

PHYTOCHEMISTRY AND PHARMACOGNOSY

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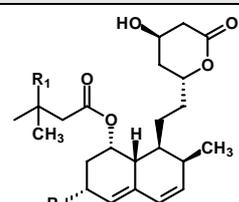
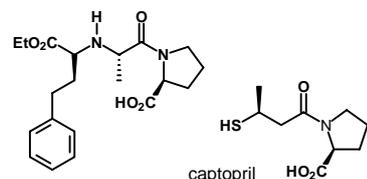
Summary

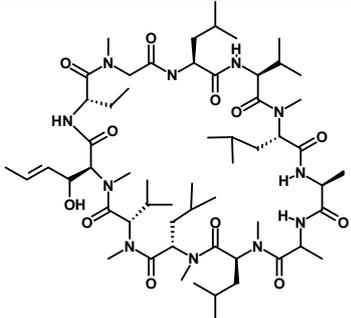
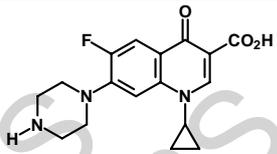
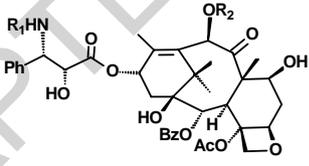
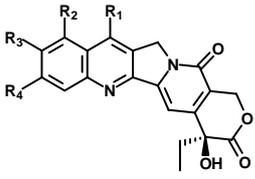
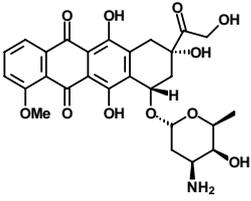
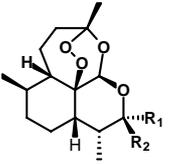
Pharmacognosy is the study of natural products and their application in the improvement of health. The scope of pharmacognosy has expanded from the traditional morphological description of plants and other organisms, to encompass the most modern aspects of molecular science relating to the exploration of naturally occurring bioactive compounds, their mode of action and, ultimately, their application in all economic and social activities. The search for new therapeutics was initially focused on plant species used in traditional medicine, but the development of specific and sensitive bioassays and efficient methodologies for the isolation and structure determination of bioactive constituents has facilitated the high throughput screening of the enormous molecular diversity found in plants, microorganisms and animals. The exploitation of nature as a source of bioactive products has been very successful with hundreds of new drugs having been developed and marketed. Despite the wide-ranging importance of biodiversity components, the pledges enshrined in the Convention on Biological Biodiversity still await more effective implementation in the form of research programs and partnerships with biodiversity rich countries. The present challenge is the establishment of integrative programs focusing on conservation, ecology, bioactivity, chemical analysis, organic synthesis and evolutionary studies in order to preserve, understand and exploit the full potential of biodiversity.

1. Introduction

Nearly all activities in modern society involve natural products at some point, especially in the form of drugs, food additives (see *Natural Products as Sources of Spices, Dyes and Cosmetics*), perfumes, aromas, cosmetic products and the innumerable toiletry items that ultimately influence human lifestyles and relationships. Within each type of application, demand is increasing and significant investments have been made by the private sector in order to exploit the world of natural products. Medicine, for example, has become a huge business with an annual growth of 5 – 8%, and it is presently estimated that global sales of pharmaceuticals, including phytotherapies, will top \$1 trillion in 2014.

In this context, natural products or phytochemicals are still recognized as one of the most important resources of bioactive compounds. Currently, more than half of the world's population relies on plants as the unique source of remedies with which to treat a wide variety of disorders (see *Medicinal plants and phytomedicine*). Additionally, around 40 - 80% (depending on the target) of new drugs approved and under commercialization are derived from natural products. Important examples of such drugs are the statins (i.e. lovastatin and simvastatin) as lipid-lowering compounds, enalapril maleate to reduce blood pressure, the antitumor agents taxol, docetaxel, camptothecin and doxorubicin, the antimalarials artemisinin and quinine, the immunosuppressant cyclosporine, and the antibiotic ciprofloxacin (Table 1) which, together, account for annual sales of over US \$20 billion.

