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REVIEW

Neotropics and Natural Ingredients for Pharmaceuticals: Why isn't South American Biodiversity on the Crest of the Wave?

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Despite the advent of biotechnology and modern methods of combinatorial chemistry and rational drug design, nature still plays a surprisingly important role as a source of new pharmaceutical compounds. These are marketed either as herbal drugs or as single active ingredients. South American tropical ecosystems (or the Neotropics) encompass one-third of the botanical biodiversity of the planet. For centuries, indigenous peoples have been using plants for healing purposes, and scientists are making considerable efforts in order to validate these uses from a pharmacological/phytochemical point of view. However, and despite the unique plant diversity in the region, very few natural pharmaceutical ingredients from this part of the world have reached the markets in industrialized countries. The present review addresses the importance of single active ingredients and herbal drugs from South American flora as natural ingredients for pharmaceuticals; it highlights the most relevant cases in terms of species of interest; and discusses the key entry barriers for these products in industrialized countries. It explores the reasons why, in spite of the region's competitive advantages, South American biodiversity has been a poor source of natural ingredients for the pharmaceutical industry. Copyright © 2010 John Wiley & Sons, Ltd.

Keywords: Neotropics; South American medicinal plants; herbal drugs; active ingredients.

INTRODUCTION

For thousands of years, man has relied on nature as a source of medicines in order to treat and cure illnesses. Only in the twentieth century has the pharmaceutical industry turned to modern methods of combinatorial chemistry and rational drug design as a means of obtaining new chemical structures with potential drug uses. But these technologies proved to be limited when it came to synthesizing compounds with the complexity of those in nature, developed through millions of years of biological evolution. The limitation of these methods, together with the new technologies for extraction and identification of compounds from complex mixtures such as plant extracts, is drawing the pharmaceutical industry's interest back toward nature.

In 2001, and in the eight most industrialized countries – Canada, France, Germany, Italy, Japan, Russia, UK and USA – extracts formulations derived from 1350 plants were widely commercialized. Of these, 202 were formulations of single pure compounds, whereas the rest were extracts prepared according to various pharmacopeias (Bombardelli, 2001). And these figures do not include the nutraceuticals and cosmetics industries, both of which rely heavily on natural products.

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South American tropical ecosystems (or the Neotropics) encompass one-third of the botanical biodiversity of the planet. For centuries, indigenous peoples have been using plants for healing purposes, creating a strong tradition which becomes a challenge for scientists to validate the folkloric medicinal use of herbs. However, and despite the unique plant diversity in the region, very few pharmaceutical ingredients from this part of the world have reached the markets in industrialized countries.

The present review has a dual purpose since it addresses the actual and potential importance of single active ingredients and herbal drugs from South American flora as natural ingredients for pharmaceuticals, and discusses the key entry barriers for Neotropical products in industrialized countries. It explores the reasons why in spite of the region's competitive advantages, South American biodiversity has been a poor source of natural ingredients for the pharmaceutical industry.

THE MARKET OF NATURAL INGREDIENTS FOR PHARMACEUTICALS

The market of natural ingredients for pharmaceuticals can be classified into two major segments: (1) herbal drugs, and (2) single active ingredients.

Herbal drugs. Herbal medicine products are dietary supplements that people take to improve their health:

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Table 1. Single active ingredients isolated from plants and approved as drugs

Generic name	Indication	Common name	Scientific name	Origin
Artemisinin	Malaria	Wormwood	*Artemisia annua*	China
Curcumin	Cancer, inflammation	Turmeric	*Curcuma longa*	Far East
Digoxin	Heart conditions	Digitalis	*Digitalis purpurea*	Europe
Galantamine	Alzheimer's disease	Snowdrop	*Galanthus worownii*	East Europe
Guggulsterone	Sterol	Guggul plant	*Commiphora wightii*	Africa, Asia
Indole-3-carbinol	Cancer	Crucifers	*Brassica* spp.	Europe
Paclitaxel (Taxol)	Cancer	Yew Tree	*Taxus brevifolia*	USA
Resveratrol	Cancer	Red grapes	*Vitis* spp.	Europe
Salicylic acid (aspirin)	Analgesic	Willow tree	*Salix* spp.	Europe
Silymarin	Liver disease, etc	Milk Thistle	*Silybum marianum*	Europe
Vincristine, Vinblastine	Cancer	Periwinkle	*Catharanthus roseus*	Madagascar

many herbs have been used for a long time for claimed health benefits. They are sold as tablets, capsules, powders, teas, extracts, and fresh or dried plants. In contrast to single active ingredients, such drugs usually contain more than one active principle. Accurate statistics for the herbal market are difficult to obtain, because many herbal products are sold in the health and natural food trade, through direct sales and multilevel marketing organizations, and through alternative healthcare practitioners. These channels of distribution are usually not well measured by the leading organizations that track retail sales in the mainstream channels (Anonymous, 1999). After a boom in the late 1990s, total estimated herb sales in all marketing channels leveled around $4,500 million a year in the USA (Cavaliere *et al.*, 2009). The data also shows that the top ten herbs sold in the USA market account for about 80% of the total sales for this country, leaving all the rest of the products within the remaining 20%. As in the case of single active ingredients, none of the top ten herbs mentioned are original or native to South America. This scenario is not very different in Europe, where South American herbs (or products manufactured with them) also capture a very small share of the market.

Single active ingredients. From a chemistry point of view, natural products are *single* and *pure* substances that are synthesized via secondary metabolism in plants, insects, fungi, and many other living organisms. From the data presented in a study published by Newman *et al.* (2003), between 1981 and 2002, 48 of 65 drugs approved for cancer treatment where natural products, based on natural products, or mimicked natural products in one form or another. An updated version of the referred study (Newman and Cragg, 2007) states that at the time this survey was completed 47% of all the compounds studied in the area of cancer were actually natural products or directly derived from them. This pattern is also similar in other pharmacological fields such as the case of antihypertensive and antimigraine drugs. On the other hand, the authors pointed out that no *de novo* combinatorial compounds have been approved as a drug in this timeframe. Natural products thus continue to play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases. Another interesting fact is that the overall percentage of new medicines derived from natural products – in excess of 35% – remained constant during half a century despite relatively lower levels of investment in this field of R&D (Kursar *et al.*, 2007). Table 1 shows some reputed natural products obtained from plants and currently approved as drugs. None of these drugs have been isolated from Neotropical plants.

