007. The invention of traditional knowledge. *Law and contemporary problems*, 70(2): 97–325.
- **45.** Vogel, J.H. 2000. "The legal foundations for benefit sharing: the Convention on Biological Diversity". In *The biodiversity cartel: transforming traditional knowledge into trade secrets*, Edited by: Vogel, J.H. 5–9. Quito: CARE, Proyecto SUBIR.
- **46.** Wahlberg, A. 2008. Pathways to plausibility: when herbs become pills. *BioSocieties*, 3(1): 37–56. [CrossRef], [Web of Science ®]
- **47.** Werning , H. , 1999 . Streit um Froschgene . Reptilia , 15 , 11 – 13 . Available from: http://blogs.taz.de/reptilienfonds/2010/09/30/wem_gehoeren_die_gene_der_froesche/

[Accessed 21 January, 2011] .