

CHAPTER 5

PHARMACOGNOSY IN ACTION. OUR PARTNERS ABROAD

A Brief History of Natural Products Research in Africa¹

Berhanu M. Abegaz^a and Michael T. Davies-Coleman^b

^aDepartment of Chemistry, University of Botswana, Private Bag 00704, Gaborone, Botswana;

^bDepartment of Chemistry, Rhodes University, Grahamstown, South Africa

1. Historical aspects and the pioneers

Although modern natural products research in Africa may have begun almost simultaneously in many countries, it appears to have first taken roots in South Africa and West Africa, particularly, in Nigeria and Ghana. This was soon followed by Cameroon, Kenya, Rwanda, Tanzania and Ethiopia, with Botswana coming onto the scene only during the last decade. Historically, the University of Ibadan was, undoubtedly, the pioneering center in West Africa with the first generation of natural product chemists (Bevan, Taylor, Akisanya, Ekong, Ogan, Powell, Nwaji and Arene) emerging in the late 1950s, and the second group (Eshiet, Adesogan, Olagbemi, Okogun, etc) following soon after.² Taylor continued his natural products research at the University of Natal in South Africa and provided the foundation for the successful Natural Products Research Group established later at this institution by Mulholland (1991-2006). Cameroonian scientists (Sondengam, Ayafor and Fomum) were trained in Makerere and Ibadan, and soon formed active research groups in Yaounde. Natural products research in Kenya also has a long history and much of it comes from the Universities, predominantly the University of Nairobi, but equally, and significantly, from the famous International Center for Insect Physiology and Ecology (ICIPE). The latter was established in the late 1960s and early 1970s through the initiatives of the late Thomas Odhiambo and the support of international scientists like Nakanishi, Djerassi, and Meinwald. Research in natural products in Tanzania can also be traced in 1965 to the pioneering efforts of Ntamila and Hassanali. In Ethiopia, such research began with the discovery of Endod (*Phytolacca dodecandra*) as a molluscicidal agent by Aklilu Lemma who realized the potential of the plant to avoid infection from Bilharziasis and invited chemists to investigate it. Much broader work began a decade later by Abegaz and Dagne at Addis Ababa University. Rwandese efforts to study indigenous medicinal plants was heavily supported by Belgian scientists, and led to the development of a center which was popularly known as CURPHAMETRA, but this was essentially decimated during the genocide in the early 1990s. Botswana, established good facilities for natural products in the early 1990s and attracted Abegaz and the NABSA network, which has allowed it to pursue vigorous research in natural products during the last decade. The history of South African natural products chemistry research, stretching back more than half a century, was recently comprehensively reviewed by Drewes and Mulholland.³ Internationally recognized pioneers of South African natural product chemistry include Warren (Natal), Roux (Free State), Perold (Witwatersrand), Enslin (CSIR/NCRL), Rivett (Rhodes) and others. As has occurred elsewhere in Africa the second generation of South African natural product chemists e.g., Drewes, Ferreira, Mulholland, Horak and van Heerden continued to build on the foundations laid by these early pioneers while some engaged with relatively unexplored areas of African natural product chemistry e.g., mycotoxins (Steyn) and marine natural products (Davies-Coleman).

2. Notable outcomes

Phytochemical research is, relatively speaking, more developed than many of the other sciences in Africa. Given the low number of scientists and the vulnerable scientific environments they work in, their research outcome is not insignificant. Although there is often some level of research in most universities in Africa, those that do produce steady publications are KwazuluNatal, Johannesburg, Rhodes, Orange Free State and Pretoria in South Africa, Ibadan and Obafemi Awolowou in Nigeria, Nairobi in Kenya, Dar es Salaam in Tanzania, Addis Ababa and Botswana. New metabolites discovered in these institutions are estimated to be well into four figures, and embrace the whole range of known classes of secondary metabolites. However, some may be regarded as particularly noteworthy because of novelty in molecular architecture, or because they have served as lead molecules for subsequent intensive investigation, or simply because they are the active constituents of widely used in traditional procedures. Some of these include: the limonoid gedunin from Ibadan⁴ the alkaloid cryptolepine from Ghana,⁵ knipholone and geshoidin from Addis Ababa^{6,7} and the anti-microbial caespitin, anti-cancer rooperol, and anti-inflammatory ocobullenone from South Africa.³ Equally important was the search for anti-sickeling agents by Nigerian researchers: Sofowora and Elujoba in Ife (Nigeria) studied *Xanthoxylum xantoxylodes* and published interesting papers.⁸ The landmark achievement in this field is that of Wambebe and others which eventually resulted in the marketing of a drug (NICOSAN) which is now used for the management of the disease. Several plant families have been widely investigated by African scientists. These include Aloes (Dagne group, Addis Ababa; van Wyk group, South Africa), the Burseraceae (Dagne group), the Ebenaceae and Annonaceae (Nkunya group, Tanzania), the Polygonaceae family (Midiwo group, Nairobi), the Hyacinthaceae (Abegaz group, Botswana; Mulholland group, Durban). Medicinally and/or economically important genera that have been studied include *Dorstenia* (joint Abegaz-Ngadjui group, Botswana and Cameroon), and *Erythrina* (alkaloids by Dagne, Addis Ababa; prenylated flavonoids by the Fomum group in Cameroon and the Majinda group in Botswana). With over 27 million indigenous medicine consumers in South Africa, a country with one of the world's greatest diversity of plant species, it is not surprising that several South African plant extracts are now commercially available e.g. *Hoodia currori* and *Sutherlandia frutescens*.³ Increasing South African government financial support for research into Indigenous Knowledge Systems bodes well for a new renaissance in natural product chemistry in southern Africa.

- (1) This section is devoted to the history of pharmacognosy research on the African continent excluding North Africa and the islands off the African coast.
- (2) We are grateful to Joe Okogun for this information.
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Natural Products and Pharmacognosy Research in Australasia

John W. Blunt,^a Robert J. Capon,^b Benjamin R. Clark^b and Murray H. G. Munro^a

^a*Department of Chemistry, University of Canterbury, Christchurch, New Zealand*

^b*The Centre for Molecular Biodiversity, Institute for Molecular Biosciences, The University of Queensland, St Lucia Qld 4072, Australia*

A common feature of the investigation of natural products in both Australia and New Zealand was the efforts by early chemists to establish the structures of compounds found in the vast array of species endemic to each of these countries. Pharmacognosy aspects received little attention, but this early research was of great significance to subsequent pharmacological studies by providing knowledge of compounds that would be later investigated, and for the training of chemists who would go on to develop the biological studies.

Australia

Early research into the chemistry of Australian organisms began in the mid-1850s,¹ focusing mainly on the essential oils of plants. Notable here were Richard Baker, a botanist, and Henry Smith, an organic chemist, who together carried out extensive work on local pines.² Another early focus was on the chemistry of plants causing agricultural stock losses.³ During WW2, extensive and successful investigations into obtaining large quantities of medicinally important alkaloids from natural sources⁴ led to the establishment of the Australian Phytochemical Survey (1945-1970),⁴ carried out by the CSIR (now the CSIRO), in combination with several leading academics, with the focus being mainly on alkaloids and their biological activities.⁵ Since 1970 the profile of Australian natural products research changed significantly, shifting from basic to

Table 1: Australian natural product researchers, government agencies and companies