NEOTROPICAL PLANTS AND THEIR ROLE IN INDUSTRIALIZED COUNTRIES MARKETS

So far, a case is being made for natural products and their importance to the pharmaceutical industry, and for the fact that a major proportion of global biodiversity is currently found in Latin America. Although figures regarding the importance of Neotropical plants seem to be discouraging, it's important to note that some names are already gaining popularity, mostly in the field of herbal drugs. Once again, accurate data are not available for these products, although a quick market survey using secondary sources can provide a picture of the most renowned South American herbs (Table 2) whose main scientific studies are summarized as follows:

Açai. *Euterpe oleracea* (Arecaceae) is a species native to the Amazon Basin. The fruit of this palm tree has become reputed for its high antioxidant activity, mostly due to the presence of a complex mixture of antioxidant polyphenolic compounds, namely anthocyanins (Del Pozo-Insfran *et al.*, 2004; Lichtenthäler *et al.*, 2005; Rodrigues *et al.*, 2006; Chin *et al.*, 2008; dos Santos *et al.*, 2008; Mertens-Talcott *et al.*, 2008; Pacheco-Palencia *et al.*, 2008).

Boldo. *Peumus boldus* (Monimiaceae) is a shrub native to Chile. The leaves of Boldo are traditionally used as a hepatoprotective. Boldo leaves are rich in several aporphine-like alkaloids, of which boldine is the most abundant. This compound has shown antioxidant, cytoprotective, antitumor promoting, anti-inflammatory, antidiabetic and anti-atherogenic actions (O'Brien *et al.*, 2006). Regarding antioxidant activity, boldine has been reported to protect intact red cells against the haemolytic damage induced by free radical initiators in a dose-dependent manner (Jiménez *et al.*, 2000). Based on the TEAC assay, 150 mL of tea prepared from *P. boldus* would be equivalent to around 200 mg of Trolox, a synthetic analogue of vitamin E (Speisky *et al.*, 2006). More recently, Fernández *et al.* (2009) showed that

Table 2. Most popular South American herbs in industrialized countries

Common name	Scientific name	Uses	Active principles
Açai	*Euterpe oleracea*	Antioxidant	Phenolic compounds
Boldo	*Peumus boldus*	Hepatoprotective	Boldine
Brazil Nut	*Bertholletia excelsa*	Food supplement	Selenium, fatty acids, etc
Camu-Camu	*Myrciaria dubia*	Antioxidant	Vitamin C
Cat's Claw	*Uncaria tomentosa*	Anti-inflammatory	Quinovic acid glycosides, alkaloids
Copaiba Oil	*Copaifera officinalis*	Anti-inflammatory	Copalic acid
Dragon's Blood	*Croton lechleri*	Cicatrizant, anti-ulcerative	Proantocyanidins, taspine
Graviola	*Annona muricata*	Antitumor	Acetogenins
Guaraná	*Paullinia cupana*	Stimulant	Caffeine
Maca	*Lepidium meyenii*	Stimulant	Isothiocyanates
Mate	*Ilex paraguariensis*	Stimulant, tonic, etc	Caffeine, polyphenols, xanthine alkaloids
Stevia	*Stevia rebaudiana*	Low caloric sweetener	Stevioside
Pau d'Arco, Lapacho	*Tabebuia impetiginosa*	Antitumor	Lapachol
Yacón	*Smallanthus sonchifolius*	Diabetes	Fructooligosaccharides

Boldo infusion (5%) and boldine (50 mg/kg) acted as a protector with respect to the oxidative hepatic damage caused by cisplatin in mice liver. Antioxidant activity could also be involved in the anti-atherogenic action claimed for boldine, *since in vivo* studies have shown that 1–5 mg of this compound per day for 12 weeks induces a 40% decrease on atherosclerotic lesion formation in LDLR(-/-) mice (Santanam *et al.*, 2004).

Brazil Nut. *Bertholletia excelsa* (Lecythidaceae) is widely reputed and used as a food supplement due to its high content of selenium (36.1 microg per gram) and fatty acids such as palmitic, oleic, linoleic, myristic and stearic acids, and phytosterols (Moodley *et al.*, 2007; Strunz *et al.*, 2008; Thompson *et al.*, 2008).

Camu-Camu. *Myrciaria dubia* (Myrtaceae) is mostly found in countries from the Western Amazon Basin such as Peru. Its fruit is considered to be one of the richest sources of vitamin C (2.4 to 3.0 g/100 g in the pulp) (Justi *et al.*, 2000). One recent clinical trial has shown that Camu-Camu juice may have powerful antioxidative and anti-inflammatory properties, compared to vitamin C tablets containing equivalent vitamin C content, suggesting the existence of unknown antioxidant substances besides vitamin C or unknown substances modulating *in vivo* vitamin C kinetics in the fruit (Inoue *et al.*, 2008).

Cat's Claw. *Uncaria tomentosa* (Rubiaceae) is a large and woody vine that grows in the rainforests of the Western Amazon Basin in Peru, Bolivia and Ecuador. Cat's Claw is perhaps the Neotropical medicinal plant that has been subject of the largest number of studies, with more than one hundred publications in the fields of pharmacology and phytochemistry alone. Heitzman *et al.* (2005) published an extensive review as an attempt to cover the more recent developments in the ethnobotany, pharmacology, and phytochemistry of this species, explaining that 53 novel structures had already been reported for the genus Uncaria including alkaloids, terpenes, quinovic acid glycosides, flavonoids, and coumarins. The review describes pharmacological studies on *U. tomentosa* according to cytotoxicity, anti-inflammatory, antiviral, immunostimulation, antioxidant, CNS-related response, vascular, hypotensive, mutagenicity, and antibacterial properties.

Copaiba Oil. The resin extracted from large rainforest *Copaifera officinalis* (Fabaceae) trees has been used for centuries for internal and external inflammations. Clinical research has validated the resin's anti-inflammatory effects against various laboratory-induced inflammations in animal models, and has been linked to the presence of sesquiterpenes, diterpenes and terpenic acids (caryophyllene, calamenene, and copalic, coipaiferic, copaiferolic, hardwickic, and kaurenoic acids) (Basile *et al.*, 1988; *Veiga et al.*, 2001; 2006; 2007; Paiva *et al.*, 2002; Gomes *et al.*, 2007). Copaiba oil is the highest known natural source of caryophyllene, a well-documented anti-inflammatory compound.

