Expert Opinion on Therapeutic Patents

ISSN: 1354-3776 (Print) 1744-7674 (Online) Journal homepage: https://www.tandfonline.com/loi/ietp20

Patenting bioactive molecules from biodiversity: the Brazilian experience

Renata Campos Nogueira, Harley Ferreira de Cerqueira & Milena Botelho Pereira Soares

To cite this article: Renata Campos Nogueira, Harley Ferreira de Cerqueira & Milena Botelho Pereira Soares (2010) Patenting bioactive molecules from biodiversity: the Brazilian experience, Expert Opinion on Therapeutic Patents, 20:2, 145-157, DOI: 10.1517/13543770903555221

To link to this article: https://doi.org/10.1517/13543770903555221

Published online: 25 Jan 2010.

Expert Opinion

Patenting bioactive molecules from biodiversity: the Brazilian experience

Renata Campos Nogueira†, Harley Ferreira de Cerqueira & Milena Botelho Pereira Soares

† *Fundação Oswaldo Cruz, Centro de Pesquisas Gonçalo Moniz, Laboratório de Engenharia Tecidual e Imunofarmacologia, Rua Waldemar Falcão, 121-Candeal, Salvador, 40296-750, Bahia, Brazil*

The use of natural compounds from biodiversity, as well as ethnobotanical knowledge, for the development of new drugs is the gate leading to support the conservation of natural resources in developing countries. Recent technological advances and the development of new methods are revolutionizing the screening of natural products and offer a unique opportunity to replace natural products as major source of drug leads. Over the past decades, the Brazilian government established a legislation aiming to grant patent protection in all technological fields. The Convention on Biological Diversity, an international agreement that recognizes the sovereign rights of States over their natural resources, and the Brazilian legislation (Decreto n° 2186-12/01) set for legislative, administrative or policy measures regarding the share of research and product development benefits could be the key for progress in issues related to rational employment of the Brazilian biodiversity and economy, but are far from being effective. Based on literature review, this article provides a brief description of the Brazilian legislation policy regarding intellectual property and biodiversity access, places natural drug discovery in context, analyzes patent cases and highlights critical key issues responsible for the drawback of the whole process that has a direct impact on industrial and research development, nature protection and benefit share with our society.

Keywords: biodiversity, Brazilian legislation, chemical diversity, drug development

Expert Opin. Ther. Patents (2010) ***20****(2):145-157*

1. Introduction

The contribution of natural products in pharmaceutical discovery and development process is unquestionable. Over the last 25 years, 77.8% of the non-biological anticancer drugs were either natural products (*per se* or based thereon) or mimicked natural products in one form or other [1]. In the 1990s, about 80% of the drugs were either natural products or analogues inspired by them. Antibiotics (e.g., penicillin, tetracycline and erythromycin), antiparasitics (e.g., avermectin), antimalarials (e.g., quinine and artemisinin), lipid control agents (e.g., lovastatin and analogues), immunosuppressants (e.g., cyclosporine and rapamycins) and anticancer drugs (e.g., taxol and doxorubicin) have revolutionized medical treatment [2].

Despite this successful record, many pharmaceutical companies have scaled back their natural product research in the past 2 decades. In part, this could be explained by the development of high-throughput screening (HTS) technologies combined with the introduction of combinatorial chemistry. The development of these technologies has led the pharmaceutical companies to believe that their combined use would boost the discovery of novel drug leads. Due to the extreme complexity of natural products libraries, they were incompatible with HTS technologies in the late

informa healthcare

10.1517/13543770903555221 © 2010 Informa UK Ltd ISSN 1354-3776

1980s. Although no conclusive data exist, it is possible that the decreased emphasis on natural products in drug discovery contributed to the decline in the number of new chemical entities (NCE) launched in recent years [3].

Difficulties with ongoing legislation for biodiversity and traditional knowledge access may also have contributed to the decline of natural product research in private sectors [4,5]. A while ago, genetic resources were considered to be a common heritage of humanity, but the United Nations Convention on Biodiversity and the meetings in Rio de Janeiro in 1992 changed the rules and redefined biodiversity ownership. Since then, biodiversity belongs to the country of origin. To address such issues, initially the US National Cancer Institute, then other institutes within the National Institutes of Health and other agencies of the US government, collaborated in the establishment of the International Co-operative Biodiversity groups, modeled on successful, but US oriented, National Cooperative Natural Product Drug Discovery groups in order to aid in biodiversity oriented projects with the first awards in 1992 [6,7]. After this legal mark, all patents from bioactive molecules generated from Brazilian biodiversity would have to clearly state the origin of its source. However, when the European Patent Office and the Brazilian National Institute of Industrial Property (INPI) databases were reviewed, most of the applications involving Brazilian native plants published in the 2003 – 2008 period belonged to Brazilian research centers and universities [8]. However, it should be noted that by stating that the bioactive molecule was synthesized instead of bioprospected or derived from pharmacophore groups based on structures isolated from Brazilian biodiversity, an inventor can avoid the problems with benefit share brought up with ongoing legislation. Considering that 95% of the patent deposits in the world belong to developed countries, this is a potential problem [9].

Nowadays, the advent of new tools for screening predicts a revival of drug discovery inspired by natural sources [2,3,10]. Pharmaceutical companies have reconsidered the role of natural products in drug discovery. In this context, a revision of the Brazilian legislation is mandatory in order to assure public and private sectors access to biodiversity, as well as patent protection, of the discoveries generated. This will contribute to enhancing product development in the country, leading to a sustainable use of our resources.

In this paper, we discuss Brazilian biodiversity potential and ethnobotanical knowledge as a source of new drugs, update the technologies applied in screening of natural products and critically review intellectual property and biodiversity access under Brazilian legislation.

2. The potential of Brazilian biodiversity as a source of new drugs

According to Myers *et al.* (2000), ~ 70% of the world's plant species are found in only 11 countries: Australia, Brazil, China, Colombia, Ecuador, India, Indonesia, Madagascar, Mexico, Peru and Democratic Republic of Congo [11]. The tropical forests of the world are believed to contain > 50% of the plant species on earth. The Amazonian forest, however, is not the only place with high biodiversity in South America. Brazil has two additional biodiversity hotspots, the Atlantic Forest in the Coast and the Cerrado in Central Brazil (**Figure 1**). A biodiversity hotspot is defined as an area containing at least 0.5% of the world's 300,000 known plant species as endemics [11]. In addition, the Caatinga region, located in the Northeastern region, is characterized by high temperatures and low average humidity, with an annual rainfall of 250 – 500 mm. The name 'Caatinga' is a Tupi (indigenous language) word meaning 'white forest' or 'white vegetation' (kaa = forest, vegetation; tínga = white). It covers between 700,000 and 1,000,000 km^2 (depending on the source), > 10% of the Brazilian territory. On the other hand, the Araucaria forest located in the South of Brazil is characterized by a regular distribution of rainfall, in contrast to other country parts, and wide differences among the seasons, temperatures and photoperiods (**Figure 1**).

A large country with different soil types and a wide range of climates provides a unique set of selective pressures for the adaptations of life. The biodiversity and the struggle for life in these different ecosystems provoke the generation of an incredible chemical diversity in living organisms. Plants living under stress develop and survive under intense competition for resources and nutrients. They also need to develop an extraordinary array of defenses, most of which are chemical compounds, to protect themselves from viral, bacterial and fungal pathogens, insects and mammalian predators. The combination of biodiversity with a rich traditional medicine places Brazil in a strategic and privileged position for drug discovery programs.

