Brazilian biodiversity as a source of new medicines

A Biodiversidade brasileira como fonte de novos medicamentos.

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RESUMO

O uso de plantas medicinais está presente em todas as culturas e o Brasil, além da sua biodiversidade, tem uma longa tradição no seu estudo. Entretanto, substâncias isoladas de organismos marinhos, escorpiões, aranhas, répteis e anfíbios também podem ser usadas com a mesma finalidade. O objetivo deste trabalho é traçar uma análise histórica do que foi feito nessa área na época Colonial e no Império e as pesquisas mais recentes feitas no Brasil abrangendo nesta área no período 2011-2012. O artigo apresenta 25 substâncias isoladas de 23 espécies de plantas medicinais utilizadas como antihipertensiva, anti-inflamatória, antitumoral, antiparasitária, antidiurética, antinociceptiva, antibiótica, no tratamento doenças cardíacas e contra mordida de cobras. Mostra ainda o desenvolvimento de agentes antihipertensivos a partir da descoberta da bradicinina. A importância de substâncias farmacologicamente ativas obtidas de organismos marinhos (esponjas e algas) também é discutida.

Palavras-chave: diversidade biológica, plantas medicinais, produtos naturais

ABSTRACTS

The use of medicinal plants is present in all cultures and Brazil has a long tradition in its study. However, substances isolated from marine organisms, scorpions, spiders, reptiles and amphibians could also be used with the same purpose. The aim of this paper is to analyze what was described in the Colonial and Imperial epochs and compare with more recently research made in the period 2011- 2012. 25 substances are describe isolated from 23 species of medicinal plants used as antihypertensive, antiinflammatory, antitumoral, antiparasitic, antidiuretic, antinociceptive, antibiotic, in the treatment of cardiac diseases and against snake bites. The development of antihypertensive agents based on the discovery of bradykinin as well as the importance of pharmacologically active substances isolated from marine organisms (sponges and algae) are also discussed.

Keywords: biological diversity, medicinal plants, natural products

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INTRODUCTION

The term biodiversity is a neologism, a contracted form of biological diversity, that appeared for the first time in the scientific literature in the second half of 1986 at the National Forum on Biological Diversity held in Washington, D.C. Two years later, biologist Edward Wilson (1988) used the term as the title of a book he edited with the proceedings of that forum. The term has been used to describe 'the variety of life forms, the ecological roles they perform, and the genetic diversity they contain (Murphy, 1988). Thus, biodiversity means not only the huge variety of life that exists in our planet, but also the dynamic interaction between genes, populations and their ecosystems.

The origin of life is a matter of interest for philosophers and scientists since Antiquity. .

According to Wilson (1988), there are approximately 750,000 species of insects, 41,000 of vertebrates, and 250,000 of vascular plants and bryophytes living on the earth. The remainder comprise a complex array of invertebrates, fungi, algae and microorganisms. He also stressed that no one knows the number of species, nor even to order of magnitude, but based on his own experience, he suggests that the absolute number falls somewhere between 5 and 30 millions.

The fact is that independently of this number more than a half of living organisms are concentrated in 15 countries: Australia, Brazil, China, Colombia, Congo, Costa Rica, Ecuador, India, Indonesia, Madagascar, Malaysia, Mexico, Panamá, Peru and Zaire.

This biodiversity is a potential source of among other things pigments, dyes, fragrances, aromas, flavors, cosmetics, perfumes, insecticides and medicines.

Brazilian biodiversity

In 1997, the Brazilian Environment Ministry began a project to evaluate the number of each group of organisms (birds, insects, plants, reptiles, amphibians, mammals, fishes) that form the country's biological diversity. The first data were organized and analyzed in 1999 and available in the site of that Ministry from 2003. The results show that with a territory of 8,515,767 km^2, Brazil harbors 525 species of mammals (among them 75 primates, 32 carnivores, 36 cetaceans), 600 amphibians, 468 reptiles, 1.688 birds, 4.450 fishes, 670 mollusks, 4.000 spiders, 26.000 moths and butterflies, 700 termites, 30,000 beetles, 1,500 mites, 3,125 bryophytes, 1,200-1,400 Pteridophytes, 15 Gymnosperms and 40,000-45,000 Angiosperms (MMA, 2003). Table 1 shows a comparison of the Brazilian biodiversity with that of the whole world.