Dragon's Blood. This red viscous latex is obtained from the bark of *Croton lechleri* (Euphorbiaceae), and used as a wound-healing, anti-inflammatory, antiviral and antitumor agent in the westernmost part of the Amazon Valley. Several compounds have been isolated during the 1990s from this sap, including the alkaloid taspine and the lignan 3′,4-O-dimethylcedrusin considered as the active principles responsible for the anti-inflammatory activity and wound-healing properties (Vaisberg *et al.*, 1989; Pieters *et al.*, 1993). Pharmacological studies have demonstrated that polyphenols, which account for 90% of the dried weight of Dragon's Blood (Cai *et al.*, 1991), also play an important role in the wound-healing properties of the latex (Spencer *et al.*, 1988), probably due to their oxygen free radical scavenging activity (Desmarchelier *et al.*, 1997). More recently, clinical studies have focused on the use of the sap and its proanthocyanidins in the treatment of traveler's and watery diarrhea. For instance, standardized proanthocyanidin extracts have been shown to act as antisecretory agents in human colonic epithelial cells by inhibiting the action of structurally unrelated prosecretory chloride channels (Fischer *et al.*, 2004; Tradtrantrip *et al.*, 2010).

Graviola. The Annonaceae family has been reported to possess a large number of acetogenins, a group of compounds that can only be found in this botanical family. Acetogenins are of extreme interest in cancer chemotherapy, mostly due to their ability to inhibit multi-drug resistance in cancer cells. At least 300 studies have been performed so far regarding the chemistry and pharmacology of acetogenins, many of which have been isolated from Graviola (*A. muricata*) (Rieser *et al.*, 1993; 1996; Wu *et al.*, 1994; 1995a; 1995b; 1995c; Zeng *et al.*, 1996; Kim *et al.*, 1998a; 1998b; Chang and Wu, 2001; Liaw *et al.*, 2002).

Guaraná. *Paullinia cupana* (Sapindaceae) is an Amazon Rainforest plant with caffeine-rich fruit. Guaraná has long been used as a tonic and medicinal plant, and in recent years it has also emerged as an ingredient in energy drinks and sodas; more recently it has also been claimed to boost libido, either taken alone or in combination with other herbs (Smith and Atroch, 2007). Guaraná seeds are considered to be the highest source of caffeine in nature with levels from 2 to 7.5%, or about four times as much as coffee (Beck, 2005). Theobromine, theophyline and other alkaloids from the xanthine group have also been reported in this species (Pizza *et al.*, 1999).

Maca. *Lepidium meyenii* (Brassicaceae) is also known by some as the 'Peruvian or Andean Ginseng' due to its alleged stimulant properties. The hypocotyl of this plant that grows at 4000 meters above sea level in the Andes has been used for centuries, not only as energy booster, but it is also believed to enhance fertility in man. Valentová and Ulrichová (2003) have published a review that deals with the botany and the composition, the structure of main constituents, and the biological activity of Maca, explaining that alkaloids, steroids, glucosinolates, isothicyanates, and macamides are probably responsible for its aptitude to act as a fertility enhancer, aphrodisiac, adaptogen, immunostimulant, and anabolic and to influence hormonal balance. More recently, some clinical trials have also confirmed that the consumption of Maca at ranges of 3.0–3.5 g of powdered root per day can modify certain sexual physiological and psychological parameters in man (Gonzales *et al.*, 2001; 2002; 2003; Gasco *et al.*, 2007; Brooks *et al.*, 2008; Dording *et al.*, 2008; Valentová *et al.*, 2008; Zenico *et al.*, 2009).

Mate. *Ilex paraguariensis* (Aquifoliaceae) is native to north-eastern Argentina, southern Brazil, and Paraguay. The leaves of this shrub, traditionally used by the ancient Guarani inhabitants of the region as a social and medicinal infusion, are extensively cultivated and taken orally either alone or in combination with other herbs. In recent years, the use of mate is being rapidly introduced to the world market, either as a tea itself or as an ingredient in formulated foods or dietary supplements, gaining public attention namely in the United States and Europe, and research on this tea has been expanding. Heck and de Mejia (2007) have reviewed the scientific literature of this plant, which has been shown to be hypocholesterolemic and hepatoprotective, a central nervous system stimulant, a diuretic, an antioxidant, beneficial to the cardiovascular system, and effective for obesity management.

Pau d'Arco-Lapacho. *Tabebuia impetiginosa* (Bignoniaceae) is a canopy tree indigenous to the Amazon Rainforest and other parts of South America. The inner bark of the tree is usually taken as a decoction to treat numerous conditions, but during the 1970s, Lapacho became very popular in the treatment of cancer, and this led to the isolation of two bioactive components known as lapachol and beta-lapachone, the latter being considered as the main antitumor compound. Although the isolated compounds showed interesting activity, side-effects of the treatment during clinical trials were undesirable, and to date the use of Lapacho is still restrained to the botanical drug.

Stevia. *Stevia rebaudiana* (Asteraceae) is a native herb from the Amambaí region in Paraguay that has become well known for the presence of stevioside in its leaves, an intense non-caloric sweetener used in foods and beverages in several countries. Rebaudoside A (also known by the common name of rebiana), is the second most abundant component of *S. rebaudiana* leaves, and has also shown similar properties to those reported for stevioside (Prakash *et al.*, 2008). Although the safety of the use of stevioside and rebiana has been questioned in the past, several mutagenicity, carcinogenicity, acute and sub-acute toxicity, fertility, and teratogenicity studies have concluded that Stevia, stevioside and rebiana are safe when used as a sweetener (Geuns, 2003; Brusick, 2008; Carakostas *et al.*, 2008). Stevioside, along with related compounds, may also offer therapeutic benefits, as they have antihyperglycemic, antihypertensive, anti-inflammatory, antitumor, antidiarrhoeal, diuretic, and immunomodulatory actions (Chatsudthipong and Muanprasat, 2008).

Yacón. *Smallanthus sonchifolius* (Asteraceae) is a crop that has been grown and used for centuries by the native populations that live in the temperate valleys of the tropical Andes. Although mostly used as food, the tubers are also considered effective in the treatment of hyperglycemia and kidney problems, and for skin rejuvenation, mostly due to the presence of oligofructans and phenolic compounds. However, probably the most interesting aspect of Yacón is related to the high content of fructo-oligosaccharides in the tubers, since these compounds have a favorable influence on the human intestinal flora and can modify some hyperlipidemias, therefore being classified as prebiotics. Probably through this action they also modulate lipid metabolism, calcium absorption, childhood immune systems and gut function (Valentová and Ulrichová, 2003). These facts have made Yacón popular in the functional foods and dietary supplements markets in industrialized countries.