The Brazilian biodiversity has been a source of compounds for drug development. Many compounds commercialized nowadays by pharmaceutical companies had an origin in plants and animals growing in tropical forests. One of the main drugs used for the treatment of glaucoma is pilocarpine, which is extracted from the plant leaves of genus *Pilocarpus*, mainly *Pilocarpus jaborandi* Holmes (Rutaceae) (**Figure 2**). Pilocarpine has been used in the treatment of chronic open-angle glaucoma and acute angle-closure glaucoma for > 100 years [12]. Pilocarpine is also used to treat dry mouth (xerostomia), a side effect of radiation therapy for head and neck cancers. Pilocarpine stimulates the secretion of large amounts of saliva and sweat. It is interesting to observe that this last indication was described by the American natives centuries ago; in fact 'jaborandi' is the indigenous way of saying 'slobber-mouth plant'.

Another important drug discovered from a Brazilian tropical plant was d-tubocurarin. The compound was first isolated from the 'curare', a common name for various arrow poisons in South America. In the 1930s, Squibb, Inc. of New Jersey (USA) introduced in the market the first drug based on a curare extract called Intocostrin®. The extract was made with

Figure 1. The Brazilian ecosystems.

Chondrodendron tomentosum Ruiz & Pav. (Menispermaceae), one of the 26 different species of liana collected by Richard Gill in Ecuador [13]. Because the extract contains a mixture of different quaternary alkaloids, each batch was standardized by the biological rabbit head-drop test, but different batches were later shown to vary widely in their content of the main active compound d-tubocurarin. Intocostrin was first used to modify drug-induced convulsions [14]. Eventually, the use of this drug would be replaced by electroshock, which was easy to standardize and control. The Intocostrin® (curare) was introduced into anesthesiology by Harold Randall Griffith and Enid Johnson in the early 1940s as a muscle relaxant for surgery, and this methodology was considered a revolution in surgical anesthesia [15]. D-tubocurarin was isolated in 1935 by Harold King (1887 – 1956) in London, working in Sir Henry Dale's laboratory. He also established its chemical structure [16]. D-tubocurarin is an antagonist of nicotinic neuromuscular acetylcholine receptors and is used to paralyze patients undergoing anesthesia. Curares are active (i.e., toxic or muscle relaxing, dependent on the intention of their use) only if given/applied parenterally, that is, by an injection, or direct wound contamination by poisoned dart/arrow tips. It is harmless if taken orally because curare compounds are too large and too highly charged to pass through the lining of the digestive tract to get absorbed into the blood [16]. This is crucial, because the native tribes use curares mainly for hunting purposes, and thus the curare-poisoned prey remained safe to eat. Currently, D-tubocurarin has been replaced by other muscle relaxants. Most of them, such as Atracurium®, however, are in fact developed from the structural information of compounds isolated from plants used for centuries as arrow poisons (**Figure 2**) [17].

Emetine, an alkaloid with emetic properties, was isolated from *Psychotria ipecacuanha* (Brot. Stokes) or *Cephaelis ipecacuanha*, plants belonging to the Rubiaceae family. The name of the plant is the Portuguese form of the native word, i-pe-kaa-guéne, which is said to mean 'road-side sick-making plant'. Emetine was used as a drug to induce vomiting [18,19]. Dehydroemetine is a synthetically produced drug similar to emetine in its anti-amoebic properties [20]. In the US and Europe, it is manufactured by Roche (**Figure 2**).

The poison of the Brazilian snake Bothrops jararaca was the source of a major discovery, the ACE inhibitors used for the treatment of hypertension and some types of congestive heart failure. In the 1960s, the Brazilian scientist Sérgio Ferreira *et al.* described a peptide isolated from the snake poison that inhibits the ACE [21-23]. In 1977, based on this discovery, the pharmaceutical company Squibb (now Bristol-Myers Squibb) developed captopril [24]. Captopril was among the earliest successes of the revolutionary concept of structure-based drug design. The peptide described by Ferreira's group was used as a base for the development of a much simpler compound with the same properties (**Figure 3**).

The benefits that these examples brought to humanity are enormous. It is impossible to estimate the profit for the companies who patented those compounds. The country of Brazil has not received any economic return with these discoveries. The above mentioned episodes happened before the convention of biodiversity when natural resources were considered a common heritage of humanity, and before the patent law of Brazil [25]. Therefore, they are not legally considered misappropriation of traditional knowledge or biopiracy.

Natural product chemical libraries can be constructed based on ethnobotany information, random selection and field observations [26]. Random screening is classified as low rational search process in which the discovery of new hits occurs at lower probability when compared to ethnobotanical selection. Plants collected on an ethnobotanical basis depending upon the disease(s) studied may give higher hit rates than the random approach [27]. Fabricant and Farnsworth identified 122 compounds of defined structure obtained from only 94 species of plants, used globally as drugs, and found that 80% of these plants have had an ethnomedical use identical or related to the current use of the active elements of the plant [28].

3. Natural products in drug discovery process using emerging technologies

The importance of natural products in modern medicine is evident when we analyze the rate of NCE derived from this source introduced in the market. Including the compounds serving as templates for semi-synthetic and total synthetic modification, it represents nearly 50% of all small molecules launched in the years 2000 – 2006 [1]. The high amount of