Alewood, Paul (<i>University of Queensland</i>)	<i>Marine: cone shell toxins (1994-)</i>
Blackman, Adrian (<i>University of Tasmania</i>)	<i>Marine: algae & bryozoans (1976-)</i>
Bowden, Bruce; Coll, John (<i>James Cook Univ.</i>)	<i>Marine: soft corals (1977-)</i>
Capon, Robert J. (<i>ANU/U. Melb./U. Queensland</i>)	<i>Marine: sponges and microbes (1985-)</i>
Craik, David (<i>University of Queensland</i>)	<i>Terrestrial: plant peptides (1994-)</i>
Elix, Jack (<i>Australian National University</i>)	<i>Terrestrial: lichens (1972-2004)</i>
Garson, Mary (<i>University of Queensland</i>)	<i>Marine: sponges and molluscs (1989-)</i>
Ghisalberti, Emilio; Jefferies, Phillip R. (<i>UWA</i>)	<i>Terrestrial: desert plants (1959-)</i>
Hawkins, Clifford J. (<i>University of Queensland</i>)	<i>Marine: ascidians (1989-1992)</i>
Karuso, Peter H. (<i>Macquarie University</i>)	<i>Marine: sponges (2000-)</i>
MacLeod, John (<i>Australian National University</i>)	<i>Terrestrial: plant & insect toxins (1975-2001)</i>
Quinn, Ronald; Carroll, Anthony (<i>Griffith Univ.</i>)	<i>Marine invertebrates. Terrestrial plants (1993-)</i>
Rickards, Rodney (<i>Australian National Univ.</i>)	<i>Terrestrial: bacteria (-1999)</i>
Ritchie, Ernest (<i>University of Sydney</i>)	<i>Terrestrial: plants (1948-1976)</i>
Taylor, Walter C. (<i>University of Sydney</i>)	<i>Marine: sponges. Terrestrial: plants (-1997)</i>
CSIRO	<i>Terrestrial: plant alkaloids (-1984)</i>
AIMS	<i>Marine (1997-)</i>
AstraZeneca	<i>Terrestrial and Marine (1993-)</i>
RRIMP	<i>Marine (1976-1984)</i>
Peplin	<i>Terrestrial: plant anticancer (1997-)</i>
Marinova	<i>Marine: algal sulfated polysaccharides (2003-)</i>
Microbial Screening Technologies Pty Ltd	<i>Terrestrial and Marine: microbes (1994-)</i>
Xenome	<i>Marine: conopeptides and pain (1998-)</i>

applied research more focused on biological activity, with the dominance of plant alkaloids gradually being replaced by an interest in marine natural products, and further expansion of the scope in more recent years to include peptides. This has come in conjunction with an overall decline in the number of publications and number of research groups working in natural products chemistry. Historically, natural products research in Australia has been strong nationwide, but recently Queensland has established itself as a leader in the field. While universities are still the dominant force driving Australian natural products chemistry, the number of active groups has decreased significantly. Government institutions have largely faded from the field, and small companies are now playing a larger part in the research. Biological activity and commercial applications play a much larger role in driving the research: the basic science of isolation and structural elucidation of new natural products is not as prevalent as it once was. **Table 1** lists a selection of Australian natural product researchers, together with organizational affiliation and area of specialty, as well as government agencies and companies engaged in natural products research with some focus on biological activity.

New Zealand

The indigenous peoples of New Zealand, the Maori, practiced herbal medicine, and this is related in their oral history. Subsequently, European explorers, early travelers, missionaries and settlers recorded the medicinal use of the endemic plants, and several books on the traditional and early use of native plants have been published.⁶ Otherwise, the development of natural product research in New Zealand was similar to that in Australia, with significant initial interest in compounds impacting on livestock and plant production. Much of this work was conducted in Government institutions (DSIR) and more latterly in Crown Research Institutes (CRIs). Significant early contributions to natural product discovery and pharmacology were made by TH Easterfield (Victoria College, Wellington) and BC Aston (Dept. Agriculture), LH Briggs and then RC Cambie (U. Auckland), RE Corbett, PK Grant and FN Fastier (U. Otago) and various investigators (including GB Russell and KR Markham) in branches of the DSIR. For over 25 years, the University of Canterbury group of JW Blunt and MHG Munro has explored bioactive compounds, mostly of marine origin. More recently, several other academic groups have been involved with bioactive discoveries: BR Copp (U. Auckland), MR Prinsep (U. Waikato), and PT Northcote (Victoria U. of Wellington). The small companies Terramarine (V Webb) and BioDiscovery NZ (P Wigley, S Bloor and D Crump) have recently been active, while groups of investigators have made contributions, some with significant focus on bio-actives related to agricultural and aquacultural production: NR Towers, RE Mitchell, GA Lane, DD Rowan, CO Miles (CRIs) and AL Wilkins (U. Waikato), NB Perry (PERU), PT Holland, AL Mackenzie and D Mountfort (Cawthron Institute). Thus, the emphasis in natural products research has moved rapidly from establishing the chemotaxonomic profiles of endemic plants to a more commercial and economic consideration of the value of endemic natural products, including biological potential. This move towards the economic and biological potential has been accompanied by a marked decrease in personnel and the number of active research groups, and a change in location from Government institutions to private companies. Over this period the Universities remained a bastion of research activity, but that too is now in decline.

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- (6) e.g.: Brooker, S. G. et al. *New Zealand Medicinal Plants*, Heinemann: Auckland, 1987, 268p. Riley, M., *Maori Healing and Herbal*, Viking Sevenses NZ Ltd. Paraparaumu NZ, 1994, 528p.

Pharmacognosy in Austria and Germany: Past and present contributions

Rudolf Bauer

Institute of Pharmaceutical Sciences, Karl-Franzens-University Graz, Universitätsplatz 4, 8010 Graz, Austria

Pharmacognosy, considered as the knowledge of medicinal products of natural origin, represents the oldest branch of the profession of pharmacy. Although there have been worldwide efforts in the compilation and scientific evaluation of medicinally used natural products, Europe and the German speaking countries, Austria and Germany, have played a major role in the scientific development of this discipline. Several important historic books on *materia medica* have been published, including those by Hildegard von Bingen (1098–1179), Hieronymus Bock (1498–1554), Leonhart Fuchs (1501–1566), Jacob Theodor, named Tabernaemontanus (1522–1590), and Adam Lonitzer (1528–1586). It is evident that the authors often were botanists or medical doctors.

The term “pharmacognosy” was established and first used early in the 19th century by Johann Adam Schmidt (1759–1809), professor of pathology, therapy, *materia medica* and prescription in Vienna, and was used two years later by Wilhelm Joseph Schmitt (1760–1827) in his text book of *Materia Medica*, where it is defined as knowledge of medicinal materials (drugs), in contrast to pharmacodynamics, which is defined as knowledge of the activity of drugs.¹ In 1815, the term “pharmacognosy” can be found in the title of a M.D. thesis (*Analecta pharmacognostica*) by C.A. Seydler at the Univ. Halle, Germany. “Pharmacognosy” was also used by the first professor of pharmacy and pharmacognosy in Germany, Theodor Wilhelm Christian Martius (1796–1863) at the U. Erlangen, in his books on “*Das Neueste auf dem Gebiet der Pharmakognosie*” (1830), and “*Grundriss der Pharmakognosie des Pflanzenreichs*” (1832). He defined pharmacognosy as the material science devoted to the analysis of drugs of natural sources in terms of origin, quality, and purity. At the same time, pharmacognostic collections were established in most universities for teaching purposes, like the one at the U. Vienna, which was initiated by Carl Damian Schroff (1802–1887), who became professor of pathology, pharmacology and pharmacognosy in 1849, one year after the newly established university curriculum for pharmacy had been established in Austria.

The department of pharmacognosy in Innsbruck was established in 1886 with Joseph Moeller (1848–1924) as head and professor of pharmacology and pharmacognosy; in 1893, he moved to Graz, and finally to Vienna, thereby influencing all three universities. His main interest was morphological aspects of pharmacognosy, but also included the elucidation of the active

principles, and he was known as one of the most excellent researchers of his time. In 1925, an independent Institute of Pharmacognosy was established in Innsbruck, and Ludwig Kofler (1891–1951) was appointed as professor and head in 1926. He focused on microscopic and micro-chemical investigations of natural and synthetic drug substances, developing the hot stage microscope (“Koflersches Thermomikroskop”) and the hot bench (“Koflersche Heizbank”) which were essential for the new field of thermo microscopy. In 1909, the pharmacologist and later Nobel laureate, Otto Loewi (1873-1961), became head of the institute of pharmacology at the U. Graz, and included “pharmacognosy” in the name of the institute.² Thus, in Austria, the departments or institutes of pharmacognosy developed from the institutes of pharmacology, while in Germany, the proponents were mainly botanists, like Carl Friedrich Philipp Martius in Munich, Matthias Schleiden in Jena, or Albert Wigand in Marburg.