KEY ENTRY BARRIERS FOR NEOTROPICAL PRODUCTS IN INDUSTRIALIZED COUNTRIES

So far, a case is being made for natural products and their importance to the pharmaceutical industry, and for the fact that a major proportion of global biodiversity is currently found in Latin America. However, several barriers are yet to be overcome in order to allow translation of the enormous biodiversity and traditional knowledge of the region into new products for the Northern Hemisphere.

History and cultural barriers. Contrary to most of the developing world, the Neotropics are also known as the

'New World', that is to say that they were 'discovered' by western civilization only about five centuries ago. As such, a certain lag in the uptake of its culture is understandable. This is in contrast to African and Asian cultures that have been in contact with Europe for thousands of years. For instance, many of the plant-based agents used in traditional Ayurvedic and Chinese medicine including ginseng, soy, gingko and ginger have gone through a long process of cultural acceptance in industrialized countries, gaining competitive advantages and in consequence an important share of their markets.

Thus, a natural process of initial awareness has led to a slow but constant increase in the demand of these products that has taken several centuries. Probably the same process is taking place with South American rainforest remedies, but since this process started later in history, it will take a while for them to overcome cultural barriers and reach parity with 'Old World' herbs.

Regulatory barriers. Once cultural barriers have been overcome and the market is ready to absorb a product, regulatory issues have to be complied with either for raw materials or end products. In this sense, regulatory authorities in Europe and the USA increasingly demand detailed documentation concerning safety, efficacy, and stability of drugs based on compounds of natural origin, regardless of the nature of them being single active drugs or multi-active complexes in herbal drugs. There also is a trend toward increasing efforts in follow up on medical claims made by synergistic actions between multiple compounds, or multiple pharmacological actions of single active principles. Mucke and Aschauer (2001) have presented a comprehensive outlook of the regulatory scenario in industrialized countries.

Regarding drugs consisting of a single active ingredients obtained from natural sources, regulatory authorities from both sides of the Atlantic are more or less consistent in their attitudes in the sense that they are not, in principle, concerned with the origin of the active compounds, provided that production methods are validated and result in a standardized product – criteria that also apply to synthetic ingredients. However, there are different attitudes of the US Federal Drug Agency (FDA) and the European Medicines Agency (EMEA) concerning herbal drugs, which are unlikely to be reconciled in the near future.

As stated by Mucke and Aschauer (2001), drugs based on standardized extracts present health authorities with complex regulatory and quality control problems, which have been addressed in quite different ways on either side of the Atlantic. While phytotherapy has been part of the medical tradition for many years in Europe, there is no such tradition or practice in the USA. Medicinal plants in Europe, their extracts, active components, and finished products have been described in many national pharmacopeias that have ultimately lead to a unified European Pharmacopeia (EP), setting the standards for these products in the region regarding their use as drugs. More recently, and in the UK in particular, new regulations from the Medicines and Healthcare products Regulatory Agency (MHRA) will come into force in 2011. However, in the USA, the scenario is somewhat different in the sense that herbals are regulated by the FDA as food rather than as drugs.

Adding to the complex regulatory issues that natural products have to confront in order to enter the markets in industrialized countries, businesses and scientists in Latin America have to overcome additional (local) regulatory barriers regarding export of their products. This is because until 1992 the world's genetic resources had been regarded as a common heritage of mankind. However, this situation was reverted when the Convention on Biological Diversity (CBD, 1992) came into force, and developing countries successfully achieved the right to exploit their own resources pursuant to their own environmental policies. As a consequence, and in order to protect their 'green gold', particularly tight legal restrains were introduced in several South and Central American countries such as Costa Rica, Colombia, Peru, and Brazil, adding difficulties for scientists from outside the region carrying out research in South and Central America. For example, removal of plant material, even just for herbarium specimens, has been prohibited in many cases. This discourages both researchers from investigating the plants and companies from investing in such research, and has become a major barrier to research and development.

Scientific barriers. One of the most important problems is the fact that there is very little scientific information on Neotropical plants, in comparison to medicinal plants from other parts of the world. For instance, it is widely believed that only 1% of the plants that grace the Earth have been subject to exhaustive pharmacological and phytochemical research. But when it comes to South American plants, this figure is probably overstated by one order of magnitude: from the 50,000–100,000 plants that are native to the region, maybe no more than 50 (0.1%) have been subject to exhaustive scientific investigation (Desmarchelier and Witting Schaus, 2001). This fact makes it even harder for South American natural products to compete in overseas markets, since both consumers and regulatory agencies not only expect empiric information but also scientific validation in order to embrace new products.

This is in sharp contrast to many Asian and European medicinal plants. For instance, while many South American plants claimed to be effective in the treatment of some types of cancers have only been subject to scattered preclinical studies, there is strong evidence indicating that many of the plant-based agents used in traditional Ayurvedic and Chinese medicine indeed suppress multiple pathways that have been implicated in tumorigenesis (Aggarwall *et al.*, 2007)

Obviously, encouraging ongoing research on medicinal plants in local universities and pharmaceutical companies is the most logical way to overcome this hurdle. Several international projects have also tackled this issue. For instance, the International Cooperative Biodiversity Groups (ICBG) from the National Institutes of Health (NIH) has been working for several years on research of the pharmacological potential of Panamanian plants. The *Institute de Recherche pour le Dévelоppment* (IRD) of France has also entered several collaborative agreements with local universities in Bolivia, Paraguay, French Guyana, and more recently Peru, in order to uncover the pharmaceutical potential of these countries' biodiversity. Perhaps one of the most renowned examples is that of the National Biodiversity Institute of Costa Rica (INBIO), who in the 1990s entered a collaborative agreement with Merck in order to study the country's rainforests. More recently, the Global Institute for Bio-Exploration (GIBEX) is also showing a particular interest in the region.