Table 1 Comparison of the Known biodiversity of Brazil and the world

Organism	Brazil	World
Virus	310-410	3,600
Bacteria and Archaea	800-900	4,310
Fungi	13,090-14,510	70,600-72,000
Algae	4,180-5,770	37,700-42,900
PLANTS		
Bryophytes	3,125	14,000
Pteridophytes	1,200-1,400	9,000-12,000
Gymnosperms	15	802
Angiosperms	40,000-45,000	250,000
ANIMALS		

VERTEBRATES		
Amphibians	600	5,504
Birds	1,696	9,900
Reptiles	633	8,163
Fishes	3,400	28,400
INVERTEBRATES		
mollusks	670	30,000
spiders	4,000	38,000
mites	1,500	35,000
moths and butterflies	26,000	255,000

Compiled MMA, 2003.

This megabiodiversity is distributed in six biomes: the Amazon forest, the Atlantic forest, Caatinga, Cerrado, Pampas and Pantanal (Figure 1). Table 2 shows the total and the percentage area of each biome.

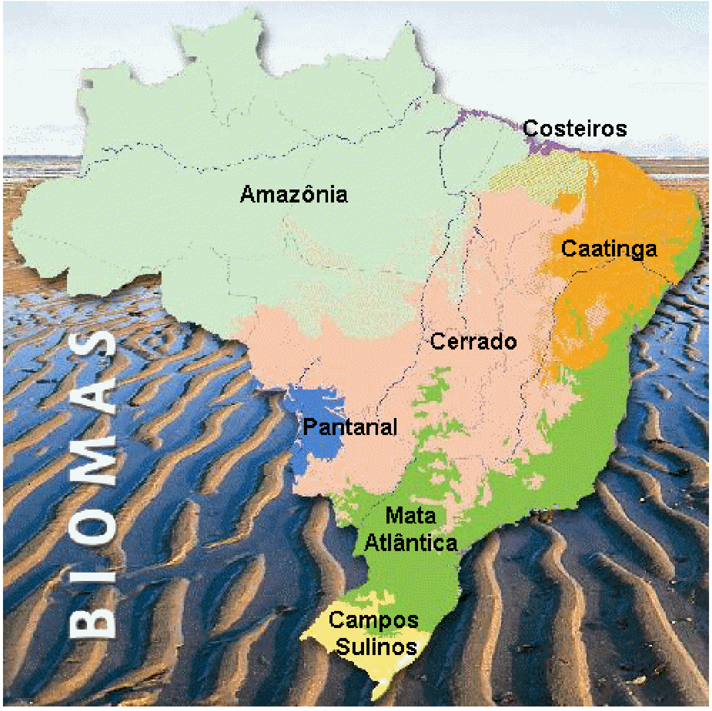


Figure 1 Brazilian Biomes (IBAMA, 2013)

Table 2 Distribution the percentile area of each biome

Biome	Area	
	km²	%
Amazonia	4,196,943	49,29
Cerrado	2,036,448	23,92
Atlantic Forest	1,110,182	13,04
Caatinga	844,453	9,92
Pampa	176,496	2,07
Pantanal	150,355	1,76

Source: IBGE, 2004.

The Amazon Forest is the largest of the Brazilian biomes and occupies of 4,196,943 km^2, which corresponds to 49,29% of its territory. It covers 100% of five states (Acre, Amapá, Amazonas, Pará and Roraima), 98% of Rondônia, 54% of Mato Grosso, 34% of Maranhão and 9% of Tocantins.

With 1,111,872 km^2, the Atlantic Forest is an environmental complex of mountains, valleys, plains and plateau along the continental coast. It covers 100% of the states of Espírito Santo, Rio de Janeiro and Santa Catarina, 98% of Paraná and areas in other 11 states.

'Caatinga' is an indigenous name for 'clear and open jungle'. It covers 11% of the Brazilian territory and occupies 100% of Ceará, 95% of Rio Grande do Norte, 92% of Paraíba, 83% of Pernambuco, 63% of Piauí, 54% of Bahia, 49% of Sergipe, 48% of Alagoas, 2% of Minas Gerais and 1% of Maranhão.