In the 19th century, the isolation of plant constituents was mainly a domain of chemists, although the pharmacist Friedrich Wilhelm Sertürner (1783-1841) marked the birth of alkaloid chemistry by the isolation of morphine from opium in 1805. Later many contributions to natural product chemistry came from German speaking countries (e.g. the isolation of veratrine by C.F.W. Meissner, 1819; berberine by R. Brandes, J.A. Buchner and J.E. Herberger, 1824; atropine by H.F.G. Mein, 1831; colchicine by P.L. Geiger, 1833; cocaine by A. Niemann, 1860; and scopolamine by E Schmidt, 1888). In the following years, glycosides were discovered, with major contributions by Hermann Thoms (ouabain, 1904), Max Cloetta and Adolf Windaus (gitoxin and gitalin, 1925), and Rudolf Tschesche (steroid structure of cardenolides, 1935), adding to the important contributions in the fields of cardiac glycosides, antibiotics and alkaloids made by Swiss scientists, like Arthur Stoll (1887-1971), Nobel laureate Thaddeus Reichstein (1897-1996), and Albert Hoffmann.

Natural product synthesis and semi-synthesis became an important aspect of drug development (e.g. coniine, A. Ladenburg in Kiel; salicylic acid, H. Kolbe). The isolation of salicin from willow bark in 1828 by Johann Andreas Buchner (1783-1852), head of a private institute and professor of pharmacy in Munich, set the stage for the synthesis of salicylic acid by Hermann Kolbe (1818-1884) and later the industrial production of aspirin by the company Bayer. Several pharmaceutical companies like, Merck, Boehringer, Knoll, Riedel, and Trommsdorff were established in Germany which started to produce natural products like quinine, morphine, and atropine on an industrial scale.³

The major impetus for the establishment of the discipline of pharmacognosy at the university level, and for its transition from a material science involving microscopic investigations to natural products chemistry, came from pharmacists like Friedrich August Flückinger (1828-1894) and Alexander Tschirch (1856-1939), who had been working mainly in Strasbourg and Bern. Both contributed important text books in pharmacognosy (*Lehrbuch der Pharmakognosie des Pflanzenreichs* and *Handbuch der Pharmakognosie*, respectively). Tschirch understood pharmacognosy to involve the investigation of all aspects of drugs of herbal and animal origin, besides physiological activity. Since 1920, Richard Wasicky (1884-1970), head of the Institute of Pharmacognosy in Vienna, had emphasized the importance of the analysis of the active principles of medicinal plants and the development of pharmacognosy into a biological and experimental science. He defined it as the overall science of the chemical and physical properties of drugs, dividing it into two subgroups, pharmaceutical chemistry (pure chemicals) and physiopharmacognosy (drugs of natural origin). In his text book, *Physiopharmakognosie*, he listed for the first time all herbs in an order of indications, and under his direction, the Institute

made many contributions in areas such as cardiac glycosides, the biological determination of LD₅₀ values by the Knaffl-Lenz method, and the introduction of micro-chemical methods in the study of alkaloid-containing herbs.

The increasing importance of synthetic drugs and antibiotics in the first half of the 20th century, however, led to a de-emphasis of pharmacognosy, and in 1949 there was only one chair of pharmacognosy left in pharmacy in Germany. As a reaction, in 1953 the Society for Medicinal Plant Research (Gesellschaft für Arzneipflanzenforschung, GA) was launched, with the founding fathers, mainly medical doctors, stressing that medicinal plant research needed more support. In the same year, the journal *Planta Medica* was established,⁴ and over the years GA became an international society with a current membership of ca. 1300 from 84 countries. After World War II, pharmacognosy developed in several directions, with an increasing number of scientists interested in the isolation and analysis of active constituents. In Munich, Ludwig Hörhammer (1907-1975) and later Hildebert Wagner promoted phytochemistry, contributing greatly to flavonoid biochemistry, and several other classes of compounds. Activity-guided isolation became a strategy applied by many scientists in Austria and Germany, and Wagner was the first to establish in-house pharmacological assays for that purpose. Together with the improvement of spectroscopic techniques (e. g., UV, IR, ¹H- and ¹³C-NMR, MS), the output of identified active constituents increased substantially.

Egon Stahl (1924–1986), professor of pharmacognosy in Saarbrücken, developed TLC for routine laboratory use. This turned out to be extremely effective in the analysis of plant extracts, and together with paper chromatography, gas liquid chromatography (GLC), and later GLC-MS, played an important role in the performance of chemotaxonomic studies, including essential oil analyses, at several institutes of pharmacognosy, with Robert Hegnauer (1919-2007) in Leiden/The Netherlands being the leading figure. When HPLC became available it was immediately applied to the standardization of herbal medicinal products, which had become a requirement of the German drug law in 1978.⁵ Establishment of the Commission E led to the evaluation of the existing data on the efficacy and safety of medicinal herbs, and the publication of monographs on ca. 300 herbs. This exemplary work, undertaken with major contributions from many German pharmacognosists, has also revealed the lack of scientific evidence for the efficacy of many herbs. This has prompted increased clinical studies, and led to the founding of scientific societies on phytotherapy in Germany and Austria, with pharmacognosists contributing to clinical and pharmacokinetic investigations of herbal medicinal products. New trends, like TCM, are a challenge for western medical systems and require knowledge in this field in order to guarantee safe use. Systems biology and metabolomics may be scientific tools for the elucidation of the complex mode of action of herbal products, and may allow a renaissance of the field. Several pharmacognosists have compiled valuable data on medicinal plants in text books and compendia, including Rudolf Hänsel, Free U. Berlin, Max Wichtl, U. Marburg, and Eberhard Teuscher, U. Greifswald, to mention just three.

New aspects of pharmacognosy dealing with the biosynthesis of secondary metabolites and plant physiology were introduced by Kurt Mothes (1900-1983) in Halle, where he established an Institute of Plant Biochemistry in 1950. Techniques like isotope labeling were used intensively, and many of his students proceeded to become professors of pharmacognosy in Eastern and Western Germany. Later, scientists in this field, such as Meinhard Zenk at the Univ. Munich became involved in the elucidation of the enzymatic pathways, and finally in the genetic basis of the biosynthesis of secondary metabolites, and biotechnology involving plant cell and tissue

culture also became an area of intensive study by pharmacognosists like Ernst Reinhard (1926-2005) in Tübingen.

All these fields increasingly influenced the development of pharmacognosy from a descriptive discipline into a modern multidisciplinary plant science,⁶ and, with the establishment of a new pharmacy curriculum in Germany in 1971, the name *pharmacognosy* was replaced by *pharmaceutical biology*, and courses in phytochemistry became obligatory. Currently pharmaceutical biology in Germany is highly diverse with scientists working in fields like phytochemistry, plant physiology, ethnopharmacology, marine chemistry, biotechnology, microbiology, and human biology. Natural product research is also being performed in other disciplines, including enzymatic and genetic aspects of biosynthetic pathways,⁷ symbiotic microbes and combinatorial biosynthesis,⁸ environmental aspects of naturally occurring compounds,⁹ and the synthesis of libraries of bioactive compounds based on models from nature.¹⁰

In Austria pharmacognosy remains more homogenous, mainly focused on medicinal plants. The Herbal Medicinal Products Platform Austria (HMPPA) with activities in research and education was recently founded, and a national research network of HMPPA, *Drugs from Nature Targeting Inflammation*, established combining a classical phytochemical/pharmacological approach to drug discovery with the new strategy of *in silico* screening. Moreover, a TCM Research Cluster Austria has been established, which focuses on the investigation of Chinese medicinal plants.