The role of pharmaceutical companies and their involvement in research activities in the region is less clear. Several local companies have R&D projects, although they are mostly focused on herbal drugs. Products are based on ethnobotanical information, and usually (but not always) this information is validated to some extent by scientific research. However, private bio-exploratory activities in pursuit of new single active compounds usually remain undisclosed. One high-profile case was that of Shaman Pharmaceuticals, a US company developing antiviral agents based on a molecule isolated from Dragon's Blood. However, the company got into financial trouble earlier this decade due to lack of cash for financing clinical trials, and now their lead product Crofelemer, indicated for HIV-associated acute infectious diarrhea, has been transferred to Napo Pharmaceuticals (NAPL.L), a publicly traded company on the London Stock Exchange. Crofelemer is currently in Phase III clinical trials for the treatment of chronic diarrhea in people living with HIV/AIDS.

Economic barriers. Last but not least, economic barriers play a major role in this field. The key issue in this sense is the low levels of direct investments and technology in local companies that provide raw materials and finished products. South American companies focus their efforts in exporting raw materials (such as dried and ground leaves, etc.) to be used in manufacturing herbals in the industrialized countries. However, raw material cost is said to be only 3% of the final manufactured drug price. Less often, standardized extracts are also manufactured, and only in very few cases finished products (i.e., tablets) are produced locally for export.

Regarding raw materials in the region, agronomic production of medicinal plants is mostly represented by introduced species rather than native plants, obviously due to market requirements. For example, in the State of Paraná in Brazil alone, in 2008 Bellini reported that medicinal plants production yields approximately 19 million Brazilian Reals annually (US$10.7 million). Adding the gains of herb varieties harvested in the Paraná forests – 2600 tons – to the mentioned production total we arrive at 22 million Reals (US$ 12.4 million). Chamomile is amongst the most cultivated species as is ginger, whose exports represent an impressive 95% of the overall production of medicinal plants in that state (Bellini, 2008). Neither of these species is native to South America.

Regarding transformed (further processed) materials, standardized extracts are amongst the most common in terms of exports. In most industrialized countries, buyers are not interested in plant material, but in plant extracts. Usually, standardized extracts are the raw materials used in manufacturing final products such as tablets, capsules, etc. As in the case of raw materials, the production of standardized extracts depends on the international market, which is largely represented by plants that are not native to South America. However, and when compared to the volumes of plant material that are exported, standardized extracts comprise a very small percentage.

There are only a few developing countries that are able to supply extracts conforming to the requirements of the western industry. According to Gupta (2006) the extracts of South American plants more frequently used in industrialized countries are Boldo (*Peumus boldus*), Quina (*Cinchona calisaya*), Carqueja (*Bacharis trimera* or *Baccharis* spp.), Dragon's Blood (*Croton* sp.), Cat's Claw (*Uncaria tomentosa*, *U. guianensis*), Marcela (*Achyrocline saturoides*) and Sarsaparilla (*Smilax campestris*). To this we should add natural colorants such as *bixin*, which is obtained from *Bixa orellana*, and *curcumin* from *Curcuma longa*, which represent the largest share of natural ingredients exports for some countries such as Peru (78%). Many of these products are believed to be at a maturity stage in terms of the product-market cycle.

Statistical information available regarding market share of South American products in this sense is hard to find. For example, in a 131-page EU market survey published in 2005, the only information presented on this issue was the fact that Chile is amongst the leading developing country suppliers of medicinal and aromatic plants to the EU, and that Brazil supplied more than 8% of the total value of alkaloids originating in developing countries (Anonymous, 2005).

These figures become bleaker when it comes to finished products, especially regarding those that have risen from local R&D. In this sense, South American biotechnology and pharmaceutical industries are still underrepresented. However, some interesting examples are showing that it is possible to develop effective medications for a low price from plants' active principles. For example, thanks to a vegetal polymer derived from an undisclosed Brazilian plant, Brazilian company Pelenova Biotechnologies (www.pelenova.com.br) claims to have developed biomembranes capable of inducing neo-angiogenesis, or the production of new blood vessels that help multiply cells used during the wound-healing process. Pelenova's product is currently in clinical use and marketed under the brand BIOCURE™.

CONCLUSIONS

Only a few well-known herbs account for most of the sales volume in industrialized countries and they do not belong to the Neotropics. Thus, it could be said that the Pareto Principle (or the 80-20 rule) applies to the herbal market (and probably also to the single active ingredients market), in the sense that Neotropical plants are represented in the lowest segment of sales volumes (which is also shared with many other less known herbs from Asia and Africa). The present analysis describes some key market entry barriers that include cultural, historical, regulatory, scientific, and economic issues, all of which could account for this uneven pattern.

In the particular case of herbal drugs, and in spite of these discouraging figures, it is important to note that some names are already gaining popularity. Once again, no accurate data is available for these products, although a quick market survey using secondary sources can provide a picture of the most renowned South American herbs (Table 2).

Furthermore, some natural ingredients such as Yacon (*Smallanthus sonchifolius*), used as a food supplement to reduce the risk of diabetes, Maca (*Lepidium meyenii*), an effective revitalizer and invigorating food, Tara Gum (*Caesalpinia spinosa*), anthocyanins of Purple Corn (*Zea mays*) and Açaí (*Euterpe oleracea*), natural dyes from Genipap (*Genipa americana*), and vitamin C – rich extracts of Camu-Camu (*Myrciaria dubia*) are growing in recent years. Most of these new products are in an introductory stage of the product life cycle.

As in the case of other developing countries, the economies in Latin America have been traditionally based on raw material production and exports, and this scenario does not seem to be too different in the case of pharmaceutically active natural products. Unfortunately, and perhaps with the sole exception of Brazil and Chile, policy-makers have done very little in order to change this scenario during the last few decades.

This historical constriction is aggravated, as mentioned earlier, by scientific and economic issues, such as lack of investment in research and development. Traditional drug discovery involves high levels of investment and economic risk, since it is usually based on screening of libraries of chemicals, and isolation and purification of active compounds, two processes that are characterized by low rates of success, high costs, and lengthy timeframes for a product to reach the market.

One alternative way to succeed in this scenario could be to cooperate in strategic alliances with complementary organizations and thus create virtual drug development corporations (VDDCs). Such joint ventures were first described during the 1990s (Lightfoot, 1996) as a matrix approach capable of doing business across traditional company boundaries by means of strategic alliances. As explained by Lightfoot, 'when the strategic alliance is thoroughly defined and complementary core competencies are identified, a VDDC can achieve quicker product approvals and greater profits than are possible when a company attempts to manage the development process alone.'