Cerrado is the second largest biome of South America, with an area of 2,036,448 km^2. It covers 22% of Brazilian territory and occupies 100% of the Distrito Federal, 97% of Goiás, 91% of Tocantins, 65% of Maranhão, 61% of Mato Grosso do Sul and 57% of Minas Gerais. It also occupies smaller areas of six other states.

The Pampas (or Campos Sulinos) has an area of 176,496 km^2, is present only in the state of Rio Grande do Sul and covers 63% of this state.

With an area of 150,355 km^2 the Pantanal covers 25% of Mato Grosso do Sul and 7% of Mato Grosso.

Thus, we should be concerned with the preservation of such biodiversity not only for its potential source of economic and scientific development, but also for ethical and esthetic reasons and, perhaps more importantly, for the equilibrium of natural ecosystems provided by millions of its constituent species.

Research with medicinal plants in Brazil

The use of medicinal plants and preparations made thereof can be found in many cultures around the world, from the modern developed societies to the more traditional ones. Phytotherapy, a term coined by the French physician Henry Leclerc in 1935, in his book *Précis de Phytothérapie: essai de thérapeutique par les plantes françaises,* is the treatment of diseases using plants, plant parts or preparations made from them.

However, the use of plants as therapeutic agents is, of course, much older than this. Archeological and historical evidences show that herbal medicines were used by our ancestors since the Neolithic Period (about 10,000-12,000 years ago). The Egyptian Papyrus Ebers (c. 1600 BC), clay cuneiforms and tablets from the Ashurbanipal library (c. 650 BC) are some examples. Physicians like Hippocrates (460-377 BC), Galen (129-199 DC), Avicenna (980-1037 DC) and Paracelsus (1493-1541 DC), to name a few, described the therapeutic properties of medicinal herbs in their writings (Gragg and Newman, 2012).

And in Brazil? What could be said about the history and uses of medicinal plants among us?

The first description of Brazilian natural richness is the letter Pero Vaz de Caminha sent to D. Manoel, king of Portugal, soon after the arrival of Cabral in 1500. Caminha asserted that they were unable to talk about gold, silver, iron or any kind of metal in the colony, but 'the vastness of the enormous trees, with abundant foliage, is incalculable', and yet 'There is a great, an infinitude of waters. The country is so well favored that if it were rightly cultivated, it would yield everything' (Caminha, [1500], 2000).

Aware of the wealth of the colony and of its own inability to defend it, Portugal adopted a restrictive policy interdicting the entrance of any foreigner into the territory. Thus the few records about the people, the daily life and flora and fauna of Brazil were limited to the Portuguese themselves. The first and most important of of these men was Gabriel Soares de Sousa. His *Tratado Descritivo do Brasil* is divided into more than 270 chapters. Medicinal herbs, which he calls trees of virtues', occupy only a small part. Most of them were indicated for wound healing.

A few years later, the Jesuit Fernão Cardim arrived in Brazil. Like Gabriel Soares de Sousa, he also described the climate, flora, fauna, the land, the Indians and the medicinal plants (most of them already mentioned by his predecessor) in *Do Clima e da Terra do Brasil,* a book smaller and inferior to *Tratado Descritivo do Brasil.*

However, due to the restrictive policy mentioned above, the first scientific description of Brazilian flora and fauna was produced by William (Willem, in Dutch, Guilherme in Portuguese) Piso, personal physician to Mauricio de Nassau who came to Brazil in 1637 in an attempt to colonize the northeast of the country. In 1648, Piso published *História Natural do Brasil* and, ten years later, *História Natural e Médica da Índia Ocidental.* In these books he described some diseases common in the northeast of the country like ulcer, cholera, dysentery, and to treat them, animals (birds, insects, spiders, bats, snakes, frogs, etc. and medicinal plants and their uses.

In 1808, fleeing from the French troops, the Portuguese Royal family arrived in Brazil. The colony then became the center of the empire and the beginning of a new era in the study of Brazilian biodiversity began. Among those who dedicated themselves to the study of medicinal plants, the names of Carl Friedrich von Martius, Auguste de Saint-Hilaire, and Theodore Peckolt come to mind.