Target (Trade names)	Structures and source
<p>Cholesterol-lowering agents Lovastatin [R₁=H; R₂=CH₃] (Mevacor) Simvastatin [R₁= CH₃; R₂= CH₃] (Zocov) Pravastatin [R₁= H; R₂= OH] (Precavol) Compactin [R₁= H; R₂= H] These drugs, collectively named statins, inhibit the biosynthesis of cholesterol and are effective for the prevention of cardiovascular disease associated with elevated cholesterol. Estimates for the worldwide market are around \$25 billion.</p>	 <p><i>Aspergillus terreus</i> and several other microorganisms</p>
<p>Blood pressure control Enalapril (Vasotec, Renitec, Lixel, Vaseretic) This is a modulator of the renin-angiotensin-aldosterone system. It is an analog of Captopril with the sulphhydryl replaced by a carboxyl group. Enalapril is a pro-drug which is hydrolyzed <i>in vivo</i> producing enalapril (dicarboxylate). Sales in the US market were almost \$1 billion in 1999.</p>	 <p>A peptide isolated from venom of the pit viper <i>Bothrops jararaca</i>.</p>
<p>Immunosuppressor Cyclosporin or FTY720 (Sandimmune, Neoral, Cicloral, Restasis) This is a cyclic nonribosomal peptide with 11 amino acid residues widely used for inhibiting the activity of a patient's immune system and reducing the risk of organ transplant rejection. It is also used to treat psoriasis and other autoimmune diseases.</p>	

	 <p>Isolated from soil fungus <i>Tolypocladium inflatum</i></p>
<p>Antibiotics Ciprofloxacin (Baycip, Ciloxan, Ciflox, Cipro, Cipro XR, Cipro XL, Ciproxin, Prociflor, and Proquin)</p> <p>Cipro was the 11th most prescribed drug in USA in 1999 with gross sales over \$1 billion.</p>	 <p>Synthetic second-generation fluoroquinolone antibacterial.</p>
<p>Antitumor Taxol (Paclitaxel) $R_1 = \text{COPh}$; $R_2 = \text{OAc}$ This is used to treat patients with lung, ovarian, breast cancer, head and neck cancer, and advanced forms of Kaposi's sarcoma. Is also used for the prevention of restenosis.</p> <p>Docetaxel (Taxotere) $R_1 = \text{CO}_2\text{t-Bu}$; $R_2 = \text{OH}$ Used for treatment of breast, ovarian, and non-small cell lung cancer. It has an FDA approved claim for the treatment of locally advanced or metastatic breast or non small-cell lung cancer in which anthracycline-based chemotherapy failed. It is approved in Europe for use in hormone-refractory prostate cancer.</p> <p>Camptothecin This compound showed anticancer activity in clinical trials but due to low solubility and high adverse side effects several analogues such as Topotecan and Iridotecan were developed and approved in cancer chemotherapy.</p> <p>Topotecan ($R_1 = R_4 = \text{H}$; $R_2 = \text{CH}_2\text{N}(\text{CH}_3)_3$; $R_3 = \text{OH}$) and Iridotecan ($R_2 = R_4 = \text{H}$; $R_1 = \text{CH}_2\text{CH}_3$; R_3: </p>	 <p><i>Taxus brevifolia</i> (Pacific yew or Western yew, Taxaceae)</p>  <p><i>Camptotheca acuminata</i> (happy tree, native to China, Nyssaceae)</p>
<p>Doxorubicin (Adriamycin) Used to treat leukemias and Hodgkin's lymphoma, as well as cancers of the bladder, breast, stomach, lung, ovary, thyroid, soft tissue sarcoma, multiple myeloma, and others.</p>	 <p><i>Streptomyces peuceitius</i></p>
<p>Antiparasitary Artemisin ($R_1 + R_2 = \text{O}$) A research program set up by Chinese Army in 1960s listed 200 traditional Chinese medicines for treating malaria, in which the leaves of <i>Artemisia annua</i> was the more effective than any other pure drug. It is used to treat falciparum and vivax malaria. The</p>	