With the acceptance of herbal medicinal products by consumers remaining high in Germany and Austria, the need for pharmacognostic expertise is evident. In addition, the new developments in drug discovery and development from nature will continue to make essential and expanding contributions to medicine and will guarantee pharmacognosy a bright future, even if under a different name.

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Evolution and Current Status of Natural Products Science in Brazil

Vanderlan da Silva Bolzani and Douglas Gatte Picchi

São Paulo State University, Institute of Chemistry, NuBBE – Nucleus of Bioassays, Biosynthesis, and Ecophysiology of Natural Products, Araraquara, SP, Brazil.

Brazil, known worldwide as the country of soccer and samba, also has a fascinating history in the chemistry of natural products. It began with the first settlers, when several European scientists came aiming to discover and study plants. Since then, several important ethnographies have been published. Among these, *Historia Naturalis Brasiliae* by W. Piso and G. Marcgraf in 1648 is considered the most important document, describing the potential of the vast biodiversity.¹ Early chemical studies by Pelletier and Caventou identified several alkaloids in Brazilian plants,² and as early as 1838 the pharmacist Ezequiel C. Santos isolated “pereirine” from the bark of “pau-pereira” [*Geissospermum laeve* (Apocynaceae)], known by Native Brazilians as a remedy to treat malaria, inflammation and fever. Pereirine was identified much later as geissoschizoline,³ also a constituent of several other Apocynaceae species.

Modern phytochemical research was introduced by three scientists, who established the basis for the development and consolidation of this area. In São Paulo, Otto Gottlieb and his collaborators studied plants from Amazonia, especially Lauraceae and Myristicaceae, isolating ~350 neolignans and ~120 lignans,⁴ as well as studying chemosystematics and biosynthesis, particularly phenylpropanoids, and establishing important connections between secondary metabolites and plant phylogeny of various taxonomic groups. In Rio de Janeiro, Walter Mors and Benjamin Gilbert dedicated their efforts mainly to medicinal plants, and published several articles on traditionally used plants which helped all Brazilians in providing scientific evidence to support the popular uses of several plant species. As a result of their outstanding work, natural products chemistry in Brazil gained recognition more as a discipline of organic chemistry, rather than as pharmacognosy. Thus, there are now 315 active researchers registered as members of the Natural Products Chemistry Division (DPN), a section of the Brazilian Chemical Society (SBQ), created in 1993. SBQ, a flourishing Brazilian scientific society, currently has about 3,500 members. The DPN-SBQ database indicates that ~48.4% members conduct research on the isolation and structure elucidation of secondary metabolites from plants; ~19.4% on bioactive secondary metabolites, 10.2% on analytical methodology, 6.2% on microorganisms 4.7% on chemical ecology, 3.4% on insects, and 2.5% on marine organisms, with smaller numbers involved in chemosystematics, biotechnology, molecular biology, biosynthesis, bio-transformation, and the synthesis of natural products. Marine organisms and microorganisms are largely unexplored in Brazil, and are proving to be promising sources of new secondary metabolites. The creation and consolidation of new research groups in biosynthesis and molecular biology are also developments which are changing the face of Brazilian natural products research. The progress in this area, and the substantial contribution being made by Brazilian researchers to natural products chemistry and pharmacognosy, is evidenced by the growing number of papers published in some of the most important peer review journals. Based on data from the Web of Science compiled in the last 5 years, the average percentage of Brazilian articles in the *J. Nat. Prod.* was 1.6%, *J. Ethnopharmacol.* 8.1%, *Planta Medica* 4.8%, *Phytochemistry* 2.9%, *Phytochem. Research.* 5.9%, and *Phytochem. Analysis* 5.5%.

The Brazilian Society of Pharmacognosy (BSP), created in 1986, has about 350 members, publishes its own journal and organizes bi-annual meetings focused mainly on medicinal plants. With the growing contribution of the younger generation of scientists, pharmacognosy in Brazil

is now increasingly recognized. Significant contributions being made by this new generation are exemplified by José Barbosa Filho (Editor-In-Chief) and Emídio Leitão da Cunha (Assoc. Editor) in their revision and editorial improvement of the *Brazilian Journal of Pharmacognosy*. They have worked with great enthusiasm, increasing the average citation number of the articles published, and aiming to establish an international reputation for this journal.

Recently Brazilian biodiversity has become a major source of active principles used by local pharmaceutical companies for the development of new medicines. A rich history of use of traditional medicine places Brazil in a privileged position, especially for companies interested in the commercialization of herbal medicines. The Brazilian government has created policies protecting and improving the use of the local biodiversity, and in the last decade there has been a rapid development of authentication and quality control methods of herbal medicines, resulting in their improvement, and stimulating the local market. Aché Laboratories, the biggest pharmaceutical company in South America, is exploring local biodiversity, based on the use of ethnopharmacology and modern chemical screening techniques, to discover new chemical entities.⁵ Acheflan[®] developed from *Cordia verbenacea* (Boraginaceae), known popularly as “erva baleeira” and used in folk medicine for the treatment of several inflammatory processes, had sales of approximately US \$5.1 million in 2007, and is a great example of the successful application of local pharmacognosy research. Likewise, Hebron Pharmaceutical Co. launched a herbal medicine derived from *Schinus terebinthifolius* to treat gynecologic infections, and Herbarium Laboratories, better known for selling herbal medicines prepared from Asian and European plant species, has significantly increased its net profits through sales of a herbal medicine produced from *Pfaffia glomerata*, known as Brazilian ginseng.

The recently established Biota Program supported by FAPESP (<http://www.fapesp.br/>) is considered a valuable tool to map and catalog the biodiversity of the main biomes of the State of São Paulo, including flora, fauna, microorganisms, and insects. This new approach to the rational exploration of local biodiversity aimed at its preservation and sustainable use, nicely matches the expertise of Brazilian chemists, biologists and pharmacists whose research is focused on the search for new biologically active compounds. The strong multidisciplinary approach of this Program should be important for advancing, not only biotechnology, but also the characterization of medicinal plants using the tools and techniques of molecular biology. Recent efforts in the training of scientists in proteomics and metabolomics open exciting opportunities for expanding the knowledge of tropical and equatorial plant species, and also for studying the safety, quality and efficacy of medicinal plants. With these considerations in mind, developments in natural products chemistry and plant science undoubtedly have contributed greatly to the advancement of science in Brazil.

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Natural Products and Pharmacognosy in Canada: a Brief History

Colin J. Briggs

Faculty of Pharmacy, University of Manitoba, Winnipeg, MB, Canada. R3E 0T5

A Centennial panel concluded that sustained medical research in Canada began in the early 1920s, with the work of Banting and discovery of insulin. Connaught Laboratories, founded by the University of Toronto in 1914, made major contributions to basic research and production of insulin, vaccines and sera. Pasteur, Merieux, Connaught remains a leader in development and manufacture of biological products. In the 1940s, Connaught and Ayerst, McKenna, Harrison were innovators in research and production of penicillin.

G. H. Neil Towers was a pioneer of phytochemical research in Canada. Author of over 425 papers, his research included photobiology, chemical ecology of plants and fungi, tissue culture chemistry and ethnopharmacology. After 9 years at McGill he moved to the Halifax NRC Laboratory in 1962, working on biochemistry of lichens and fungi. Joining the University of British Columbia (UBC) in 1964, Towers made significant research contributions for 40 years. Adam Szczawinski was a botanist at UBC from 1953. He specialized in mushrooms, edible and poisonous plants of Canada, identifying “new” species and exploring plant diversity in the Yukon and BC for 53 years. He promoted phytochemical investigation, with colleagues including Nancy Turner, an expert on First Nation botanical knowledge. At the Royal BC Museum she studied biodiversity and ethnobotany for 30 years, working particularly with Haida elders. Many phytomedicines that she reported have been evaluated by modern chemical and therapeutic means. Also, A. McCutcheon, a UBC pharmacognosist, investigated West Coast aboriginal medicines. A broad study of traditional plant use in Canada’s Northwest boreal forest by Cree, Dene and Metis people was prepared by R. Marles, now with the Natural Products Directorate. Phytochemical aspects were included. Currently, P. Haddad in Montreal leads a national project on diabetes in aboriginal people and evaluating traditional treatments.