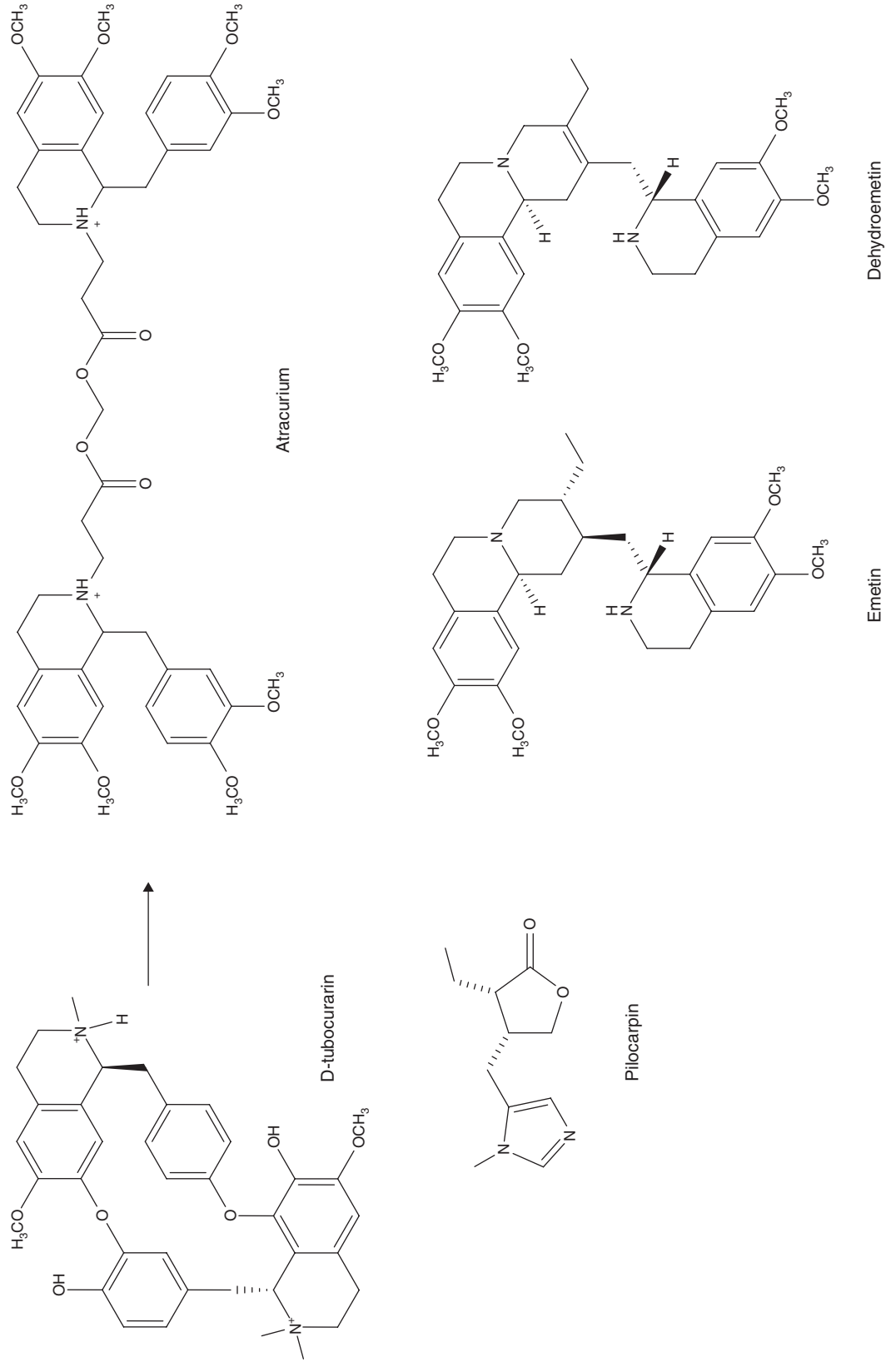

Figure 2. Some important compounds identified from Brazilian biodiversity.

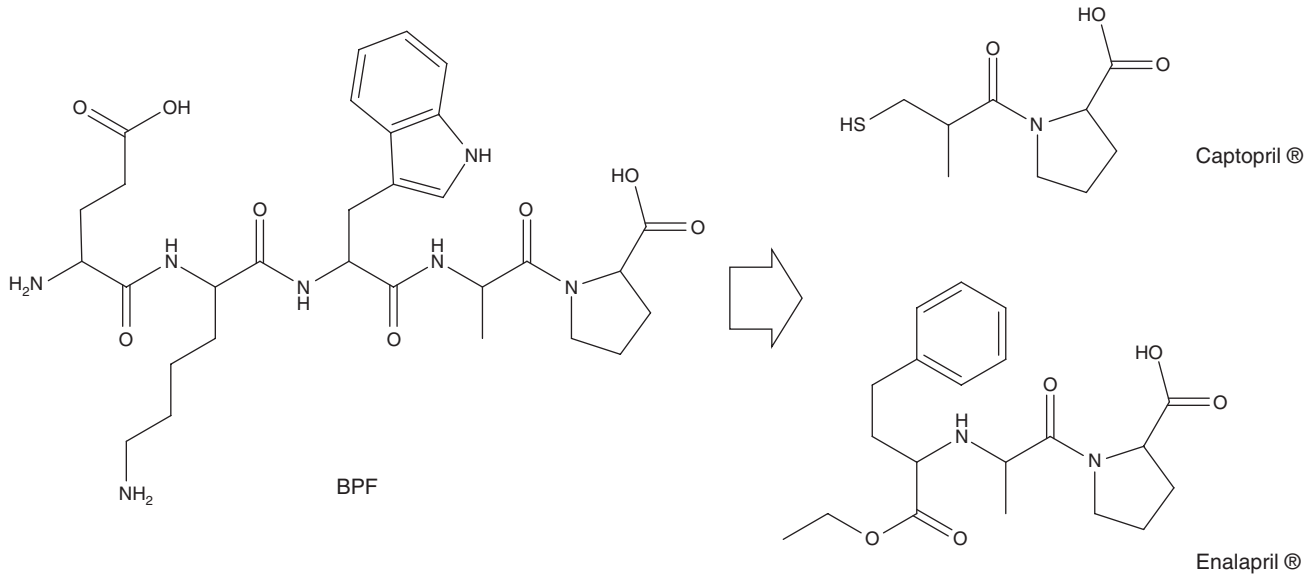

Figure 3. BPF, the peptide isolated from *Bothrops jararaca* snake and the synthetic compounds Captopril® and Enalapril®.
BPF: Bradykinin potentiating factor.

bioactive compounds isolated from natural products may be explained by the evolutionary selective pressure of chemical structures able to interact with a wide variety of proteins and biological targets for specific purposes [29]. Historically, screening of natural materials for biological activity has worked well. Considering only polyketide metabolites, just > 7000 known structures have led to > 20 commercial drugs with a 'hit rate' of 0.3%, which is much better than the < 0.001% hit rate for HTS of synthetic compound libraries [30].

A successful drug is a combination of drug-like properties and biological activity with tolerable toxicity. Poor pharmaceutical properties due to poor solubility, permeability and metabolic stability account for about 40% of compounds that fail to reach the market [31-33]. During the hit identification stage, chemical libraries from different origins can be screened over a defined target using high-through put methods.

A series of studies reveals that natural products have a greater number of oxygen-containing substituents and chiral centers increasing the steric complexity than either synthetic drugs or combinatorial libraries [34]. Moreover, the active compounds are present sometimes in very small amounts in natural matrices, representing a challenge for scientists working on isolation and structure elucidation. This slows the identification process and contributes to the problems of supply and manufacture.

Recent technological advances and the development of new methods are revolutionizing the screening of natural products and offer a unique opportunity to re-establish natural products as a major source of drug leads [3]. The process of natural screening has been streamlined. The methodology of extract preparation and bioassay-guided fractionation are increasingly automated. The last years have witnessed major developments in fermentation technology process, purification, dereplication and structural elucidation of natural products, accounting for sufficient amounts of pure compounds for drug development [29,35-37].

The recent development of hyphenated techniques with combined separation technologies, such as high pressure liquid chromatography (HPLC) with UV detection (LC-UV), mass spectrometry (LC-MS) and NMR (LC-NMR), provided plenty of structural information, leading to a partial or a complete online *de novo* structure determination of the natural products of interest. The combination of metabolite profiling and LC/bioassays gives the possibility of distinguishing between already known bioactive compounds and new molecules directly in crude plant extracts (dereplication). Thus, the tedious isolation of compounds of low interest can be avoided and replaced for a targeted isolation of new bioactive products [26,38,39].

A great range of methods are widely used in predictive and multi-mechanisms screens based on chemical libraries in search for drugs with therapeutic potential [33,40,41]. The goal of those procedures is to evaluate, with reasonable accuracy, the potential of a compound to become a drug. A hit compound is a structure identified by an *in vitro* biological activity screening of a chemical library. In the hit identification stage, compounds with demonstrated initial feasibility of interaction with a target are selected [42]. Based on the affinity to a given target, it is possible to explore the structure–activity-relationship of a chemical structure. After the process of properties optimization of pharmacokinetic/toxicity and before it has reached the drug candidate status, the compound is at lead stage [32].

The lead discovery process can be improved by rational drug design using the pharmacophores of compounds from ethnobotanical information or hits identified with automated HTS of natural products. A drug can be chemically designed, enabling the construction of libraries of new lead active compounds. When the discovery project is focused on orally bioavailable drugs, physicochemical parameters that benefit drug-like properties are enhanced during the lead stage development. This whole process requires very little amount of natural sample using the new technological advances.

4. Intellectual property and biodiversity access under Brazilian legislation

It was the signing of the international environmental law entitled 'Convention on Biological Diversity' (CBD) on 5 June 1992 by 156 countries except the US, in a meeting held in Rio de Janeiro, known as ECO '92, which placed a significant milestone in the settlement of the contemporary ideal of biological diversity protection.