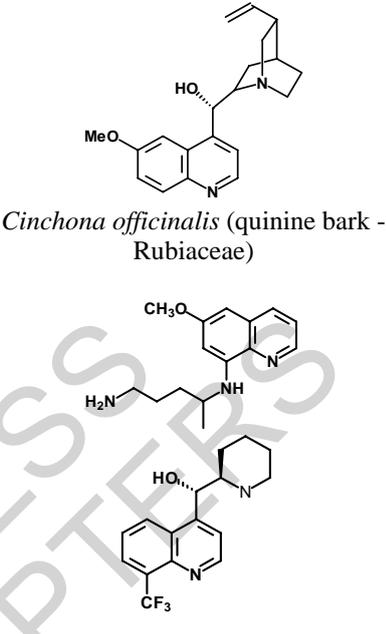
<p>endoperoxide group is of particular importance for activity. Artesunate ($R_1=OCOCH_2CH_2CO_2H$; $R_2=H$, water soluble for oral, rectal, intramuscular or intravenous use). Artemeter ($R_1=OCH_3$; $R_2=H$, lipid soluble, oral, rectal, or intramuscular use) (Coartem – Artemeter + Lumenfratine).</p>	<p><i>Artemisia annua</i> (“Qinghaosu”, a Chinese herb, Asteraceae)</p>
<p>Quinine This is an 8-aminoquinoline alkaloid isolated from the bark of quinine, a common plant in Peru and Bolivia. It was the first effective drug for treatment of malaria caused by <i>Plasmodium falciparum</i>. While it was used in a crude form since the early 17th century, it became the most important commodities exported from Peru to Europe around 1850. Its structure inspired the synthesis of several analogs such as Mefloquine and Primaquine.</p> <p>Primaquine This compound is used to treat malaria caused by <i>P. vivax</i> and <i>P. ovale</i>. It should be used in association with chloroquine or mefloquine to provide a complete cure. It is also used to treat fungal infections caused by <i>Pneumocystis pneumonia</i>, common in patients with AIDS.</p> <p>Mefloquine (Lariam, Mefaquin) This is a quinine analog developed at Walter Reed Army Institute of Research (USA) and was used for the prophylaxis of malaria and also for treatment of chloroquine-resistant <i>falciparum</i> type.</p>	 <p><i>Cinchona officinalis</i> (quinine bark - Rubiaceae)</p> <p>Primaquine</p> <p>Mefloquine</p>

Table 1. Examples of drugs of natural origin derived from different sources.

One of the major driving forces behind the continued demand for novel bioactive molecular entities is the need to develop new therapies for disorders that are associated with our modern lifestyle, such as cardiovascular disease (currently the main cause of death), ischemic heart disease, malignant neoplasms (cancers) and cerebrovascular disease (stroke), and the necessity to replace older drugs that have been used against bacterial, viral and parasitic infections. Over the last few decades, there has been a marked decline in the efficacy of a wide range of medications owing to the development of resistant strains of parasites and microorganisms. Unfortunately, the timeline for acquiring such resistance has diminished dramatically since the first reported case in 1950, and one of the major causes has been the widespread misuse and overuse of antibiotics in medicine and in veterinary practice. Various bacteria readily acquire resistant genes by mutation as part of their evolutionary process. Thus, *Streptococcus aureus* was able rapidly to develop resistance to penicillin, introduced in the 1950's, and later to the semi-synthetic methicillin that was employed from 1959 onwards. The impact of this type of acquired resistance was such that by 2003 more than 50% of *S. aureus* isolates recovered in US hospitals were of the methicillin resistant (MRSA) type. Presently, antibiotic resistance represents a significant concern for public health authorities, especially since there has been a relative decline in the number of newly approved drugs during the last decade.

A key requirement for the discovery of novel bioactive entities is access to molecular diversity. In the 1990's, the ready availability of a myriad of organic reactions, associated with the development of combinatorial chemistry, led to the adoption of this

strategy for the provision of novel molecular entities. However, not only was this approach somewhat unsuccessful, but various environmental and toxicological issues appeared. For instance, in the 1980's severe problems were identified in agricultural chemistry relating to the use of "hard" pesticides such as methyl bromide, one of the most effective soil sterilants and multipurpose fumigants. The levels of methyl bromide detected in well water were claimed to cause sterility in male workers and were suspected of adding to the depletion of the ozone layer above the polar caps. Another critical case was associated with the use of chlorinated hydrocarbons, such as DDT, which were used successfully in the early 1940's for the elimination of yellow fever and malaria vectors. In this instance, persistence of the agent in the downstream food chain caused a number of toxicological problems including the thinning of eggshells in wild birds leading to a decline in avian populations. Additionally, in the late 1980's and through the 1990's, numerous disasters were attributed to the misuse of chemicals in various human activities, and it was again realized that Nature was still far from being exhausted in terms of molecular diversity. Interest was thus rekindled in prospecting plants, microorganisms and animals for novel bioactive natural compounds.

