NEOTROPICS AND NATURAL INGREDIENTS FOR PHARMACEUTICALS: WHY ISN'T SOUTH AMERICAN BIODIVERSITY ON THE CREST OF THE WAVE?

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Table of Contents

INTRODUCTION

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 single active ingredients. Although South America is said to host one third of the planet's biodiversity, few pharmaceutical ingredients from this part of the world have reached the markets in industrialised countries. Several cultural, historical, regulatory, scientific and economic issues can be accounted as market entry barriers to these products in the Northern Hemisphere.

GENERAL OVERVIEW

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 to obtaining new chemical structures with potential drug uses. But these technologies proved to be limited when it comes 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 plants extracts, is drawing the pharmaceutical industry's interest back towards nature.

Since 2001, and in the eight most industrialized countries – Canada, France, Germany, Italy, Russia, UK and USA – extracts formulations derived from 1350 plants were widely commercialised. 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.

South American tropical ecosystems (or the Neotropics) encompass one third of the botanical biodiversity of the planet. For centuries, natives to the region have been using plants for healing purposes, creating a strong tradition which becomes a challenge for scientists to discover the quintessence of 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 industrialised countries.

The present study has a dual purpose since it addresses the 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 industrialised countries. It explores the reasons why in spite of the regions competitive advantages, South American biodiversity has been a poor source of natural ingredients for the industry.

THE MARKET OF NATURAL INGREDIENTS FOR PHARMACEUTICALS

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

Herbal drugs: Herbal medicine products are dietary supplements that people take to improve their health: 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 organisations, 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 90´s, sales of herbals levelled at about $ 700 million a year in the USA. Table I (Page 11) shows the top ten herbs in the USA market, according to sales. These herbs account for about 80% of the total sales for this country, leaving all the rest of the products within the remaining 20% (Blumenthal, 2005). As in the case of single active ingredients, none of the top ten herbs mentioned in Table I (Page 11) 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 synthesised via secondary metabolism in plants, insects, fungi, and many other living organisms. From the data presented in a survey 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. This pattern is also similar in other pharmacological fields such as the case of antihypertensive and anti-migraine drugs. On the other hand, the authors point out that no *de novo* combinatorial compounds have been approved as a drug in this time frame. 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 this period (see also Figure I, page 12), despite relatively lower levels of investment in this field of R&D (Kursar et al, 2007). Table II (Page 13) shows some reputed natural products obtained from plants and currently approved as drugs. None of these drugs have been isolated from Neotropical plants.

KEY ENTRY BARRIERS FOR NEOTROPICAL PRODUCTS IN INDUSTRIALISED 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.

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 civilisation 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 have gone through a long process of cultural acceptance in industrialised countries,

gaining competitive advantages and in consequence an important share of their markets. Some of the examples include Ginseng, Soy, Gingko and Ginger, all ranked amongst the top ten selling herbs in the region (Table I, Page 11)

Thus, a natural process of initial awareness has lead 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 pare 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 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 to 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 the industrialized countries.

Regarding drugs consisting of a single active ingredients obtained from a 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 **United States of America 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 standardised 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. However, in the USA, the scenario is somewhat different in the sense that herbals are regulated by the FDA as foods rather than as drugs.

Adding to the complex regulatory issues that natural products have to confront in order to enter the markets in industrialised 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 after the **Convention on Biological Diversity** (CBD, 2008) 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.

Scientific barriers: So far it is clear that South American natural products are exposed to cultural and regulatory barriers when trying to enter industrialised countries markets. A good part of these issues can be overcome with scientific and economic solutions, both of which at the same time also constitute barriers in themselves.

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 one percent 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 science.

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 pre-clinical 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 Développment (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 nineties entered a collaborative agreement with **Merck** in order to study the countries rainforests. More recently, the **Global Institute for Bio-Exploration (GIBEX)** is also showing a particular interest in the region.

The picture for 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 focussed 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 pursue 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, a red latex obtained from the Western Amazon tree

Croton lechleri However, the company went 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 diarrhoea, has been transferred to **Napo Pharmaceuticals** (NAPL.L), a public traded company in the London Stock Exchange.

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 grinded leaves, etc) to be used in manufacturing herbals in the industrialised countries. However, raw material cost is said to be 3% of the final manufactured drug price. Less often, standardised extracts are also produced, and only in very few cases finished products (i.e. tablets) are produced locally for export.

Regarding raw materials, many countries in the region also still import more of these products than they export. Furthermore, 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, 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 - 2,600 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 impressing 95% of the production (Bellini, 2008). Both of these species are not native to South America.

Regarding transformed materials, standardised extracts are amongst the most common in terms of exports. In most industrialised 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, standardized extracts´ production depends on 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, standardised 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 industrialised 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 ad natural colorants such as *bixin*, which is obtained from *Bixa orellana*, and *curcumin* form *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 product life.

Statistical information available regarding market share of South American products in this sense is hard to find. For example, in a 131 pages 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 8 percent 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 bio-membranes capable of inducing neo-angiogenesis, or the production of new blood vessels that help multiply cells used during the wound healing process. Thus, chronic lesions such as skin ulcers that are resistant to conventional treatment can now be cured at a considerably lower cost.