Unfortunately, and although the virtual company model is gaining acceptance in many industrialized countries, in South America this kind of multilevel cooperation project between companies, academia and NGOs is still unpopular, mostly due to cultural issues. One interesting case in the field of pharmaceutical product development from medicinal plants and worth benchmarking is that of Phytopharm (www.phytopharm.co.uk), a British virtual company whose model is centered on a lean cash burn with all laboratory, manufacturing, and clinical work outsourced to specialists, while core competencies such as strategy and management are maintained in-house. The company's efforts are focused on Asian and African plants; it is publicly traded on the London Stock Exchange under the symbol PYM.L, and earlier last year had a market capitalization of US$10M. Although Phytopharm has suffered commercial setbacks lately due to withdrawal of support from major development in the industry, its product development model is still an example to be followed.

While many core technologies for drug discovery and development are actually available in universities and companies throughout South America, a culture of cooperation is still virtually non-existent in the region. There seems to be a vacuum at the interface of the different organizations, which has made the orchestration of joint activities hard to accomplish. Working at this interface and matching efforts in order to bring together the different parts of the equation is thus essential at both horizontal (different organizations within South America) and vertical (South America – industrialized countries) levels. This should be accomplished by means of small, virtual and efficient organizations (i.e., consultancy services) capable of acting within these interfaces, bringing together local complementary capacities on one hand, and making the outcome of these joint ventures visible and available to market stakeholders in industrialized countries on the other.

REFERENCES

Aggarwal B, Sethi G, Baladandayuthapani V, Krishnan S, Shishodia S. 2007. Targeting cell signalling pathways for drug discovery: An old lock needs a new key. *J Cel Biochem* **102**: 580–592.

Anonymous. 1999. Herb market levels after five years of boom: 1999 sales in mainstream market up only 11% in first half of 1999 after 55% increase in 1998. *HerbalGram* **47**: 64.

Anonymous. 2005. *Natural ingredients for pharmaceuticals: EU market survey 2005*. Centre for the Promotion of Imports from Developing Countries. 131 pp.

Basile A, Sertié J, Freitas P, Zanini A. 1988. Anti-inflammatory activity of oleoresin from Brazilian Copaifera. *J Ethnopharmacol* **22**: 101–109.

Beck H. 2005. Caffeine, alcohol, and sweeteners. In Prance GT (ed.). *The Cultural History of Plants*. Routledge: New York; 173–190.

Bellini N. 2008. With everything to be a green powerhouse Brazil keeps importing its herbs. *Brazzil Magazine* http://www.brazzil.com/content/view/10030/1/ January 19 [access: 1 August 2009]

Bombardelli E. 2001. Approaches to the quality characterization of medicinal plants derivatives. *The European Phytojournal* **1**: 30–33.

Brooks N, Wilcox G, Walker K, Ashton J, Cox M, Stojanovska L. 2008. Beneficial effects of *Lepidium meyenii* (Maca) on psychological symptoms and measures of sexual dysfunction in postmenopausal women are not related to estrogen or androgen content. *Menopause* **15**: 1157–1162.

Brusick D. 2008. A critical review of the genetic toxicity of steviol and steviol glycosides. *Food Chem Toxicol* **46**: 83–91.

Cai Y, Evans F, Roberts M, Phillipson JD, Zenk M, Gleba Y. 1991. Polyphenolic compounds from *Croton lechleri*. *Phytochemistry* **30**: 2033–2040.

Carakostas M, Curry L, Boileau A, Brusick D. 2008. Overview: the history, technical function and safety of rebaudioside A, a naturally occurring steviol glycoside, for use in food and beverages. *Food Chem Toxicol* **46**: 1–10.

Cavaliere C, Rea P, Lynch M, Blumenthal M. 2009. Herbal supplement sales experience slight increase in 2008. *HerbalGram* **82**: 58–61. [access: 1 August 2009]

Chang F, Wu Y. 2001. Novel cytotoxic annonaceous acetogenins *from Annona muricata*. *J Nat Prod* **64**: 925–931.

Chatsudthipong V, Muanprasat C. 2008. Stevioside and related compounds: Therapeutic benefits beyond sweetness. *Pharmacol Ther* **121**: 41–54.

Chin Y, Chai H, Keller W, Kinghorn A. 2008. Lignans and other constituents of the fruits of *Euterpe oleracea* (Acai) with antioxidant and cytoprotective activities. *J Agric Food Chem* **56**: 7759–7764.

Del Pozo-Insfran D, Brenes C, Talcott S. 2004. Phytochemical composition and pigment stability of Açai (*Euterpe oleracea* Mart) *J Agric Food Chem* **52**: 1539–1545.

Desmarchelier C, Witting Schaus F, Coussio J, Cicca G. 1997. Effects of Sangre de Drago from *Croton lechleri* Muell.-Arg. on the production of active oxygen radicals *J Ethnopharmacol* **58**: 103–108.