The richness of the biodiversity of the tropics had been described since the discovery of the New World by numerous explorers from Italy (Christopher Columbus, 1451-1506), Portugal (Pedro Álvares Cabral, 1467-1520), Spain (Francisco de Orellana, 1490-1550; Francisco Pizarro, 1476-1541), Germany (Hans Staden, 1525-1579; Alexander von Humboldt, 1769-1859), Britain (Charles Darwin, 1809-1882; Richard Wallace, 1818-1980; Richard Spruce, 1817-1893), North America (Richard Evans Schultes; 1915-2001) and Sweden (Bo Holmstedt, 1919-2002) (see *The Discovery of the New World's Plants*). Exploitation of the spices, rubber trees and quinine provide prime examples of how natural biodiversity could be applied in the introduction of novel products ranging from new materials to drugs (see *The Discovery of the New World's Plants*). More recently, insecticides such as pyrethroids, which are based on the natural product pyrethrin, have been developed and their particular advantages recognized, including target specificity, elevated activity and, most importantly, biodegradability (see *Natural products from plants as insecticides in agriculture and human health*). Additionally, the discovery of various antitumor drugs (see *Natural Products as a Source of Antitumor Agents*) and other important lead compounds from plants, marine organisms (see *Natural Products from Marine Microorganisms*) and microorganisms (see *Natural Products from Bacteria and Fungi*) has renewed the interest in bioprospecting programs (see *Origin of Pharmaceuticals*).

The search of natural sources for novel bioactive molecules as potential drugs can be conducted through three major disciplines or activities: i) Ethnobotany and the associated traditional knowledge: this is one of the most useful approaches to investigate plant species since it facilitates targeted searches (see *Ethnobotany of Natural Products*); ii) Chemotaxonomy (phylogenetic approach): this method can be employed to target a specific taxonomic group containing classes of compounds that are similar to those present in species, genera or families that have previously exhibited high hit rates for a particular type of bioactivity; iii) High throughput-based bioprospecting programs: this is a random approach using robotic technology to screen thousands of samples per day. Although this last approach may be compared to "finding a needle in a haystack", it can disclose novel chemical entities and, depending on the

number and nature of the bioassays involved, may reveal novel mechanisms of action. All three of these approaches can be applied simultaneously in order to maximize the chances of finding new lead compounds (Figure 1).

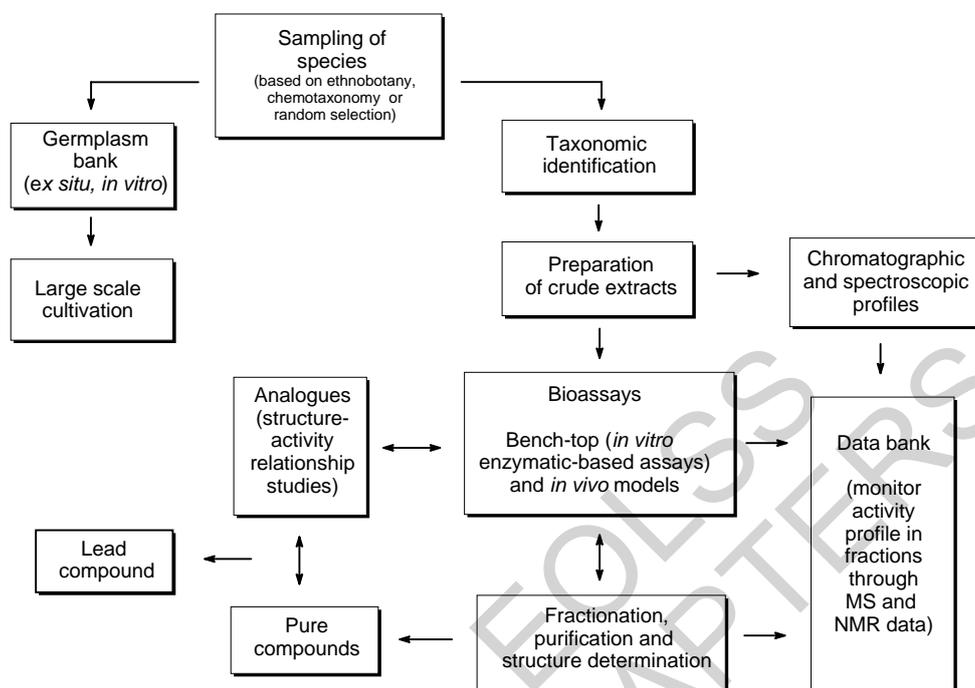


Figure 1. Major steps required for initial bioprospecting studies of natural products.