The attention given by the CBD extended beyond the legitimate and necessary protection and biodiversity conservation, concerning the sustainable use of natural resources and fair equitable sharing of benefits arising from their use. This is because biodiversity, besides having intrinsic and intangible value, such as life maintenance, has also a tangible nature, as they hold genetic resources as containing the genetic material of actual or potential value.

It is noticeable that the CBD brought changes of paradigms. The first was about the concept of conservation, which earlier faced a strong preservationist view, that is, conservation of biodiversity would be limited to the creation of protected areas. The CBD incorporated the dimension of conservation through sustainable use of biodiversity, coupled with the idea of sharing benefits derived from its use. In this respect, the model of sustainability is the creation of a system to reconcile and balance the economic development, environmental protection and welfare of the community. The second grants the States sovereign rights over their biological resources, including the traditional knowledge of local communities and indigenous people, in present or potential use or value for humanity. In other words, the genetic resources are no longer considered patrimony of humanity, that is, with free access and use. Thus, the access to a genetic resource, aiming at its application, in industry or not, is subject to authorization by the country holding the genetic resource.

In addition to ensuring the need to seek previous authorization from the country holding the resources, the CBD also guarantees the fair and equitable sharing of benefits arising from the utilization of genetic resources. In other words, in exchange for providing access to genetic components, the donor country should benefit by participating in research (Article 15-6°) or in the search results and benefits of commercial exploitation (Article 15-7°), or in the access and transfer of technology derived from (Article 16-1°) [43]. In this regard, the Article 15 of the CBD indicates that the sharing of benefits and results should be given by mutual agreement between the parties through terms established by the contract of access and benefit sharing.

Brazil, aiming to regularize items 1°, 8° (j), 10° (c), 15°, and 16° (3) and (4) of the CBD, issued a law (Provisional Measure No 2186-16, 2001) which regulates access to genetic heritage of Brazil, both with regard to components as well as associated traditional knowledge. It is worthy to note that, even before the CBD, since 1988, Brazil has launched its commitment to the protection of biological diversity, inserted into the federal constitution [44]. The Provisional Measure No 2186-16/01 adopted the term 'genetic heritage' instead of 'genetic resources', as did the CBD, aiming at strengthening the economic nature of the genetic susceptible monetary valuation as well as any other goods. Moreover, it entered the dimension of conservation through sustainable use, coupled with the idea of sharing benefits derived from this use of biodiversity [45].

The legal definition given to the Genetic Heritage (Item I, Article 7) of the Provisional Measure No 2186-16/01 is the genetic information contained in samples of all or part of plant, fungal, microbial or animal in the form of molecules and substances from the metabolism of the organisms and from the extracts of live or dead organisms, found *in situ*, including domesticated, or kept in *ex situ* collections. This piece of legislation also establishes the conditions for use, marketing and utilization of genetic resources in order to ensure fair and equitable sharing of benefits. In order to do so, it establishes the terms on which will be given the legal relationships, focusing on the following vectors: i) required previous authorization to have access to genetic resources (components or associated traditional knowledge); ii) the formalization of Contract for Use of Genetic Heritage and Benefit-Sharing, as a way to ensure fair and equitable sharing of benefits derived from exploitation of the genetic resource and iii) access to the technological development, the obligation to facilitate access to and transfer of technology as a means of conservation and use of biological diversity of the country.

Indeed, any practice that seeks to access (more specifically, collect, identify and use) samples of genetic heritage components, alive or dead, in their natural habitat (*in situ*) or information from traditional knowledge, for industrial or commercial application, or for any other purpose, except with regard to human genetic resources (Article 3°), is conditional upon the authorization of the Board of Management of Genetic Resources (Article 2°) [46].

It is noteworthy that the Provisional Measure No 2186-16/01 only allow foreign companies to bioprospect the Brazilian genetic patrimony if the activities occur in conjunction and under the coordination of a national public institution (§. 6°, Article 16), being assigned to duty in charge of state (§. 1, Article 16) and deposit sub-samples of (§. 3, Article 16) the genetic components in accessible *ex situ* condition [47].

Also, under the Brazilian law, the granting of industrial property rights of a process or product obtained from samples of genetic heritage components is contingent on evidence that it has met the requirements of Provisional No 2186-16/01, and the applicant must inform the source of genetic material and associated traditional knowledge used, when appropriate.

Thus, the INPI, in Brazil, became critical to achieving the objectives of the Provisional Measure No 2186-16, establishing an instrument of control of the distribution of benefits from the use of genetic resources and other requirements imposed by the above mentioned legislation. At this point, the CBD has recognized that patents and other intellectual property rights may affect the implementation of this convention and shall cooperate in this regard subject to national legislation and international law to ensure that such rights are supportive and not contrary to the purposes of this convention (Article 15-5).

The meeting of this specific requirement, determined by the above mentioned resolution, shall be checked only and solely in Brazilian territory, an issue being particularly discussed, in addition to the CBD, at the World Trade Organization and the World Intellectual Property Organization.

Another important point that needs to be raised is the fact that the Brazilian patent law, unlike almost all other legislation, including the North American, does not allow the patenting of isolated molecules from biodiversity with a particular application. The patenting is restricted to the process of obtaining the given molecule and its application, leaving the document extremely fragile. With the arrival of new technologies explained in the previous section, and re-interest of corporations in the natural sources for the development of new drugs, there is a clear need for an immediate review of intellectual property laws in order to prepare the country to be more competitive.

As previously mentioned, the pharmacologically active ingredients derived from biodiversity, such as extracts and chemicals, are of paramount importance for the development of many innovative products and processes. It seems that the largest number of patents that use biodiversity elements comes from developed countries such as the US and Japan and from the European Community. In these countries, the laws allow almost unrestrictedly the patenting of products and processes that have material which is isolated from its natural environment or derivatives, even pre-existing in nature.

As an example, the article 3°, item '2' Directive 98/44/EC of the European parliament and of the council on the legal protection of biotechnological inventions can be mentioned. It states that a biological material isolated from its natural environment or produced by a technical process may be the subject of an invention even if it pre-exists in nature [48]. In practice, the Directive 98/44/EC applies the same criteria used for chemical molecules to support the patenting of products that contain natural ingredients (substances, extracts, etc.). However, the Brazilian Industrial Law Property (Article 10 of Law 9279/96) does not consider biological material found in nature as inventions and discoveries, even if it is a molecule or a new substance, or even if the product has a feature not attainable by the species under natural conditions and has a new functional purpose, and if it holds the ability to promote a new state of the art, they are not patentable [25].

What is permitted in Brazil is solely the patenting of processes used for the isolation of natural components, only if the process by which the substances and extracts obtained is new. Regarding this point, the INPI has developed a general guideline entitled Guidelines for Examination of Patent Applications in Areas of Biotechnology and Pharmaceuticals, which the examiners of INPI use for the examination of the most common cases of patent applications using biological materials [49].

In a superficial reading of the Federal Constitution articles, it appears that there are no limits to industrial protection to any technological field. The opposite is also true: there is no obligation to grant it without restriction to all fields. Indeed, the Brazilian Federal Constitution assigned to a supplemental law the limits of industrial property of each technological field, the Law 9279 of 14 May 1996 [25]. However, this law, which governs all matters of patents, was restrictive to the point that the use of biological material isolated from its natural environment or produced by a technical process, especially those that pre-determined in nature, are not recognized as inventions.