Desmarchelier C, Witting Schaus F. 2000. *Sixty medicinal plants from the Peruvian Amazon: Ecology, ethnomedicine and bioactivity.* PROTERRA Ed Lima, Peru; 114.
Dording M, Fisher L, Papakostas G, Farabaugh A, Sonawalla S, Fava M, Mischoulon D. 2008. A double-blind, randomized, pilot dose-finding study of maca root (*L. meyenii*) for the management of SSRI-induced sexual dysfunction. *CNS Neurosci Ther* **14**: 182–191.
dos Santos G, Maia G, de Sousa P, da Costa J, de Figueiredo R, do Prado G. 2008. Correlation between antioxidant activity and bioactive compounds of açaí (*Euterpe oleracea* Mart) comercial pulps. *Arch Latinoam Nutr* **58**: 187–192.
Fernández J, Lagos P, Rivera P, Zamorano-Ponce E. 2009. Effect of boldo (Peumus boldus Molina) infusion on lipoperoxidation induced by cisplatin in mice liver. *Phytother Res.* **23**: 1024–1047.
Fischer H, Machen T, Widdicombe J, Carlson T, King S, Chow J, Illek B. 2004. A novel extract SB-300 from the stem bark latex of *Croton lechleri* inhibits CFTR-mediated chloride secretion in human colonic epithelial cells. *J Ethnopharmacol* **93**: 351–357.
Gasco M, Villegas L, Yucra S, Rubio J, Gonzales G. 2007. Dose-response effect of Red Maca (*Lepidium meyenii*) on benign prostatic hyperplasia induced by testosterone enanthate. *Phytomedicine* **14**: 460–464.
Geuns J. 2003. Stevioside. *Phytochemistry* **64**: 913–921.
Gomes N, Rezende C, Fontes S, Matheus M, Fernandes P. 2007. Antinociceptive activity of Amazonian Copaiba oils. *J Ethnopharmacol* **109**: 486–492.
Gonzales G, Córdova A, Gonzales C, Chung A, Vega K, Villena A. 2001. *Lepidium meyenii* (Maca) improved semen parameters in adult men. *Asian J Androl* **3**: 301–303.
Gonzales G, Córdova A, Vega K, Chung A, Villena A, Góñez C, Castillo S. 2002. Effect of Lepidium meyenii (MACA) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia* **34**: 367–372.
Gonzales G, Córdova A, Vega K, Chung A, Villena A, Góñez C. 2003. Effect of *Lepidium meyenii* (Maca), a root with aphrodisiac and fertility–enhancing properties, on serum reproductive hormone levels in adult healthy men. *J Endocrinol* **176**: 163–168.
Gupta M. 2006. *Medicinal plants originating in the Andean High Plateau and Central Valleys region of Bolivia, Ecuador and Peru.* United Nations Industrial Development Organisation, Investment and Technology Branch, New York. 305 pp.
Heitzman M, Neto C, Winiarz E, Vaisberg A, Hammond G. 2005. Ethnobotany, phytochemistry and pharmacology of Uncaria (Rubiaceae). *Phytochemistry* **66**: 5–29.
Heck C, de Mejia E. 2007. Yerba Mate Tea (*Ilex paraguariensis*): a comprehensive review on chemistry, health implications, and technological considerations. *J Food Sci* **72**: 138–151.
Inoue T, Komoda H, Uchida T, Node K. 2008. Tropical fruit camu-camu (*Myrciaria dubia*) has anti-oxidative and anti-inflammatory properties. *J Cardiol* **52**: 127–132.
Jiménez I, Garrido A, Bannach R, Gotteland M, Speisky H. 2000. Protective effects of boldine against free radical-induced erythrocyte lysis. *Phytother Res* **14**: 339–343.
Justi K, Visentainer J, Evelázio de Souza N, Matsushita M. 2000. Nutritional composition and vitamin C stability in stored camu-camu (*Myrciaria dubia*) pulp. *Arch Latinoam Nutr* **50**: 405–408.
Kim G, Zeng L, Alali F, Rogers L, Wu F, McLaughlin J, Sastrodihardjo S. 1998a. Two new mono-tetrahydrofuran ring acetogenins, annomuricin E and muricapentocin, from the leaves of *Annona muricata. J Nat Prod* **61**: 432–436.
Kim G, Zeng L, Alali F, Rogers L, Wu F, Sastrodihardjo S, McLaughlin J. 1998b. Muricoreacin and murihexocin C, mono-tetrahydrofuran acetogenins, from the leaves of *Annona muricata. Phytochemistry* **49**: 565–571.
Kursar T, Caballero George C, Capson T, Cubilla Ríos L, Gerwick W, Heller M, Ibañez A, Linington R, McPhail K, Ortega Barría E, Romero L, Coley P. 2007. Linking bioprospecting with sustainable development and conservation: The Panama case. *Biodiversity Conservation* **16**: 2789–2800.
Liaw C, Chang F, Lin C, Chou C, Chiu H, Wu M, Wu Y. 2002. New cytotoxic monotetrahydrofuran annonaceous acetogenins from *Annona muricata. J Nat Prod* **65**: 470–475.
Lichtenthäler R, Rodrigues R, Maia J, Papagiannopoulos M, Fabricius H, Marx F. 2005. Total oxidant scavenging capacities of *Euterpe oleracea* Mart. (Açaí) fruits. *Int J Food Sci Nutr* **56**: 53–64.
Lightfoot G. 1996. Drug discovery and VDDCs. *DDT* **1**: 255–260.
Mertens-Talcott S, Rios J, Jilma-Stohlawetz P, Pacheco-Palencia L, Meibohm B, Talcott S, Derendorf H. 2008. Pharmacokinetics of anthocyanins and antioxidant effects after the consumption of anthocyanin-rich acai juice and pulp (*Euterpe oleracea* Mart.) in human healthy volunteers. *J Agric Food Chem* **56**: 7796–7802.
Moodley R, Kindness A, Jonnalagadda S. 2007. Elemental composition and chemical characteristics of five edible nuts (almond, Brazil, pecan, macadamia and walnut) consumed in Southern Africa. *J Environ Sci Health B* **42**: 585–591.
Muke H, Aschauer B. 2001. Drugs from natural sources: A mainstay of the industry. *Current Drug Discovery* **June**: 48–51.
Newman D, Cragg G. 2007. Natural products as sources of new drugs over the last 25 years. *J Nat Prod* **70**: 461–477.
Newman D, Cragg G, Snader K. 2003. Natural products as sources of new drugs over the period 1981–2002. *J Nat Prod* **66**: 1022–1037.
O'Brien P, Carrasco-Pozo C, Speisky H. 2006. Review: Boldine and its antioxidant or health-promoting properties. *Chem Biol Interact* **159**: 1–17.
Pacheco-Palencia L, Mertens-Talcott S, Talcott S. 2008. Absorption and biological activity of phytochemical-rich extracts from açai (*Euterpe oleracea* Mart.) pulp and oil in vitro. *J Agric Food Chem* **56**: 4631–4636.
Paiva L, Gurgel L, Silva R, Tomé A, Gramosa N, Silveira E, Santos F, Rao V. 2002. Anti-inflammatory effect of kaurenoic acid, a diterpene from *Copaifera langsdorffi* on acetic acid-induced colitis in rats. *Vascul Pharmacol* **39**: 303–307.
Pieters L, de Bruyne T, Claeys M, Vlietinck J. 1993. Isolation of the dihydrobenzofuran lignan from South American dragon's blood (Croton sp.) as an inhibitor of cell proliferation. *J Nat Prod* **56**: 899–906.
Pizza C, Rastrelli L, Totaro K, De Simone F. 1999. *Paullinia cupana* (guaraná) determinazione degli alcaloidi xantinici per la valutazione della qualitá di prodotti base di guaraná. In: Il Guaraná degli Indios Sateré-Maué, Istituto Italo-Latinoamericana, Rome: *Serie Scienza* **13**: 13–22.
Prakash I, Dubois G, Clos J, Wilkens K, Fosdick L. 2008. Development of rebiana, a natural, non-caloric sweetener. *Food Chem Toxicol* **46**: 75–82.
Rieser M, Fang X, Rupprecht J, Hui Y, Smith D, McLaughlin J. 1993. Bioactive single-ring acetogenins from seed extracts of *Annona muricata. Planta Med* **59**: 91–92.
Rieser J, Gu Z, Fang X, Zeng L, Wood K, McLaughlin J. 1996. Five novel mono-tetrahydrofuran ring acetogenins from the seeds of *Annona muricata. J Nat Prod* **59**: 100–108.
Rodrigues R, Lichtenthäler R, Zimmermann B, Papagiannopoulos M, Fabricius H, Marx F, Maia J, Almeida O. 2006. Total oxidant scavenging capacity of *Euterpe oleracea* Mart. (açaí) seeds and identification of their polyphenolic compounds. *J Agric Food Chem* **54**: 4162–4167.
Santanam, N., Penumetcha, M., Speisky, H., Parthasarathy, S. (2004) A novel alkaloid antioxidant, Boldine and synthetic antioxidant, reduced form of RU486, inhibit the oxidation of LDL in-vitro and atherosclerosis in vivo in LDLR(-/-) mice. *Atherosclerosis* 173: 203–210.
Smith N, Atroch A. 2007. Guarana's journey from regional tonic to aphrodisiac and global energy drink. *Evid Based Complement Alternat Med* Dec 5.
Speisky H, Rocco C, Carrasco C, Lissi E, López-Alarcón C. 2006. Antioxidant screening of medicinal herbal teas. *Phytother Res* **20**: 462–467.
Spencer C, Cai Y, Martin R, Gaffney S, Goulding P, Magnolato D, Lilley T, Haslam E. 1988. Polyphenol complexation. Some thoughts and observations *Phytochemistry* **27**: 2397–2409.
Strunz, C., Oliveira, T., Vinagre, J., Lima, A., Cozzolino, S., Maranhão, R. (2008) Brazil nut ingestion increased plasma selenium but had minimal effects on lipids, apolipoproteins, and high-density lipoprotein function in human subjects. *Nutr. Res.* **28**: 151–155.
Thompson C, Chisholm A, McLachlan S, Campbell J. 2008. Brazil nuts: an effective way to improve selenium status. *Am J Clin Nutr* **87**: 379–384.
Tradtrantip L, Namkung W, Verkman A. 2010. Crofelemer, an anti-secretory antiiarrheal proanthocyanidin oligomer