CONCLUSIONS

Clearly, and in spite of the enormous potential of South American biodiversity as a source of new drugs for human health, only a very small fraction of the total sales of natural derived drugs in industrialised countries comes from products from this region. Thus, it could be said that the Pareto Principle (or "80-20 Rule", Investopedia.com, 2008) applies for the herbal market (and probably also the single active ingredients market), in the sense that Neotropical plants are only represented in the lowest 20%, a fraction of the market which is also shared with many other herbs from Asia, Africa, etc. The present investigation 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's 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, which are summarized in Table III (Page 14).

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 revitaliser 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 pharmaceutical 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.

In the case of **single active ingredients**, most of the well known drugs listed in Table II (Page 13) have been discovered based on ethnobotanical information. In other words,

they have undergone a natural process that goes from medicinal plant – herbal product – pure active compound (or drug). The stages described are more likely to have been completed in plants known and used for thousands of years (i.e. Chinese, Indian, or European flora) than for South American plants, many of which have been discovered only during the past century.

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 characterised by low rates of success, high costs and time for a product to reach the market.

One alternative way to succeed in this scenario could be to cooperate in strategic alliances with complementary organisations and thus create virtual drug development corporations (VDDCs). Such joint ventures were first described during the 90´s (e.g. 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 industrialised countries, in South America this kind of multilevel cooperation projects between companies, academia and NGOs is still unpopular, mostly due to cultural issues. One interesting case in the field of pharmaceutical products development from medicinal plants and worth benchmarking is that of **Phytopharm** (www.phytopharm.co.uk), a British virtual company whose model is centred on a lean cash burn with all laboratory, manufacturing and clinical work out-sourced to specialists, while core competencies such as strategy and management are maintained in-house. **Phytopharm** believes that its route to develop pharmaceutical products and functional foods gives it a competitive advantage over other companies developing similar products. Rather than starting with a library of chemicals the company starts with a medicinal plant that has a history of clinical use, and either isolates the active chemical in order to develop it as a pharmaceutical product or develops a functional food based on a controlled extract of the plant. The company's efforts are focused on Asian and African plants; it is publicly traded at the London Stock Exchange under the symbol PYM.L, and has a current market capitalisation of US$ 40M.

While many core technologies for drug discovery and development are actually available in universities and companies throughout South America, cooperation culture is still virtually inexistent in the region. There seems to be a vacuum at the interface of the different organisations, 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 organisations within South America) and vertical (South America – industrialised countries) levels. **This should be accomplished by means of small, virtual and efficient organisations (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 industrialised countries on the other.

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Table I: Top Herbs in the United States. Source: About.com, 2007

Herb	$Millions	Condition Commonly Used In
Ginkgo biloba	147	Increase brain blood flow, prevent dementia, improve memory
St. John's Wort	104	Mild to moderate depression
Ginseng	84	Fatigue and weakness
Garlic	77	High cholesterol
Echinacea	72	Colds and respiratory infection
Saw Palmetto	45	Prostate conditions
Kava Kava	18	Anxiety and stress
Soy	18	Menopause
Valerian	10	Anxiety
Evening Primrose	9	Inflammation, premenstrual syndrome, menopause, immune disorders
Grape seed	8	Allergies, antioxidant
Milk Thistle	8	Liver disease, protects the liver
Bilberry	6	Eye disorders
Black Cohosh	6	Menopause, PMS, menstrual disorders
Pycnogenol	5	Antioxidant
Ginger	2	Nausea, poor digestion
TOTAL	**619**	

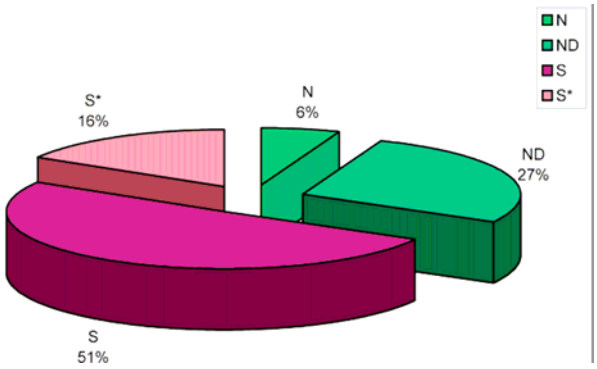

Figure 1: All small molecule new entities, 1981-2002. N: natural, ND: natural-derived, S: synthetic, S*: made by total synthesis, but the pharmacophore is/was natural. Source: Newman et al. (2003).

Table II: 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

Table III: Most Popular South American Herbs in Industrialised Countries

Common name	Scientific name	Uses	Active principles
Açai	*Euterpe oleracea*	Antioxidant	Phenolic compounds
Brazil Nut	*Bertholletia excelsa*	Food supplement	Selenium, fatty acids, etc
Boldo	*Peumus boldus*	Hepatoprotective	Boldine
Camu-Camu	*Myrciaria dubia*	Antioxidant	Vitamin C
Copaiba Oil	*Copaifera officinalis*	Anti-inflammatory	Copalic acid
Cat's Claw	*Uncaria tomentosa*	Anti-inflammatory	Quinovic acid glycosides, alkaloids
Dragon's Blood	*Croton lechleri*	Cicatrizant, anti-ulcerative	Proantocyanidins, taspine
Graviola	*Annona muricata*	Antitumour	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
Taheebo, Pau d´Arco	*Tabebuia impetiginosa*	Antitumour	Lapachol
Yacón	*Smallanthus sonchifolius*	Diabetes	fructooligosaccharides