5. Patent and trade mark cases

There are many extracts from plants such as copaíba (*Copaifera officinalis* L., Fabaceae), andiroba (*Carapa guianensis* Aubl., Meliaceae), cupuaçu (*Theobroma grandiflorum* (Willd. ex Spreng.) K. Schum, Sterculiaceae) and acerola (*Malpighia glabra* L. Malpighiaceae) being patented in cosmetic preparations around the world [50-56].

The use of a popular name as a trademark is not acceptable. The name of cupuaçu fruit, *Theobroma grandiflorum* (Willd. ex Spreng.) K. Schum, Sterculiaceae, native to the Amazon region, was registered as a trademark by a Japanese company in Japan, the US and Europe. Brazilian products composed of cupuaçu ended up being denied entry in those markets. This trademark campaign that begun in 2002 attracted a great deal of attention, launched by the Acre State-based non-governmental organization (NGO) Amazonlink.org, and pushed many NGO groups to join the fight against biopiracy in Brazil [57,58]. In addition, these groups discovered that a series of patents on the production and use of fatty material from cupuaçu seeds were under the Japanese Patent Office (JPO) analysis, despite the processing of cupuaçu seed being used by traditional communities in Amazonia [53-56]. On 1 March 2004, the JPO in Tokyo decided to cancel the trademark Cupuaçu and rejected a patent request for the production of Cupuaçu chocolate [59].

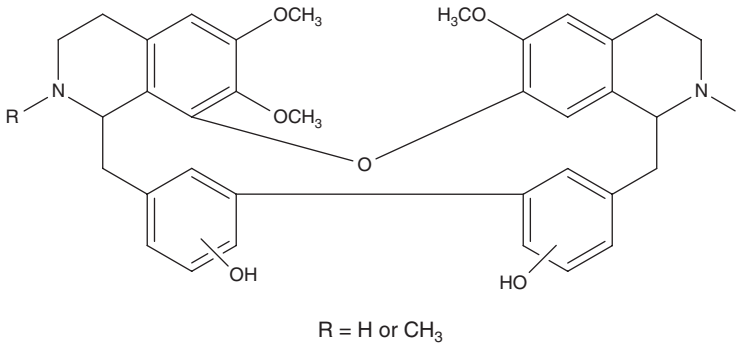

Figure 4. Rupununine derivatives isolated from *Ocotea rodiaei*.

To avoid foreign companies from registering the names popularly used in Brazil, a list with the scientific and customary names of about 3000 species of Brazilian flora was delivered to foreign patent offices and international organizations, such as the World Intellectual Property Organization, which deal with these matters [60].

When bioactive molecules bioprospected with ethnobotanical/ethnomedical studies or screened from biodiversity even when they were used as scaffolds for synthetic or semi-synthetic derivatives are patented, this represents a misappropriation of traditional knowledge or biological resources. Unless a previous agreement to follow the new rules on informed consent and benefit sharing is set up, this procedure is illegal. It is very difficult, or nearly impossible, to monitor bioactive molecules derived from biodiversity when its origin is not given in the patent document. Two cases are being discussed in Brazilian media and are worth mentioning.

5.1 Rupununine: a bioactive compound isolated from *Ocotea rodiaei* (R. H. Schomb.) Mez (Lauraceae)

Conrad Gorinsky grew up in Rupununi, a village in southern Guyana rainforest on the northern edge of the Amazon basin. He completed a Ph.D. program at Barts Hospital in London, studying the natural drugs and poisons of the forest. At that time, he was considered a campaigner for the rights of indigenous peoples and founded the UK-based Foundation for Ethnobiology. One of his studies was about the constituents of greenheart tree (*Ocotea rodiaei*). For centuries, local women used the tree's nuts as a contraceptive to control menstruation and made infusions of the bark to prevent malaria fevers [61,62]. His research led to the isolation of active bisbenzylisoquinoline alkaloids that were named rupununine (**Figure 4**). The purified compound and its derivatives are the claims of a patent named 'biologically active rupununines' deposited in 1994 followed by another deposit in 1996 claiming the treatment of lung tumors using these substances, both under his name [63-65].

It is regrettable that this same patent request would never be granted in Brazil, because living beings and molecules isolated from biodiversity, as previously mentioned, are not patentable according to Brazilian Patent Law (1996). After the CBD convention in 1992, the biodiversity resources were nationalized, the whole society begun to refer to such bioprospecting research as 'biopiracy'. Brazilian and Guyanese Wapishanas Indians prepared a lawsuit in the European court against Gorinsky, accusing him of biopiracy. Those episodes led to the banishment of researchers from entering Indian villages [61].

5.2 Peptides isolated from skin secretions of the South American frog *Phyllomedusa bicolor* (Hylidae)

Recently, the research and development of compounds from *Phyllomedusa bicolor*, a small Amazonian frog used for 'hunting magic' by several groups of Panoan-speaking Indians in the borderline between Brazil and Peru, is opening a debate regarding intellectual property rights [66].

Evolutionarily, frogs have developed the production of powerful substances to defend themselves due to the lack of physical strength and sharp teeth, making them a great source of new therapeutics [67]. Based on the indigenous people's knowledge and traditions, scientists had begun to research the active compounds present in the frogs responsible for the pharmacological activities observed.

The skin secretion of *P. bicolor*, which is rich in peptides, includes vasoactive and opioid peptides, and a new peptide named adenoregulin [68,69]. Skin secretion, previously scraped from a live frog and stored dry on a stick, is mixed with saliva and introduced into fresh burns on the arms or chest. This induces, within minutes, violent illness, including rapid pulse, incontinence and vomiting, after which the recipient lapses into a state of listlessness and, finally, into a state perhaps to be described as euphoric; the subject later claims to be a better hunter, with improved stamina and keener senses [68].

Based on this discovery, some companies have already patented the peptides from *P. bicolor*. The main applications of these patents are the use of dermorphin and deltorphin in preventing cerebral ischemia and as a method for

treating cytokine-mediated hepatic injury [70-74]. It does not appear that any group signed the share of profits they might derive from *Phyllomedusa* with Brazil, Peru or with the indigenous tribes from which the frog-based effects were identified.

Despite this, Brazilian newspapers report that at least eight of the international patents on dermorphin and deltorphin have been questioned because they had been granted after the declaration of the United Nation's CBD, which states the 'sovereign right to exploit their own resources' [75]. However, according to Cooper and Plotkin, the US patents remain legitimate because the US has not ratified the convention [66]. In 2006, The New York Times published an article about this situation: an Indian chief says that 'Kampô's use is nothing less than biopiracy; if economic gain is generated by the remedy, the Katukina tribe should get a cut' [76]. In 2004, the Brazilian national agency of health monitoring (Anvisa), prohibited all publicity of therapeutic use of *Phyllomedusa* secretions 'Vacina do sapo Kampô' and considered its exploitation an environmental crime [77]. However, it is important to point out that the original discovery was reported in 1992 [68] and this may represent an example where materials were collected before the CBD convention.

In 2003, the Brazil's Ministry of Environment launched a project named kampô, in order to identify, in the secretion of the frog, molecules or active principles for the development of pharmaceuticals and cosmetics and to study the biology and ecology of the frog, giving support to analyze the sustainability of economic use and management plan for the species and to finally perform an anthropological study of indigenous knowledge related to the use of Kampô [78,79]. The project, by integrating the traditional use of biodiversity, scientific research and technological development, is intended to be developed within an integrated approach, seeking to build the paths of promoting sustainable use of biodiversity resources, while ensuring fair and equitable sharing of benefits due to the use of such knowledge, promoting respect and appreciation for cultural diversity, and thus generating benefits to the structuring of environmental public policies more inclusive and in accordance with the demands of society.