extracted from *Croton lechleri*, targets two distinct intestinal chloride channels. *Mol Pharmacol* **77**: 69–78.

Vaisberg A, Milla M, Planas M, Cordova J, de Agusti E, Ferreyra R, Mustiga M, Carlin L, Hammond G. 1988. Taspine is the cicatizant in Sangre de Drago extracted from *Croton lechleri*. *Planta Med* **55**: 140–143.

Valentová K, Stejskal D, Bartek J, Dvorácková S, Kren V, Ulrichová J, Simánek V. 2008. Maca (*Lepidium meyenii*) and yacon (*Smallanthus sonchifolius*) in combination with silymarin as food supplements: in vivo safety assessment. *Food Chem Toxicol* **46**: 1006–1013.

Valentová K, Ulrichová J. 2003. *Smallanthus sonchifolius* and *Lepidium meyenii* – Prospective Andean crops for the prevention of chronic diseases. *Biomed Papers* **147**: 119–130.

Veiga V Jr, Rosas E, Carvalho M, Henriques M, Pinto A. 2007. Chemical composition and anti-inflammatory activity of copaiba oils from *Copaifera cearensis* Huber ex Ducke, *Copaifera reticulata* Ducke and *Copaifera multijuga* Hayne–a comparative study. *J Ethnopharmacol* **112**: 248–254.

Veiga V Jr, Zunino L, Calixto J, Patitucci M, Pinto A. 2001. Phytochemical and antioedematogenic studies of commercial copaiba oils available in Brazil. *Phytother Res* **15**: 476–480.

Veiga F Jr, Zunino L, Patitucci M, Pinto A, Calixto J. 2006. The inhibition of paw oedema formation caused by the oil of *Copaifera multijuga* Hayne and its fractions. *J Pharm Pharmacol* **58**: 1405–1410.

Wu F, Gu Z, Zeng L, Zhao G, Zhang Y, McLaughlin J, Sastrodihardjo S. 1994. Two new cytotoxic monotetrahydrofuran Annonaceous acetogenins, annomuricins A and B, from the leaves of *Annona muricata*. *J Nat Prod* **58**: 830–836.

Wu F, Zeng L, Gu Z, Zhao G, Zhang Y, Schwedler J, McLaughlin J, Sastrodihardjo S. 1995a. Muricatocins A and B, two new bioactive monotetrahydrofuran Annonaceous acetogenins from the leaves of *Annona muricata. J Nat Prod* **58**: 902–908.

Wu F, Zeng L, Gu Z, Zhao G, Zhang Y, Schwedler J, McLaughlin J, Sastrodihardjo S. 1995b. New bioactive monotetrahydrofuran Annonaceous acetogenins, annomuricin C and muricatocin C, from the leaves of *Annona muricata*. *J Nat Prod* **58**: 909–915.

Wu F, Zhao G, Zeng L, Zhang Y, Schwedler J, McLaughlin J, Sastrodihardjo S. 1995c. Additional bioactive acetogenins, annomutacin and (2,4-trans and cis)-10R-annonacin-A-ones, from the leaves of *Annona muricata. J Nat Prod* **58**: 1430–1437.

Zeng L, Wu F, Oberlies N, McLaughlin J, Sastrodihadjo S. 1996. Five new monotetrahydrofuran ring acetogenins from the leaves of *Annona muricata. J Nat Prod* **59**: 1035–1042.

Zenico T, Cicero A, Valmorri L, Mercuriali M, Bercovich E. 2009. Subjective effects of *Lepidium meyenii* (Maca) extract on well-being and sexual performances in patients with mild erectile dysfunction: a randomised, double-blind clinical trial. *Andrologia* **41**: 95–99.