Other contributors to Canadian chemical research on plants include G. Mazza at Summerland Agri-Food Research Centre with studies on chemistry of polysaccharides and proteins as nutraceuticals, flavonoids and anti-inflammatory agents. P. Faccini, Canada Research Chair in Plant Biotechnology in Calgary is making advances in biosynthesis and genetics of benzyloquinoline opium alkaloids. D. Awang, a scientist with Health Canada for 24 years, is known for research on feverfew. His later research relates to analysis of quality and efficacy claims for natural products. At the University of Ottawa, J. Thor Arnason developed assays for active components of plant-based medications and reassessed taxonomy, therapy and phytochemistry of *Echinacea* species.

F. Shahidi at Memorial University, Newfoundland, is a leading scientist in chemistry of nutraceuticals, functional foods and natural antioxidants, with extensive research on lipids and seafood components. In Halifax, the NRC’s Atlantic Research Laboratory is its lead facility for marine biotechnology, particularly for phytochemistry of marine plants. R. Kerr in Prince Edward Island is studying cytotoxic diterpenes related to eleutherobin, seeking potential bioactive compounds from marine algae and invertebrates. At UBC, R. Andersen is investigating chemistry and biosynthesis of metabolites from marine organisms eg. hemisterlin, and analogues, as potential bioactive leads for therapeutic use.

In 1944 there were 7 schools of Pharmacy in Canada. The faculties were small, with little opportunity for research. Pharmacognosy was present in all curricula, but natural product

research did not develop until the 1960s. A. and L. Goodeve taught pharmacognosy at UBC from 1960-1986. They investigated alkaloidal biosynthesis and pharmacological effects of mescaline and yohimbine. In Alberta, R. A. Locock followed his studies on chemistry of *Eupatorium* species with chromatographic and spectral analysis of biogenic amines. He identified oxindole alkaloids in *Elaeagnus commutata* and developed analyses for tetracyclines. Prior to appointment as Dean of Pharmacy in New Mexico in 1970, Carman Bliss taught pharmacognosy in Saskatchewan. He characterized iridioids of *Mentzelia* spp. and studied agronomic effects on volatile oil components of local crops. A co-worker, E. Hawes, conducted metabolic and analytical research on pyrrolizidine alkaloids, phytotherapeutic and pharmaceutical agents, specializing in glucuronidation and biotransformation. At the University of Manitoba, Gerald Blunden initiated research on steroidal saponins in 1962. R. C. S. Audette joined the faculty in 1965, starting studies on alkaloids of *Phalaris*, *Phragmites* and triticales ergot. J. Templeton obtained his Ph.D. with Nobel Laureate D. Barton, working on structure of limonin. In 1967 he began research in Manitoba on chemistry, structure and metabolism of hormones, anabolic and androgenic compounds, also investigating structure/activity relationships of cardiac glycosides. C. J. Briggs taught pharmacognosy in Manitoba from 1967. His research included analysis of non-protein aminoacids in Leguminosae (Fabaceae), identifying low toxicity *Lathyrus* cultivars and evaluating antioxidants in buckwheat. At the University of Toronto in the 1960s, S. Sim wrote a textbook on alkaloids and another on glycosides, while researching alkaloids. Later, G. Duncan pursued research on steroidal synthesis and biochemistry until appointed as the first Director of the School of Pharmacy at Memorial University. Quebec Province has a long tradition of natural products in pharmacy. Following A. Francoeur, J.-Antonin Marquis taught *Materia Medica* at Laval University from 1928-1953. His expertise in quality analysis of natural products resulted in appointment to the Canadian Formulary Committee (1949). Professor Demers succeeded M. Marquis teaching pharmacognosy and promoting research until 1968, when G. Favreau assumed the position. In Montreal, Dr. Mockle advocated development of high quality standardized phytomedicines, stressing assay requirements. From the 1950s he studied components of Canadian medicinal plants, including aboriginal sources. Emphasis was on alkaloidal identification and metabolism, interests shared by J. Beliveau, particularly for those with antibiotic properties. At Dalhousie University, Halifax, R. F. Chandler was a leader in natural products developments from the 1970s. His primary research area was herbal remedies of MicMac Indians, emphasizing phytochemical studies. He participated in several Health Canada Committees established to improve Natural Health Product regulations. Tannis Jurgens, his colleague from 1996, isolated and characterized potential biological agents from plants and is evaluating the impact of natural product impurities on clinical trials.

Biotechnology and analytical advances, combined with public interest in complementary medicine, are expected to maintain demand for research on therapeutic agents and lead compounds of natural origin in Canada.

Contributions to Pharmacognosy in Iberoamerica and the Caribbean

Mahabir P. Gupta^a and Winston Tinto^b

^a*Centro de Investigaciones Farmacognósticas de la Flora Panameña, Facultad de Farmacia, Universidad de Panama, Panama, R. de P.* ^b*Dept. Biological & Chemical Sciences, University of the West Indies, Cave Hill Campus, PO Box 64, Bridgetown, Barbados, WI BB11000*

Of the 17 megadiverse countries in the world, six are in the neotropics, which individually have more species of plants, vertebrates and invertebrates than the majority of other nations.¹ In addition to providing the world with Cinchona, Ipecac, Quassia, Jaborandi, and Balsams of Tolu and Perú, the steroid industry had its roots in *Discorea* from México. The region has had a rich history of natural products research. Scientists, *inter alia*. Antonio González (Canary Islands, Spain), Jesús del Romo (México), Venancio Deulofeu (Argentina), Otto Gottlieb (Brazil), José Medina (Venezuela), Xorge Domínguez (México), and Mario Silva (Chile), have been pioneers in phytochemical investigations in Latin America and have been mentors for many chemists and pharmacognosists in the region. Thus, pharmacognosy in this region is alive and well, and it remains a required course in most schools of pharmacy in Latin America. Currently, there are 63 (5.3%) ASP members in this region, and ASP events held in the region have included an Interim Meeting on “Intellectual Property Rights and Naturally Derived Bioactive Compounds and Resource Conservation” in San José, Costa Rica (1994), and the 42nd Annual Meeting in Oaxaca (2001). However, the founding of the Fine Pharmaceutical Chemistry Subprogram of the Iberoamerican Program of Science and Technology for Development (CYTED) in 1989, coordinated by Ceferino Sánchez (Panama) and later by Mahabir Gupta (Panama), signaled the beginning of a multidisciplinary approach to natural products drug discovery from Ibero-American biodiversity involving chemists, pharmacognosists, pharmacologists, biologists, botanists and other professionals interested in natural products research.