Like other naturalists who came before them, these men described the therapeutic uses of many plants. Martius is the author of *Sistema de Matéria Médica Vegetal do Brasil* and *Natureza, Doenças, Medicina e Remédios dos Índios Brasileiros,* among others works. The first contains, according to Martius himself, the catalog and the classification of *all* Brazilian plants known with their names, taxonomy, habitat and medicinal uses.

However, plants like rice, beans, corn, sugar cane, that are neither Brazilian nor medicinal can also be found.

In the second book, he mentions not only medicinal properties of some plants, but also that of deer antlers (against snake bites), toasted frog meat (to alleviate the pain of childbirth) and of dog skin against sciatica.

Saint-Hilaire registered his voyage throughout the country in a series of diaries, but *Plantas Usuais dos Brasileiros* contains the botanical description, scientific and popular names, habitat, etymology and the therapeutic use of 70 plants.

Peckolt was the first of them to succeed in the isolation of some compounds from plants. He was a pioneer of pharmacological and chemical analysis of medicinal plants, as well as his detailed studies on native and acclimated plants like rice, coffee, and mate.

Other names such as those of Grigory Langsdorff, George Gardner, Johann Emmanuel Pohl, Bernardino Antonio Gomes and many others could also be mentioned (Alves, 2010). In some cases, the medicinal plants they described in their works have been included in the first edition of the Brazilian Pharmacopeia (Brandão *et al.,* 2008). However, their studies were usually empirical, based on the information provided by the native population. It was only with the progress of chemistry and pharmacology that the study of medicinal plants became a rational science, based on experimental methods (Cechinel, 2012).

Living organisms, from higher plants, algae and marine animals to reptiles and microorganisms may be potential sources of substances with pharmacological properties.

According to Verpoorte (2010) 250,000 'natural products' are known and some 4,000 new ones are reported every year.

'Natural products', is a misnomer since minerals from rocks, gases from the air, water, the cell, and DNA are also 'natural products', but for the organic chemist, 'natural product' means secondary chemical metabolites, also called allelochemicals, chemical substances produced by plants, animals, bacteria, fungi and algae. From the structural point of view they may be classified as alkaloids, terpenes, flavonoids, xanthones, lignans, etc.) and should be distinguished from lipids, proteins and carbohydrates, that is, the constituents of primary metabolism.

Their roles in metabolism were unknown until 1959 when Gottfried Fraenkel established that, in plants, they act as defensive mechanisms against insect predation. At the same time, insects also try to overcome such defenses. They can also play a part in the competition between plants for water or light, a phenomenon known as allelopathy. Among animals they may function in sexual attraction between members of the same species, in alarm and defense, in territory and trail marking, etc. In every case, there is an ecological role mediated by natural products (Whittaker and Feeny, 1971).

In a recent review, Bolzani (2012) reports examples of secondary compounds isolated from plants of each of six Brazilian biomes and their therapeutic uses. She also stressed that many articles report these properties without mentioning the substance(s) responsible for the activity.

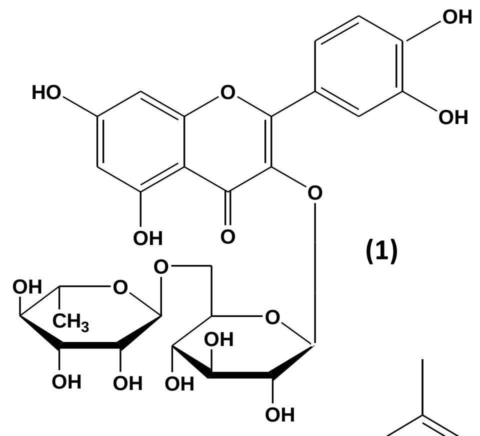
However, a survey of the literature covering the period between 2011 and 2012, shows that this situation is changing. Evaluation of Brazilian medicinal plants has revealed their role as antiulcer (Lima *et al.*, 2012), anti-inflammatory, antinociceptive (Hebeda *et al.,* 2011; Lopes *et al.*, 2012; Orlandi *et al.,* 2011; Rocha *et al.*, 2011; Rodrigues *et al.,* 2012; Silva *et al.*, 2012; Tessele *et al.,* 2011), antischistosome (Oliveira *et al.*, 2012), anticancer (Brito *et al.*, 2012), antileishmanial (Passero *et al.,* 2011), antimicrobial (Monteiro dos Santos *et al.*, 2011), antibacterial and antiparasitic (de Menezes, et al., 2012; Arruda *et al.*, 2011), antimalarial (Mota *et al.*, 2012), antiproliferative (Silva *et al.,* 2012) antiviral agents (Cecilio *et al.,* 2012), as well as in hypertension (Silva, *et al.,* 2012; Silva-Filho *et al.,* 2012; Santos *et al.,* 2011; Soncini *et al.*)*.,* 2011; in diabetes (Domingues *et al.*, 2011; Vasconcelos *et al.*, 2011; Lima *et al.*, 2012; Souza *et al.,* 2012), as diuretic agents (Gasparotto *et al.,* 2012), and against snake venom (Collaço *et al.*, 2012; Torres *et al.,* 2011).