The examples presented above show that much work remains to be done to ensure that developing countries are treated as equal partners in the research and development of traditional knowledge and biological resources.

5.3 The Samoan traditional knowledge and the discovery of prostratin: an example to be followed

The prostatin case, one of the few ethnobotanical discoveries that led directly to an active agent, is a rare example of effective compensation mechanism established between Aids Research Alliance (ARA), the University of California at Berkeley and the Samoan government.

In 1991, the National Cancer Institute isolated prostatin, a chemical compound present in the bark of the mamala tree (*Homalanthus nutans*), from samples identified and collected by the American ethnobotanist Professor Paul Cox, in the village of Falealupo used by the healers to treat a disease called locally as 'Fiva Sama Sama', a form of hepatitis. Later on, it was discovered that this compound holds enormous therapeutic potential as an anti-AIDS drug and it was patented. An agreement between ARA and the Samoan government was signed with Professor Cox's support. It was negotiated that 20% of any profits made from prostatin will go directly to Samoa. In 2004, in order to ensure the plentiful supply of prostatin without depending directly from the mamala's tree bark, the cloning of the prostatin genes was achieved aiming at its synthesis in the UC Berkeley lab. An agreement was signed establishing that any royalties from the sale of a gene-derived drug would be equally shared with the people of Samoa [66,80]. Once more, Samoa's sovereignty over its natural resources and the contributions of Samoan healers were recognized.

This collaboration provides opportunities for all the parts involved, and humanity will benefit from this discovery. The lessons from native collective knowledge can and should be used, as long as there is respect for their rights and by honoring their cultures and ensuring prosperity for all stakeholders.

6. Conclusion

The country of Brazil is in a unique position to explore its natural potential resources. However, it currently assumes the insignificant role of a raw material supplier. Biodiversity's legal access regulations and patent protection comprise a huge problem for the scientific and technological development of the national pharmaceutical industry.

While an atmosphere of anxiety surrounding the notion of biopiracy remains, few researchers are out there actually studying Brazilian biodiversity. Important science research is lost out to bureaucracy, while many species are disappearing from earth before we can protect and study them. At the deeper level, there are many different ideas about what is classifiable as biopiracy and, instead of controlling biopiracy, government and NGOs are undermining local and foreign biodiversity research.

Because it is very time consuming to collect plants with ethnomedical history, random collection followed by HTS *in vitro* assays may be the future in pharmaceutical industries [81]. However, ethnobotanical studies in research centers and universities will remain major contributors to drug discovery process [82]. Therefore, the search for bioactive compounds from biodiversity that will serve as a scaffold for lead synthetic or semi-synthetic development, assuring patent protection with the new tools available, will evolve.

7. Expert opinion

Due to the many examples of biodiversity exploration without economic return to Brazil, very negative views concerning such efforts are widely distributed among many levels of Brazilian

society, NGOs and decision makers. Strict laws governing the way Brazil's biodiversity is used for research and education discourage suitable collaborative relationships among universities, research institutes and private sectors.

We are convinced that to overcome the problems posed by patents of bioactive molecules from biodiversity outside the national boundaries, it is necessary to invest in the country's research, human resources and particularly to reformulate our legislation.

Extensive investment in research will provide conditions for more Brazilians scientists to study the potential of biodiversity. There are more plant species collections of Brazilian flora outside our boundaries than in our museums. The three biggest herbarium collections in Amazonia represent only 6% of what is found in the National Museum of Natural History of Paris in France [58]. This sole Amazonian vegetal species example illustrates that there is still a lot to be prospected from biodiversity. Human resources well trained in scientific matters, intellectual property and able to transfer the benefit of this research for private sectors are key points for the industrial development. A recent example of a native species that has been taken up as an economic opportunity outside the country is the Brazilian guava (*Acca sellowiana* O. Berg, Myrtaceae), a fruit from southern Brazil. It was introduced into New Zealand in 1908, where it serves as the raw material for > 20 products, including champagne, as well as preserves, juices and essential oils [83]. Massive education may provide a realistic definition of which are the benefits of research with sustainable use of biodiversity, and this will lead to the conservation of natural resources.

As already mentioned, the Brazilian Law of Industrial Property (Law 9279/96) does not allow the patenting of living biological material found in nature, even if isolated or modified by human intervention (e.g., plants, animals, extracts or substances), with the exception of microorganisms that are genetically modified. This restriction was motivated by the Brazilian fear, at the time the Industrial Property Law was prepared, that by allowing the patenting of products and processes of living beings and their derivatives, the country would be legitimizing and recognizing the many existing patents abroad course patented by other countries, which have elements of Brazilian biodiversity. It was feared that the recognition of these kinds of patents would cause a duty to respect (by the phenomenon of the extension of patents) the monopoly of the foreign market for an asset that is rightfully Brazilian. During the 1990s the idea that genetic resources were regarded as a world heritage was very strong. Although the CBD has recognized in that decade the sovereign right of each country over its biological resources, such fear still shows to be latent and justified, as some countries have not acceded to the CBD so far, including the US, who also have patents containing elements of Brazilian diversity. One can even understand that, at that historical moment, the option of not permitting the patenting of living biological material was justified. Nowadays, when Brazil has proved efficiency in the development of innovative technologies capable of patenting, the social and economic loss is greater.

It is worth noting that the absence of an effective universal system of patents on inventions that use biodiversity has created conflicts. There were discoveries made pre-CBD, patents issued after 1992 that might well have been in the respective patent office years before the CBD and cases of patents granted on products or processes derived from biodiversity without any authorization for access. These are very distinct situations but are being considered the same.

In order to avoid misappropriation or unfair use of genetic resources or associated traditional knowledge, the solution would be the harmonization between the access system of distribution and intellectual property system by implementing international rules. In this context, the TRIPS agreement itself, the World Trade Organization could incorporate such rules, conditioning the granting of patents to verify the legality of access and benefit sharing, as Brazil has done internally in its legal framework.

This will bring security for companies willing to invest in drug screening of natural products without being branded as 'biopirates'. Also, researchers will no longer suffer from a bad reputation caused by over-reaction of uninformed groups. The fewer the research projects, the fewer the patents registered, which leads to underdevelopment of the segment. Without the active involvement of government, this approach is bound to fail. On the other hand, efforts at the international level must be reinforced. It requires strong political will and a dedicated team of specialists able to recognize similarities between novel chemical structures patented and bioactive molecules from biodiversity, or even pharmacophore groups, in addition to being capable of deeply understanding the patent legislation. This is not easy to achieve and depends on the efforts made at the national level: investments on research, training of human resources and reformulation of our patent legislation. We cannot expect the world to change, but campaigns are necessary to provide information worldwide about the causes and consequences of biopiracy for developing countries.

There is no question that inventions related to elements of their genetic heritage, as those using pharmacologically active ingredients, such as extracts and chemicals, are of upmost importance for the development of many innovative products and processes. Extremely promising fields of technology that could boost scientific progress and the development of the national and regional production based on knowledge and innovation are being neglected without the right of patent protection.

Considering that the benefits of exploitation of biodiversity are enormous, opposing the patenting of such inventions would represent a delay in the progress of science and technology in Brazil, which are also contemplated, explicitly, in its constitution (Articles 218 and 219). It also reinforces

the dependence of foreign technology and discourages the development of industrial inventions in this field [84].