The current approach to drug discovery, based on the search for molecular diversity from natural sources, involves a number of complementary activities that necessitate multi- and interdisciplinary approaches and a multitude of players (private companies, universities, government and communities) and different professionals (anthropologists, biologists, agronomists, chemists, pharmacologists, physicians, etc.). The combination of such activities can be broadly categorized with respect to the associated disciplines of natural product chemistry and pharmacognosy as outlined in Figure 2. The term pharmacognosy (derived from the Greek words *pharmakon* - drug and *gnosis* - to acquire knowledge) was originally used to define that branch of knowledge dealing with naturally derived drugs in their crude or unprepared forms. The word was first coined in 1811 by the Austrian physician Schmidt, and later employed in a work entitled *Analecta Pharmacognostica* written by Crr. Anotheus Seydler in 1815. In modern times, however, the focus of the discipline of pharmacognosy has shifted more towards the discovery and development of new useful natural products. Important and impressive technological advances have led to the development of a multitude of sensitive biological assays in high-throughput platforms in order to detect bioactive compounds in crude extracts and associated fractions. Once the active extracts have been detected, the dereplication process (the recognition and elimination of those active components that are already known) commences with fractionation using chromatographic processes to generate sub-fractions. The active sub-fractions are further purified and structural determinations conducted using a range of modern physical and spectroscopic techniques. This step is especially important when a compound with a novel structure is obtained. Studies relating to structure-activity relationships will then be performed in

order to address the development of more active derivatives, and this stage may be coupled with combinatorial chemistry as the optimal solution to increase productivity (Figure 1).

Alongside such bioprospecting studies, the germplasm of selected plant strains will need to be conserved in an appropriate germplasm bank. Additionally, some species might be cultivated on a large scale and the natural products extracted for use in the form of an essential oil, a phytopharmaceutical, or a nutraceutical, or for further purification of one specific compound to be used *in natura* or after some transformation. These processes constitute the initial phase of discovering a lead compound that will, in turn, require a sequence of clinical phases of evaluation before the substance can be commercialized as a drug.

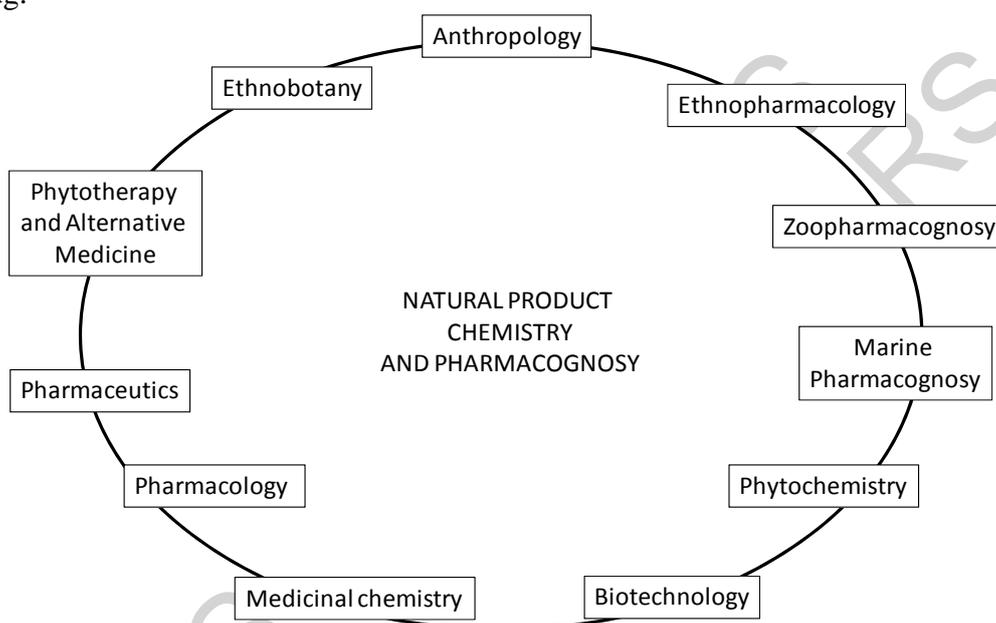


Figure 2. Interconnection and interdependence of the various research fields associated with Natural Product Chemistry and Pharmacognosy that are required for the development of novel bioactive compounds from natural sources.

In the last two decades, numerous bioprospecting initiatives have been launched in various countries around the world. The National Cancer Institute in the US, for example, has already screened over 135 000 extracts from nearly 40 000 plant species for novel anticancer compounds. Extensive sampling has been made in Africa and Madagascar in order to obtain representative samples of as many of the higher taxa occurring in these areas as possible.

Similar approaches have been undertaken with the implementation of the Instituto Nacional de Biodiversidad (INBIO) in Costa Rica, the International Cooperative Biodiversity Groups (ICBG) in Suriname and other countries in South America, and in the form of joint initiatives with the Australia government, several organizations, companies and universities. All of these endeavors are devoted to bioprospecting activity directed towards the enhancement of molecular and bioactivity inventories as well as the conservation of biodiversity.

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