In some cases, the active principle(s) and/or the mechanisms of action have been determined as shown in Table 3.

Table 3 Examples of some medicinal plants with identified active principles and/or mechanisms of action

Plant	Activity	Active principle	Mechanism of action	Reference
1. *Hancornia speciosa*	Anti-hypertensive	Rutin (1) Bornesitol (2) Quinic acid (3)	Inhibition of angiotensin converting enzyme	Sousa *et al.*, 2011
2. *Alpinia speciosa*	Cardiodepressive	Terpinen-4-ol (4) 1,8-cineol (5)	Inhibition of L-type Ca^{2+} channels	Santos *et al.*, 2011
	Vasorelaxant	(-)-borneol (6)	Calcium influx blockade	Silva-Filho *et al.*, 2012
	Anti-inflammatory and anti-ulcer	Carvacrol (7)	Interfering in release and/or synthesis of prostanoids	Silva *et al.*, 2012
3. *Luehea candicans*	Antiproliferative	Lupeol(8) Betulin (9) (-)-epicatechin (21) Vitexin (22) Liriodendrin (23)	-	Silva *et al.*, 2012
4. *Lychnophora salicifolia*	Anti-inflammatory	-	Acts on adhesive and locomotion properties of neutrophils	Hebeda *et al.*, 2011
5. *Solanum campaniforme*	Against snake venom	Solanidane alkaloids (11)	-	Torres *et al.*, 2011
6. *Vanilosmopsis arborea* 7. *Lippia sidoides* 8. *Croton zehntneri*	Antimalarial	α-bisabolol (12) estragole (13) thymol (14)	-	Mota *et al.*, 2012
9. *Baccharis uncinela*	Anti-leishmanial	Oleanolic acid (15) Ursolic acid (16) Caffeic acid (17)	-	Passero *et al.*, 2011
10. *Jacaranda cuspidifolia*	Antibacterial	Verbascoside (18)	-	Arruda *et al.*, 2011
11. *Cipura paludosa*	Anti-inflammatory	Eleutherine (19) Iso-eleutherine (20)	-	Tessele *et al.*, 2011
12. *Tropaeolum majus*	Anti-diuretic	Isoquercitrin (24)	Inhibition of angiotensin converting enzyme and of Na^{+}/K^{+}-ATPase	Gasparotto *et al.*, 2012
13. *Eugenia dysenterica*, 14. *Stryphnodendron adstringens*, 15. *Pouteria caimito* 16. *P. torta*	anti-diabetic	-	Inhibition of α-amylase and α–glucosidase	Souza *et al.*, 2012

17. *Persea americana*	anti-diabetic	-	Activation of PKB/Akt	Lima *et al.*,2012
18. *Caesalpinia ferrea*	anti-diabetic		Activation of Akt and acetyl-CoA carboxylase	Vasconcelos *et al.*, 2011
19. *Averrhoa carambola*	Anti-hypertensive	-	Inhibition of extracellular Ca^{2+} influx	Soncini *et al.*, 2011
20. *Salvia officinalis*	Anti-inflammatory and antinociceptive	-	Acts on transient receptor potential cation	Rodrigues *et al.*, 2012
21. *Arrabidaea brachypoda*	Anti-inflammatory and antinociceptive	Quercetin (25)	Inhibits leucocyte recruitment into the peritoneal cavity	Rocha *et al.*, 2011
22. *Byrsonima intermedia*	Anti-inflammatory and antinociceptive	-	Inhibits leucocyte recruitment into the peritoneal cavity	Orlandi *et al.*, 2011
23. *Mikania laevigata*	Against snake venom	-	Inhibits the expressions of anti-inflammatory cytokines TNFa and IFNg	Collaço *et al.*, 2012