CYTED is a multilateral program of cooperation aimed at fostering the scientific and technological integration of 21 participating countries. Since 1989, the Sub-program X of Fine Pharmaceutical Chemistry has been uniting over 1,300 natural products scientists in over 200 R&D centers and industries in Latin America, Spain and Portugal, through 6 Thematic Networks and 11 Collaborative Research Projects. The goal is to discover lead compounds with immunomodulatory, anticancer, cardiovascular, anti-parasitic, anti-inflammatory, anti-fungal, anxiolytic, and anti-tuberculosis properties, and for the treatment of gastrointestinal pathologies, as well as the design of monographs on the quality, safety and efficacy of Ibero-American medicinal plants. During this period, over 570 scientists have been trained in different facets of natural products drug discovery through workshops, scientific exchanges and training courses. Over 3,000 plant extracts have been screened and many novel compounds identified. In addition three Iberoeka projects among industries of the Region have been successfully executed.² In addition, important funding support for research and networking on medicinal and aromatic plants has been provided by international organizations,³ and Argentina, Chile, Costa Rica, Mexico, Panama and Perú have been participating in International Cooperative Biodiversity Group (ICBG) projects, which have permitted a systematic study of their biodiversity as a source of lead compounds.⁴ A bibliographic search⁵ of the 10 most important natural products journals from 1994 to 1998 and of NAPRALERT[®] (courtesy of Norman Farnsworth) from 1990 through 2000 indicated that the Ibero-American region contributed towards 14% (2223 out of 15920) of the natural product papers, with Spain, Brazil, Mexico, Argentina and Chile predominating.

In relation to Central America and the Caribbean countries, Puerto Rico, West Indies, Costa Rica, Guatemala, and Panama have taken leading roles in pharmacognosy research. C. H. Hassel (1948 –1969), L. Haynes and W. R. Chan at the U. West Indies (UWI), Mona have contributed significantly. The discovery of monomycin, an antibiotic from *Streptomyces jamaicensis*, provided the lead for some important hypertensive agents. Research at UWI, St. Augustine in Trinidad and Tobago is being carried out by Baldwin Mootoo and Anderson Maxwell, and at Cave Hill, Winston Tinto studies marine organisms, as well as medicinal plants, also involving cooperative arrangements with pharmaceutical companies. Puerto Rico has had a rich history ever since Columbus discovered the island of Hispaniola in 1493. Pharmacognosy became a formal academic topic when the School of Pharmacy of U. Puerto Rico was established as the first professional school in 1906. Early contributions were made by Esteban Núñez Meléndez, who published five books on medicinal and toxic plants of Puerto Rico and Costa Rica, while currently Mikhail Antoun is leading research on the development of anticancer, anti-malarial, anti-tubercular and anti-inflammatory leads. At the Rio Piedras Campus, Bill Gerwick, Nestor Carballeira, and Abimael Rodríguez have made significant contributions in the area of marine pharmacognosy, and contributions have been made by botanists, including Franklin Axelrod, George Proctor and Henri Liogier. In 1989, Puerto Rico hosted the 30th Annual ASP Meeting.

In Panama, Mahabir Gupta has established a Pharmacognostic Research Center at U. Panama which has been the site for many international training courses and collaborative multinational drug discovery projects in natural products. In Costa Rica, the National Institute of Biodiversity (INBIO) and the Center for Natural Products Research (CIPRONA) at U. Costa Rica have been instrumental in furthering the study and utilization of biodiversity. Within the context of the INBIO – MERCK Agreement, the correolides from *Spachae correae* showed significant immuno-suppressive activity and were the basis of several patents, and guanacastepene from an endophytic fungus from the rachis of *Daphnopsis americana* showed interesting antibiotic activities. Since 2000, INBIO has been actively pursuing the development of phytomedicines. With LISAN, a small pharmaceutical industry, it launched two products based on *Quassia amara* and *Justicia pectoralis*.⁶ Since 1974, CIPRONA, founded and directed by Jose Calzada at U. Costa Rica, has played a key role in the systematic scientific study of local plants; later key players have been Oscar Castro, Gerardo Mora, Alice Perez and Luis Poveda. In Guatemala, Armando Cáceres has been a leader in agrotechnological and ethnobotanical studies.

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Fifty Years of Pharmacognosy in China: A History of Undisrupted Development

Chun-Tao Che and Zhi-Xiu Lin

School of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong

The tradition of use of medicinal plants, animals and minerals in China for the treatment and prevention of diseases (TCM) spans over several thousand years. However, modern pharmacognosy did not exist as a scientific subject until the late 1950s when Xu and Zhao published an influential specialist work~~s~~ entitled *Pharmacognosy*,¹ which was followed by the publication of several related volumes in the 1960s. The ensuing 1970s and 1980s saw the advent of intensive research in pharmacognosy characterized by the government-promoted national collaboration and cooperation, epitomized by the publication of *Chinese Materia Medica* by the Nanjing Pharmaceutical College and *Encyclopaedia of Chinese Materia Medica* by the then Jiangsu New Medical College.¹ During the 1990s and into the new millennium, pharmacognosy in China has matured as an academic subject, with many scholars exploring cutting-edge technologies and modern methodologies to study nature-derived medicinal products.

Pharmacognosy in China is unique in its intrinsic and inseparable link to the study of Chinese *materia medica*, because, not only are the history of herbal medicine and the number of species and quantity of herbal materials in use among the richest in the world., so also are the philosophies and theories underpinning their application. TCM is one of the state-sanctioned therapeutic modalities, and pharmacognosy as a subject has therefore experienced rapid and undisrupted development during the past 50 years. Unlike many universities in the West, where pharmacognosy is largely removed from undergraduate pharmacy curricula, pharmacognosy in China enjoys continuing support from the government, owing to the richness of natural resources and the huge market potential of Chinese herbal medicines. The development and advance of pharmacognosy in China over the past half-century can be broadly categorized into the following areas:

1. Comprehensive Survey of Resources of Chinese Materia Medica

An ambitious state-sponsored nation-wide survey of the resources of Chinese *materia medica* was launched in mid-1980s that took over 10 years to complete.² The results of the survey, which covered 29 provinces involving about 2,000 counties, indicated that there are 12,807 kinds of Chinese *materia medica* currently available in China, 11,146 of which are plant-based. This survey is of significance in that it helped sketch the broad picture of the nation's *materia medica* resources, including the number of species, their distribution, reserves, utilization and the traditional knowledge of their application. As a result, a number of works representing the national and regional *materia medica* resources have been compiled.² Increasing attention has been placed on the protection of endangered botanical and animal species, and domestication of medicinal animals and cultivation of herbal plants have widely been introduced as a sustainable means for meeting the increasing demands for these medicines.

2. Crude Drug Authentication and Quality Evaluation

The last 50 years witnessed rapid development of authentication and quality control methods employed in studying Chinese *materia medica*. Macroscopic and microscopic methods and TLC methods are now commonly used in the authentication of a wide variety of herbal materials. Other more reliable methodologies, such as HPLC, GC, EC, UV and IR spectroscopy, trace elements analysis, and DNA fingerprinting are used for quality evaluation of crude drugs, and

numerous papers have been published both in Chinese and English to document the great advances made in this area. These include voluminous works such as *Zhonghua Bencao*,³ *Species Systematization and Quality Evaluation of Commonly Used Chinese Traditional Herbs*,⁴ and *Modern Chinese Materia Medica*.⁵ In Hong Kong, a collaborative project has been ongoing for several years to develop quality standards on the commonly used Chinese herbal medicines.⁶

3. Bioactive components of Chinese herbal medicines

The identification and characterization of bioactive compounds from Chinese *materia medica* for drug discovery has always been an intensive research area of pharmacognosy in China. Indeed, the contributions to the development of pharmacognosy by Chinese scientists are exemplified by the discovery of the following bioactive molecules from Chinese medicines.⁷

Compound name (plant)	Bioactivity
Artemisinin (<i>Artemisia annua</i>)	Anti-malaria. Artemeter and artesunate, two derivatives of artemisinin are the first line anti-malarial drugs.
Huperzine A (<i>Huperzia serrata</i>)	Selective acetylcholinesterase inhibitor; Anti-Alzheimer's Disease and myasthenia gravis. It has been approved for the treatment of Alzheimer's disease and myasthenia gravis in China.
Clausenamide (<i>Clausena lansium</i>)	Cognition-enhancing action.
Indirubin (<i>Isatis indigotica</i>)	Anti-leukemia.
Baogongteng A (<i>Erycibe obtusifolia</i>)	Miotic action.