Finally, a positive contribution from all entities involved, especially the government, is mandatory to ensure the rights of Brazilian scientists to research Brazilian biodiversity and proper procedures for those who want to bioprospect the country's biodiversity giving the world a chance to develop effective new medicines.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript. RC Nogueira had a fellowship from Fundação de Amparo a Pesquisa do Estado da Bahia (FAPESB). MBP Soares holds a senior researcher fellowship from the Brazilian National Council of Research (CNPq).

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Newman DJ, Cragg GM. Natural products as sources of new drugs over the last 25 years. J Nat Prod 2007;70:461-77
•• **An excelent review about the importance of natural products in drug discovery.**
2. Li JW, Vederas JC. Drug discovery and natural products: end of an era or an endless frontier? Science 2009;10:161-5
• **The article gives a good perspective about the future in the dug discovery with natural products using emerging technologies.**
3. Lam KS. New aspects of natural products in drug discovery. Trends Microbiol 2007;15:279-88
4. Tan G, Gyllenhaal C, Soejarto DD. Biodiversity as a source of anticancer drugs. Curr Drug Targets 2006;7:265-77
5. Calderon LA, Silva-Jardim I, Zuliani JP, et al. Amazonian biodiversity: a view of drug development for Leishmaniasis and malaria. J Braz Chem Soc 2009;20:1011-23
6. Soejarto DD, Fong HH, Tan GT, et al. Ethnobotany/ethnopharmacology and mass bioprospecting: issues on intellectual property and benefit-sharing. J Ethnopharmacol 2005;22:15-22
•• **An excellent introduction in bioprospection and benefit-share.**
7. Tedlock B. Indigenous heritage and biopiracy in the age of intellectual property rights. Explore 2006;2:256-9
8. Balbani AP, Silva DH, Montovani JC. Patents of drugs extracted from Brazilian medicinal plants. Expert Opin Ther Pat 2009;19:461-73
9. Kartal M. Intellectual property protection in the natural product drug discovery, traditional herbal medicine and herbal medicinal products. Phytother Res 2007;21:113-19
10. Harvey AL. Natural products as a screening resource. Curr Opin Chem Biol 2007;11:480-4
11. Myers N, Mittermeler RA, Mittermeler CG, et al. Biodiversity hotspots for conservation priorities. Nature 2000;403:853-8
12. Rosin A. Pilocarpine. A miotic of choice in the treatment of glaucoma has passed 110 years of use. Oftalmologia 1991;35:53-5
13. Gill RC. Provided source of Chondrodendron tomentosum for intocostrim (Squibb). In: White water and black magic. New York: Henry Holt; 1940
14. Cummins JA. Experience with 3057 administrations of curare to 232 psychotic patients treated with metrazol. Psychiatr Q 1943;17:655-70
15. Griffith HR, Johnson GE. The use of curare in anaesthesia. Anesthesiology 1942;3:418-19
16. King H. Curare alkaloids. Part V. Alkaloids of some Chondrodendron species and the origin of radix pareira bravae. J Chem Soc 1940;137:737-46
17. Raghavendra T. Neuromuscular blocking drugs: discovery and development. J R Soc Med 2002;95:363-7
18. Knight R. The chemotherapy of amoebiasis. J Antimicrob Chemother 1980;6:577-93
19. Chintana T, Sucharit P, Mahakittikun V, et al. In vitro studies on the sensitivity of local Entamoeba histolytica to anti-amoebic drugs. Southeast Asian J Trop Med Public Health 1986;17:591-4
20. Powell SJ, McLeod I, Wilmot AJ, Elsdon-Dew R. Dehydroemetine in amebic dysentery and amebic liver abscess. Am J Trop Med Hyg 1962;11:607-9
21. Ferreira SH. A bradykinin-potentiating factor (bpf) present in the venom of Bothrops jararaca. Br J Pharmacol Chemother 1965;24:163-9
22. Ferreira SH, Bartelt DC, Greene LJ. Isolation of bradykinin-Potentiating peptides from Bothrops jararaca venon. Biochemistry 1970a;9:2583-93
23. Ferreira SH, Greene LH, Alabaster VA, et al. Activity of various fractions of bradykinin potentiating factor against angiotensin I converting enzyme. Nature 1970b;24:379-80
24. Atkinson AB, Robertson JIS. Captopril in the treatment of hypertension and cardiac failure. Lancet 1979;2:836-9
25. Industrial Property Law. 1996. Available from: http://www.planalto.gov.br/ccivil_03/Leis/L9279.htm. [Last accessed 28 September 2009]
26. Queiroz EF, Wolfender JL, Hostettmann K. Modern approaches in the search for new lead antiparasitic compounds from higher plants. Curr Drug Targets 2009;10:202-11
27. Slish DF, Ueda H, Arvigo R, Balick MJ. Ethnobotany in the search for vasoactive herbal medicines. J Ethnopharmacol 1999;66:159-65
28. Fabricant DS, Farnsworth NR. The value of plants used in traditional medicine for drug discovery. Environ Health Perspect 2001;109:69-75
29. Koehm FE, Carter GT. The evolving role of natural products in drug discovery. Nat Rev Drug Discov 2005;4:206-20
30. Weissman KJ, Leadlay PF. Combinatorial biosynthesis of reduced polyketides. Nat Rev Microbiol 2005;3:925-36
31. Di L, Kerns EH. Profiling drug-like properties in discovery research. Curr Opin Chem Biol 2003;7:402-4088
32. Keller TH, Pichota A, Yin Z. A practical view of druggability. Curr Opin Chem Biol 2006;10:357-61
33. Nogueira RC, Oliveira-Costa JF, de Sá MS, et al. Early toxicity screening and selection of lead compounds for

parasitic diseases. Curr Drug Targets 2009;10:291-8

34. Feher M, Schmidt JM. Property distributions: differences between drugs, natural products, and molecules from combinatorial chemistry. J Chem Inf Comput Sci 2003;43:218-27

35. Butler MS. The role of natural product chemistry in drug discovery. J Nat Prod 2004;67:2141-53

36. Butler MS. Natural products to drugs: natural product-derived compounds in clinical trials. Nat Prod Rep 2008;25:475-516

•• **An excelent review about the importance of natural products in drug discovery. The article presents a large number of compounds under clinical evaluation.**

37. Leeds, JA, Schmitt, EK, Krastel P, et al. Recent developments in antibacterial drug discovery: microbe-derived natural products–from collection to the clinic. Expert Opin Investig Drugs 2006;15:211-26

38. Wolfender JL, Queiroz EF, Hostettmann K. The importance of hyphenated techniques in the discovery of new lead compounds from nature. Expert Opin Drug Discov 2006;1:237-60

• **Application of hyphenated techniques in drug discovery.**

39. Wolfender JL, Queiroz EF, Hostettmann K. Development and application of LC-NMR techniques to the identification of bioactive natural products. In: Colegate SM, Molyneux RJ, editors, Bioactive natural products: detection, isolation, and structural determination. 2nd edition. Boca Raton, New York: CRC. Press, Taylor & Francis Group; 2008. p. 143-190

40. Koehn FE. High impact technologies for natural products screening. Prog Drug Res 2008;65:177-210

41. Mishra KP, Ganju L, Sairam M, et al. A review of high throughput technology for the screening of natural products. Biomed Pharmacother 2008;62:94-8

42. Nwaka S, Hudson A. Innovative lead discovery strategies for tropical diseases. Nat Rev Drug Discov 2006;5:941-55

43. Varella MD. Tipologia de normas sobre controle do acesso aos recursos genéticos in Diversidade Biológica e Conhecimentos Tradicionais. Del Rey, Belo Horizonte, 2004

44. Provisional Measure No 2186-16/01. 2001. Avaliable from: http://www.planalto.gov.br/ccivil_03/mpv/2186-16.htm. [Last accessed 28 September 2009]