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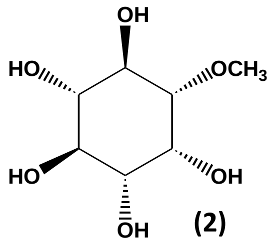

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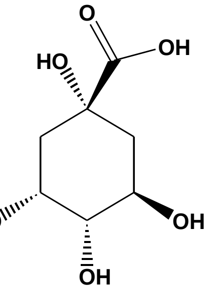

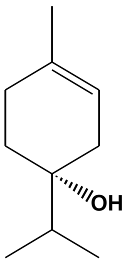

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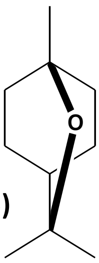

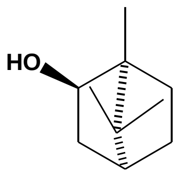

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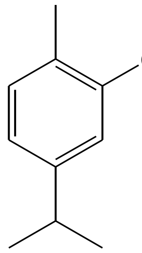
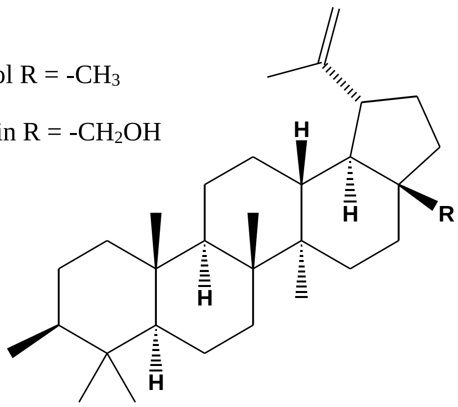
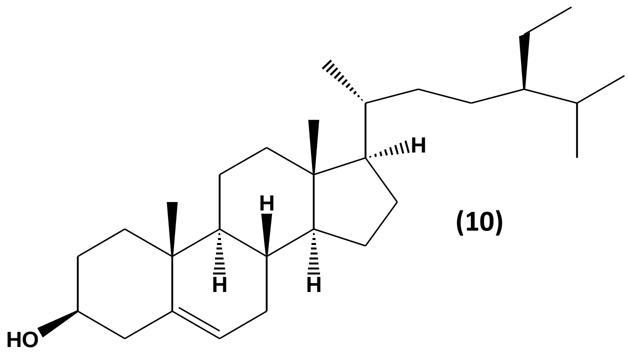


(7)

(8) Lupeol R = $-CH_3$

(9) Betulin R = $-CH_2OH$





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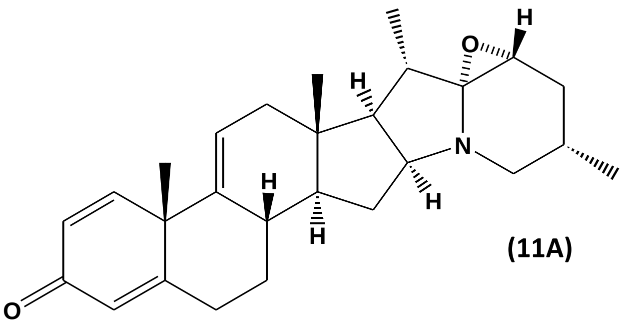

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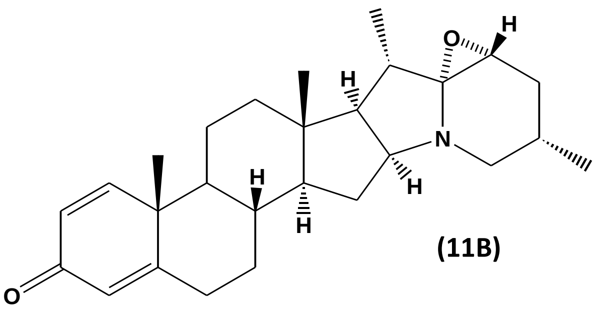