4. Outlook and Prospects

China has contributed much to the success of pharmacognosy over the past half of a century. The ever-increasing popularity of Chinese medicines worldwide will certainly spur more research in this traditional yet vibrant subject area. With rapid development of its economics, it is envisaged that China will play a more active role in advancing all aspects of pharmacognosy in the 21st century.

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Pharmacognosy in Egypt: Ancient Use of Medicinal Plants

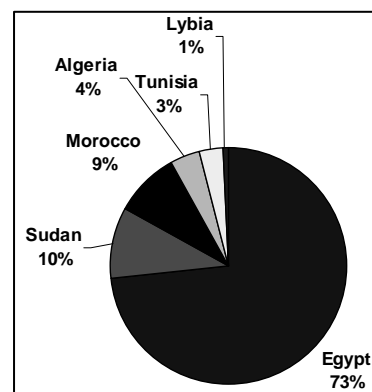
Diaa T. A. Youssef*, Ahmed Fathi and Lamiaa A Shaala

Department of Pharmacognosy, Faculty of Pharmacy, Suez Canal University, Ismailia 41522, Egypt

If you *had* to be ill in ancient times, the best place to do so would probably have been Egypt. Not that it would have been much fun. Unlike the injuries received through accidents or fighting, which were dealt with by the *zwn.w (sunu)*, or scorpion stings and snake bites for which the *xrp srqt (kherep serqet)*, the exorcist of Serqet, knew the appropriate spells and remedies, illnesses and their causes were mysterious. Herbs played a major part in the ancient Egyptian medicine. The plant medicines mentioned in the Ebers papyrus for instance include opium, cannabis, myrrh, frankincense, fennel, cassia, senna, thyme, henna, juniper, aloe, linseed and castor oil - though some of the translations are less than certain. Cloves of garlic have been found in Egyptian burial sites, including the tomb of Tutankhamen and in the sacred underground temple of the bulls at Saqqara.

Pharmacognosy in modern Egypt goes back to the early 1950s, with the investigation of the local wild and cultivated plants through study of their morphological and microscopic characters, as well as simple chemical investigation, including the isolation and identification of natural products through simple chemical derivatization and other available chemical and spectroscopic techniques. However, with the increasing knowledge of chromatographic and spectroscopic techniques, Egyptian scientists have contributed substantially to the investigation of the medicinal plants over the past four decades, with more than 2,500 scientific peer-reviewed papers representing about 75% of Pharmacognosy research performed in North Africa (see pie chart below).

It is our belief, however, that despite this success, pharmacognosy research on Egyptian flora needs more studies aimed at the exploration of their therapeutic potential. A major weakness is the absence of strong funding agencies in the country, and a real national drug discovery program. Moreover, the lack of the coordination between different universities and research institutions leads to the duplication and repetition of many previous studies on medicinal plants, resulting in most cases, in a wasting of time, money and efforts of many researchers. A coordinated national drug discovery program in Egypt is urgently needed to uncover the potential therapeutic uses of the many medicinal plants used for thousands of years by our ancestors in this part of the world.



Inspired by the unique unexplored biodiversity of the Red Sea, the lead author has emphasized to his colleagues at other Egyptian universities the importance of the Oceans as a future source for drug discovery and development, and he recently established the first station for Marine Natural Products investigation in the country. His main interest is the investigation of marine invertebrates and their symbiotic microbes and he has published over 30 papers in international journals describing the results of chemical and biological investigations of some Red Sea organisms.

Natural Products Chemistry in France

Françoise Guéritte^{†,*}, Joël Boustie[‡], Thierry Sévenet[†] and François Tillequin[§]

[†] Institut de Chimie des Substances Naturelles, 1 avenue de la Terrasse, CNRS, 91198 Gif-sur-

Yvette [‡] Faculté de Pharmacie, EA4090, Université de Rennes1, 2 av Pr Léon-Bernard, 35043

Rennes [§] Faculté de Pharmacie Paris5 UMR8638, 4 av de l'Observatoire, 75006 Paris

The first chemical studies on natural products (« matière médicale », then pharmacognosy) took place in France at the beginning of the 19th century, and this country occupied a pioneering position in the early isolation of active principles from crude drugs of plant origin. Active pure products were mainly isolated by pharmacists. At that time, the structure determination of natural products was a major challenge, since it mainly relied on chemical degradation reactions. Consequently, most of the structures of active compounds isolated during the 19th century could be elucidated only one century later. Derosne isolated narcotine from opium, the thick latex of poppy in 1803. He also purified morphine. Pelletier and Caventou isolated strychnine and brucine from *Strychnos ignatii* in 1818-1819 and the antimalarial quinine from Peruvian *Cinchona* in 1820. In 1830, Leroux obtained salicin, the antipyretic glycoside from the trunk bark of *Salix* sp., a common tree, which “grows in water and never catches cold”. Cardiotonic digitalin was crystallized from *Digitalis purpurea* by Nativelle in 1868 and colchicine from *Colchicum autumnale* by Houdé in 1884.¹

The tremendous development of chemistry in the 20th century allowed conception, after structure elucidation of the active principles, of synthetic analogs, more active, less toxic and of easier access. The first achievement in this field was the preparation by Fourneau, in 1903, of the first synthetic local anesthetic, stovaine, on the model of the natural alkaloid cocaine. In a more recent period, two leading groups were renowned for their significant contributions to natural products research, the team of Professor M.-M. Janot and his co-workers (J. Le Men, R. Goutarel, P. Potier, A. Cavé...) and the group of Professor G. Ourisson and co-workers (P. Albrecht, J.-M. Lehn, M. Rohmer...). Maurice-Marie Janot at the Institut de Chimie des Substances Naturelles (ICSN) in Gif, developed collaborations with southern countries, particularly in Western Africa, Madagascar, and New Caledonia. Guy Ourisson mainly explored the field of geochemistry and triterpene biosynthesis. Two major anticancer drugs were discovered at ICSN by the group of Pierre Potier; Navelbine[®] (vinorelbine), an analog of vinblastine isolated from the Madagascan periwinkle,² and Taxotere[®] (docetaxel), an analog of Taxol[®] (paclitaxel) extracted from the bark of the yew tree.³ These two drugs are manufactured today by Pierre Fabre Laboratories and Sanofi-Aventis, respectively. Similarly, elucidation of the structure of ellipticine, an alkaloid extracted from *Ochrosia* sp., led to the synthesis of Celiptium[®], used for a few years in the treatment of breast cancer. Acronycine, another alkaloid found in an Australian *Acronychia* led Michel Koch and François Tillequin to develop very active synthetic analogs.⁴

Up to 1990, research on natural products was essentially oriented by chemotaxonomic guidelines (alkaloids from Apocynaceae, Rutaceae, acetogenins from Annonaceae, saponins from Sapindaceae, Symplocaceae...). The current urgent need for new medicines has led to a careful inventory of the biological activity of plant extracts,⁵ lichens,⁶ marine organisms⁷, etc... New

* to whom correspondence should be addressed. Tel: (33) 1 69 82 45 80. Fax :(33) 1 43 54 47 25. E-mail: francoise.gueritte@icsn.cnrs-gif.fr

fields of research are also explored, such as zoopharmacognosy.⁸ In France today, the most prominent academic research on natural products is concentrated in the CNRS (Centre National de la Recherche Scientifique), IRD (Institut de Recherche pour le Développement), at the MNHN (Muséum National d'Histoire Naturelle, Paris), and in most of the 24 Pharmacy departments of French universities, whose annual activity reports are available on the French language Society of Pharmacognosy (AFERP) website⁹. At the ICSN (CNRS), the group "Pôle Substances Naturelles-Plantes" has established numerous cooperative programs in Asia (Malaysia, Vietnam), Africa (Madagascar, Uganda), South America (French Guyana), and Oceania (New Caledonia). All of these collaborations are established through official agreements respecting the rights and duties of each partner and in accordance with the Convention on Biodiversity. The numerous extracts prepared from the plants of primary forests are purified and evaluated biologically by means of automated technologies. In parallel, collaborative agreements with pharmaceutical and agrochemical industries combine public and private interests to enhance the discoveries. This is a part of the French National Chemical Library "Chimiothèque Nationale"¹⁰ which was created in July 2003 by an agreement between CNRS and 17 higher education and research organizations. In January 2008, this library coordinates collections of 36,000 synthetic and natural products and 11,300 natural extracts available in French academic laboratories. French and tropical flora are also actively investigated in Pierre Fabre Laboratories.¹¹

While the French researchers, in the great tradition of the 19th century naturalists, have exhibited prolific activity in the field of pharmacognosy, their actual successors are still in a good position to carry out new investigations in a more open fashion through extending collaborative networks involving studies of the largest biodiversity to the multiple focused biological targets.