45. Vélez E. A Repartição de benefícios decorrentes do acesso à biodiversidade e ao conhecimento tradicional. São Paulo: Anais do XXV Seminário Nacional da Propriedade Intelectual, ABPI, 2005

46. Pria GD. A Repartição de benefícios decorrentes do acesso à biodiversidade e ao conhecimento tradicional. São Paulo: Anais do XXV Seminário Nacional da Propriedade Intelectual, ABPI, 2005

47. Nodari RO, Guerra MP. Biodiversidade: aspectos biológicos, geográficos, legais e éticos. Farmacognosia: da planta ao medicamento. 5ª edition. Porto Alegre: UFRGS/UFSC, 2003

48. Directive 98/44/EC of the European Parliament and of the Council on the Legal Protection of Biotechnological Inventions. 1998. Available from: http://www.wipo.int/meetings/en/doc_details.jsp?doc_id=1701. [Last accessed 28 September 2009]

49. INPI. Diretrizes para o Exame de Pedidos de Patente nas áreas de Biotecnologia e Farmacêutica. 2002. Available from: http://www.inpi.gov.br/menu-esquerdo/patente/pasta_manual. [Last accessed 28 September 2009]

50. Technico-flor (S.A.). Cosmetic or food compositions containing copaiba. WO9400105; 1994

51. Amway Corporation. Skin whitener composition containing acerola cherry fermentate. US5747006; 1997

52. Yves Rocher biolog vegetale. Cosmetic or pharmaceutical composition containing an andiroba extract. US5958421; 1999

53. The Body Shop International. Cosmetic composition comprising cupuacu extract. GB2321644A; 1998

54. Asahi Foods Co., Ltd. Fat originating in cupuassu seed, process for producing the same and use thereof. EP00964765; 2000

55. Asahi Foods Co. Oil and fat derived from cupuacu, Theobroma grandiflorum seed, method for producing the same and its use. JP2001348593; 2001

56. Asahi Foods Co., Ltd. Fat originating in cupuassu seed, process for producing the same and use thereof. WO0125377; 2002

57. Schmidlehner M. Cupuaçu, a case of Amazonian self-assertion. Seedling, 2003. Available from: www.grain.org [Last accessed 14 September 2009]

58. Homma AKO. Biopirataria na Amazônia: como reduzir os riscos? Amazônia: Ci. & Desenv. 2005

59. Biopiracy in the Amazon. The cupuaçu case. 2009 Avalaible from: http://www.amazonlink.org/biopiracy/cupuacu.htm. [Last accessed 26 September 2009]

60. IP-Watch. Brazil fights to make case for international biodiversity protection. 2006. Available from: www.ip-watch.org [Last accessed 14 September 2009]

61. Vidal J. Biopirates who seek the greatest prizes. The guardian (U.K.), 15 November 2000. Available from: www.guardian.co.UK/print/0,3858,4090906,00html [Last accessed 14 September 2009]

62. Riley M, editor. Indigenous intellectual property rights: legal obstacles and innovative solutions. Walnut Creek, CA: Altana Press; 2004

63. Gorinsky C. Biologically active rupununines. US5569456; 1994

64. Gorinsky C. Biologically active rupununines. EP19940300726; 1996

65. Gorinsky C. Biologically active rupununines. US6048867; 1996

66. Cooper B, Plotkin MJ. Pharmaceuticals and frogs. The Oculusl 2006;5.2:54-69

• **A comprehensive analysis of biodiversity exploitation and partition of benefits.**

67. Plotkin MJ. Medicine quest: in search of nature's healing secrets. New York: Penguin Group; 2000

68. Daly JW, Caceres J, Moni RW, et al. Frog secretions and hunting magic in the upper Amazon: identification of a peptide that interacts with an adenosine receptor. Proc Natl Acad Sci USA 1992;89:10960-3

69. Lazarus LH, Bryant SD, Cooper PS, Salvadori S. What peptides these deltorphins be. Prog Neurobiol 1999;57:377-420

70. Oeltgen PR, Kindy MS, Bishop PD. Method for treating ischemia. WO056766; 1999

71. Oeltgen PR, Kindy MS, Bishop PD. Method for treating ischemia. US6294519; 2001

72. Oeltgen PR, McClain CJ, Barve S, Bishop PD. Method for treating cytokine mediated hepatic injury. US6380164; 2002a

73. Oeltgen PR, Kindy MS, Sanchez, Bishop PD. Use of deltorphin a and/or dermorphin h for protection against ischemia and reperfusion injury. WO022152; 2002b

74. Oeltgen PR, Kindy MS, Sanchez, Bishop PD. Use of d-leu deltorphin for protection against ischemia and reperfusion injury. WO030450; 2002c

75. Secretariat of the Convention on Biological Diversity. 2000. Sustaining life on Earth: how the Convention on Biological Diversity promotes nature and human well-being. Avalaiable from: http://www.biodiv.org/doc/publications/cbd-sustainen.pdf. [Last accessed 20 September 2009]

76. Prada P. Poisonous Tree Frog Could Bring Wealth to Tribe in Brazilian Amazon. The New York Times, 2006

77. Anvisa. Suco Noni e Vacina do Sapo Kambô têm propagandas suspensas. 2004. Avalaible from: http://www.anvisa.gov.br/DIVULGA/noticias/2004/300404.htm [Last accessed 26 September 2009]

78. Ministério do meio ambiente. Secretaria do desenvolvimento sustentável. Projeto Kampô. Avaliable from: http://www.mma.gov.br/sitio/index.php?ido=conteudo.monta&idEstrutura=35&idConteudo=3185. [Last accessed 26 September 2009]

79. Martins HM. Os Katukina e o kampô. Aspectos etnográficos da construção de um projeto de acesso a conhecimentos tradicionais. Universidade federal de Brasília, 2006

80. Lynn Y. 2004 Samoa's gift to the world. A new way to fight AIDS. Avalaible from: http://newscenter.lbl.gov/ [Last accessed 26 September 2009]

81. Turner DM. Natural product source material use in the pharmaceutical industry: the Glaxo experience. J Ethnopharmacol 1996;51:39-43

82. Schuster BG. A new integrated program for natural product development and the value of an ethnomedical approach. J Altern Complement Med 2001;7:61-72

83. Osava M. Biodiversity Goes to Market. 2007. Available from: http://ipsnews.net/news.asp?idnews=36442 [Last accessed 14 September 2009]

84. The Federal Constitution, 1988. 1988. Available from: http://www.planalto.gov.br/ccivil_03/constituicao/constitui%C3%A7ao.htm. [Last accessed 28 September 2009]

Affiliation

Renata Campos Nogueira[†1],
Harley Ferreira de Cerqueira[2] &
Milena Botelho Pereira Soares[1,3]
[†]Author for correspondence
[1]Fundação Oswaldo Cruz,
Centro de Pesquisas Gonçalo Moniz,
Laboratório de Engenharia Tecidual e Imunofarmacologia,
Rua Waldemar Falcão,
121-Candeal, Salvador,
40296-750, Bahia, Brazil
Tel: +55 71 3176 2260; Fax: +55 71 3176 2272;
E-mail: recanog@hotmail.com
[2]Pontifícia Universidade Católica de São Paulo,
PUC-SP, Rua Monte Alegre,984,
Perdizes, 05014-901,
São Paulo, SP, Brazil
[3]Centro de Biotecnologia e Terapia Celular,
Hospital São Rafael,
Av. São Rafael, 2152,
São Marcos, 41253190,
Salvador, Bahia, Brazil