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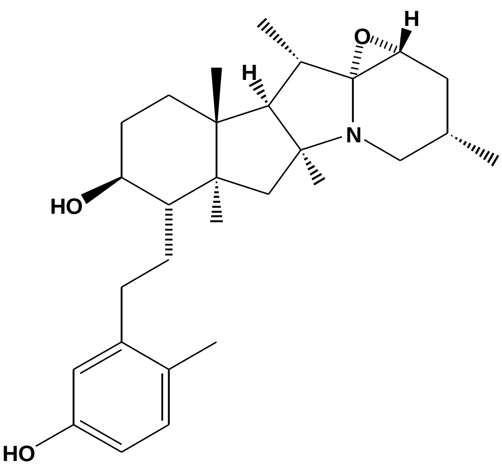

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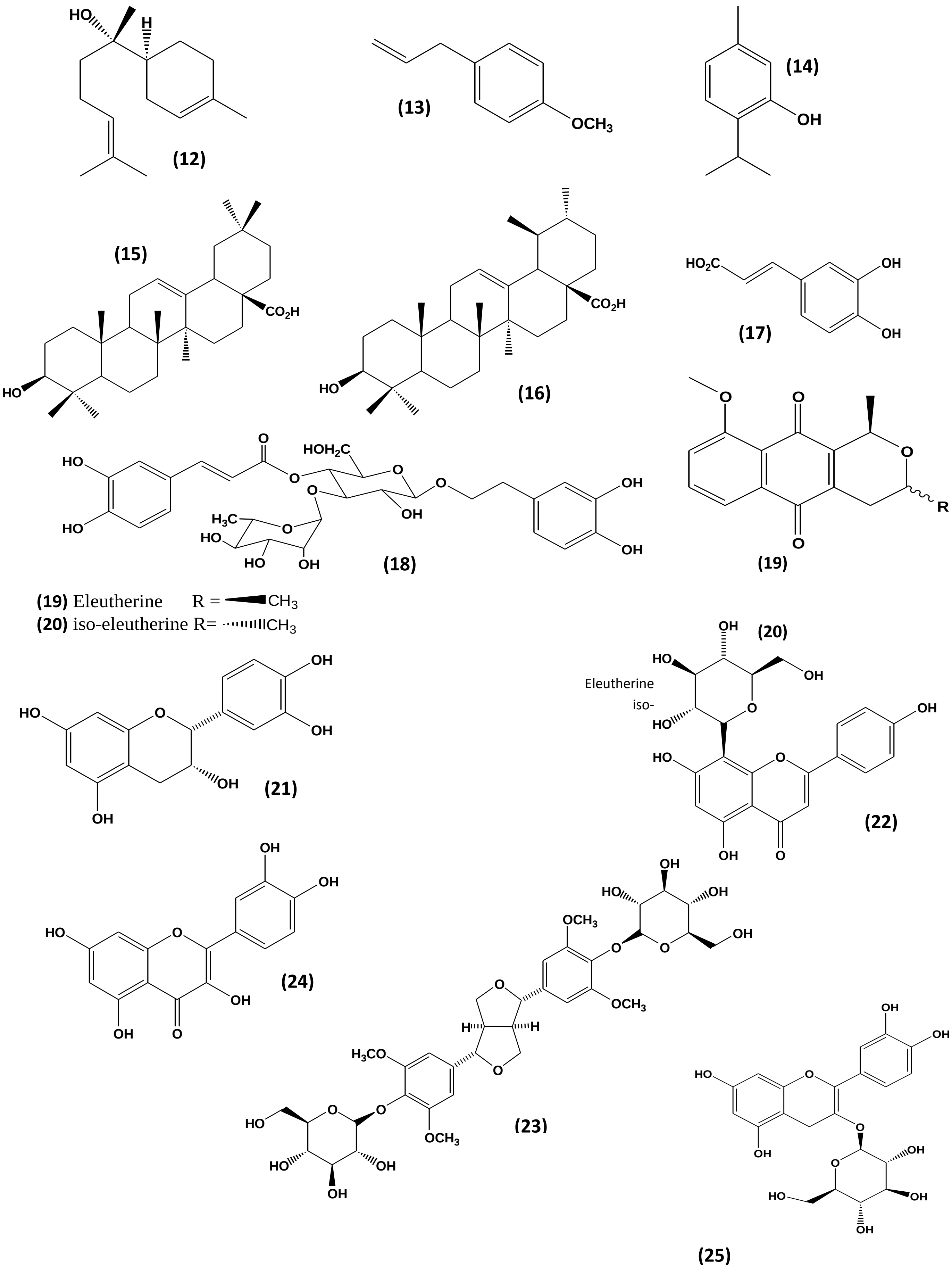

Figure 2: Chemical structure of isolated principle active in different natural source

These data provide a new approach in the study of medicinal plants.

However, pharmacological properties of allelochemicals are not restricted to higher plants and this will be discussed in the next topic.

Other potential sources for medicines from biodiversity

Higher plants are more visible and seem to be more abundant than other organisms. Therefore, their use to alleviate human maladies is more obvious. However, animals may also represent a potential source of medicines. A good example is that of bradykinin, a potent hypotensive agent. The history of bradykinin is similar to that of many other scientific discoveries. At the end of the decade of 1940, during an experiment with the venom of the jararaca (*Bothrops jararaca*), Rocha e Silva and Beraldo (1949) demonstrated that when incubated with serum, the venom gave rise to a hypotensive substance which caused a slow contraction in a smooth muscle preparation. Bradykinin, a 9 amino acid peptide, is an autopharmacolgical agent that is a pharmacological active substance released in the body by a metabolic modification from bioactive precursors. Because of this slow action, they called it bradykinin, from the Greek *brady*, that means slow and *kinein* to move.

In 1970, Ferreira, Bartelt and Greene demonstrated that a bradykinin potentiating factor from *Bothorops jararaca* venom, inhibits the conversion of angiotensin I into angiotensin II, which increases blood pressure. Later, an anti-hypertensive agent, Captopril, was developed from this peptide.

Recently, Barreto *et al.* (2012) showed the same anti-hypertensive effect for the peptide isolated from the venom of the rattlesnake 'cascavel' (*Crotalus durissus terrificus*). Other studies developed with snake venoms show that they have therapeutic activity in pre-eclampsia (Benedetti *et al.*, 2011), in tumor cells (Jorge *et al.*, 2011) and as antibiotics (Okubo *et al.*, 2012). Peptides from skins of amphibians represent a new and unexplored source of antimicrobial agents. From 1966 to 2009, more than 200 peptide sequences from different *Phyllomedusa* species were deposited in UniProt and other databases (Azevedo Calderon, 2011).

With 800.000 km^2 of continental shelf, Brazil is now exploring the rich biodiversity of this biome in search of new pharmaceutical drugs. Recent data show anti-inflammatory activity of substances isolated from marine sponges (Medeiros *et al.*, 2012) and from algae (Bitencourt *et al.*, 2011; Mata *et al.*, 2011). Antileishmanial (Santos *et al.*, 2011; Tempone, Martins de Oliveira & Berlinck, 2011) molluscicidal (Miyasato *et al.*, 2012) and antitumoral (Frota *et al.*, 2012) activities from marine organisms have also been reported.

CONCLUSION

Brazil has the largest biodiversity in the world contained in a single political unit. The Amazon basin alone is as big as Europe, excluding European Russia and Ukraine, or about half as big as the United States (Gilbert, 1999; 2000). The market for 'natural products', derived from plants and other living organisms (like algae, sponges, scorpions, amphibians and reptiles), is really remarkable. Brazil has, at least, two reasons to participate in this market: with its huge biodiversity and the scientific capacity of its scientists. Transformation of the knowledge accumulated up to now in this area, into commercial realities will take time. But the rational use Brazilian biological diversity represents a unique opportunity for the social, economic and technological development of the country.

ACKNOWLEDGEMENT

We are in debt to Dr. Benjamin Gilbert without whose perspective and constructive comments this review would have been quite different and much inferior.

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