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Pharmacognosy in Israel **Zohara Yaniv and Yoel Kashman***

*ARO, The Volcani Center, Bet Dagan, Israel and School of Chemistry, Tel Aviv University,
Ramat Aviv 69978, Israel*

Israel is known for its unique natural diversity, and for the wealth of plant species with medicinal properties that have been used since early times. The history of the use of medicinal plants in Israel is well documented, including the medicinal plants mentioned in the Bible.^{1,2} The different ethnic groups in Israel have retained, to varying degrees, their traditional medicines. A few extensive ethnobotanical surveys were conducted in Israel in the 1980s and in the late 1990s;

they include 581 medicinal plants.^{3,4} Examples are: *Sacropoterium spinosum*, used for the cure of diabetes;¹ Myrtle tea, used by the Yemenis against throat ache, afforded two antibacterial acylpholorglucinols, myrtucommulones A and B;⁵ Cannabis, well known for the THC drug which currently also has other effective therapeutic uses;⁶ and the isolation of the anti-cancer withanolides from *Withania somnifera* which was, among other uses, used as an anti depressant.⁷ The Volcani Center, and the Newe Ya'ar Research Center, make progressive use of ethnobotanical knowledge and work for the improvement, domestication and industrialization of medicinal and aromatic plants and their products.

Since humans are largely land based, they have concentrated on, and become familiar with, terrestrial plants and animals. The research of marine natural products is subsequently at an earlier stage of development. Our group (Y.K.) initiated the investigation of organisms from the Red Sea in 1972, and, since then, many active compounds have been isolated. A few examples of drug leads follow. The ichthiotoxic cembranoid, sarcophine and derivatives possess anticancer activities;⁸ the latrunculins A and B were found to inhibit actin polymerization and thus became an important tool in cell biology studies;⁹ similar activity is possessed by the polyketide, swinholide A;¹⁰ among the guanidine polycyclic alkaloids is ptilomycalin A which is a good antiviral drug lead;¹¹ the imidazole alkaloids, naamines and naamidines are cytotoxic and affect ion transfer through membranes;¹² The latter examples demonstrate the high potential of marine natural products as drug leads.

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Natural Products in Italy. A Historical Perspective

Giovanni Appendino

Facoltà di Farmacia, Largo Donegani 2, 28100 Novara, Italy

The study of natural products has flourished in Italy since the early 19th century. Of special relevance were the investigations on terpenoids by Ascanio Sobrero (1812-1888), testified by the name sobrerol given to an expectorant monoterpenoid drug, the discovery of salicylic acid by Raffaele Piria (1814-1865), and the studies on \square -santonin by Stanislao Cannizzaro (1826-1920). In modern times, the rearrangement of \square -santonin to santononic acid, a reaction pioneered by Cannizzaro, was a major source of inspiration for the development of retrosynthetic analysis by Elias J. Corey.¹ However, none of these pioneers succeeded in establishing an Italian natural

product “school”. Sobrero, who also discovered nitroglycerine, never managed to get a university chair, while Piria and Cannizzaro were essentially generalists, cultivating a wide range of interests outside natural products. Unsurprisingly, no charismatic figure emerged in the following years, even though there was no shortage of important discoveries. Thus, in 1896 Bartolomeo Gosio reported the isolation of mycophenolic acid, the first antibiotic to be discovered, and now an important immunosuppressant drug.² The Italian tradition in microbial compounds was later continued by Giuseppe Brotzu (1895-1976), who in the mid 1940s purified cephalosporin C from a Sardinian marine microorganism, by Aurelio Di Marco, Federico Arcamone and Sergio Penco, who discovered and developed the antitumor anthracyclines in the 1960s, and by Paolo Sensi and GianCarlo Lancini, who, in the very same years, reported the antitubercular antibiotics, the rifamycins. The excellence of Italian research in microbial compounds can be traced back to the seminal activity of the Nobel laureate Ernst B. Chain (1906-1979), one of the discoverers of penicillin, at the Istituto Superiore di Sanità in Rome, where he was invited in 1948 by Domenico Marotta (1886-1974) to foster research on fermentation and the microbial production of bioactive compounds. The discovery of anthracyclines and rifamycins was the result of efforts by Farmitalia and Lepetit, two companies based in Milano that eventually ended up in the Pfizer conglomerate. The commitment of Italian industrial research to natural products is further exemplified by the role that Indena, another company based in Milano, has played in the production of taxoids. By pioneering the use of standardized plant extracts and their investigation with modern techniques, Indena and Ezio Bombardelli have undoubtedly contributed to foster the current worldwide interest in botanical drugs.³

The years 1960-1980 were the golden decades of Italian chemical research. Of special relevance were the studies on phenolics by Luigi Panizzi (1909-1988), who characterized the bitter glucoside oleuropein from the olive tree, and the choleric polyphenol cynarine from artichoke, and those by Giovanni Battista Marini Bettolo (1915-1996) and Armandodoriano Bianco on curare and iridoids, respectively. During this period Franco Piozzi discovered the mitochondrial poison atractyloside, and the School of Luigi Canonica (1920-1984) thrived in Milano, with important contributions to the chemistry of terpenoids [amarogentin (Paolo Manitto), sesquiterpenoids (Giancarlo Jommi, 1932-1996), ophiobolins (Alberto Fiechi, 1928-1991)], and alkaloids (Bruno Danieli). Research on phenolics (chromenes, quinones) and terpenoids (illudanes) from plant, animal, and microbial origins was also performed in Milano by Lucio Merlini and Gianluca Nasini, while important contributions to the study of bioactive compounds from then unconventional sources came from various groups. Thus, Alfonso Quilico (1902-1982), who also mentored Panizzi and Piozzi, characterized the toxic amide pederine from the blister beetle *Paederus fuscipes*, Vittorio Erspamer (1909-1999) laid the foundation of amphibian peptides chemistry, Paola Vita-Finzi mastered the chemistry of *Basidiomycetes* in Pavia, and Mario Piattelli and Rodolfo Nicolaus established a natural product school that eventually made Luigi Minale (1936-1997), Guido Cimino, and Ernesto Fattorusso renowned in marine chemistry, and Naples one of the leading centers for natural products research in the world.

A multidisciplinary basis is required for the effective teaching and learning of natural products chemistry and pharmacognosy, and modern academic curricula make this difficult in Italy, just like everywhere else. Pharmacognosy is part of the curricula of all 29 Italian Faculties of Pharmacy. Courses on medicinal plants are also taught in the 25 Faculties that offer Diploma courses in Tecniche Erboristiche (Herbal Sciences), and natural products chemistry is part of the

curricula of a few faculties of Pharmacy and Chemistry, with Masters in Natural Products being active in Milano and Rome. Overall, while the study of natural products is firmly entrenched in the pharmacy curricula, its inclusion in chemical curricula is limited to Faculties where natural products research is an established tradition (Napoli, Milano, Pavia, Roma, Salerno, Catania, Palermo).

Several scientific societies centered on phytochemistry and medicinal plants are active in Italy. The Società Italiana di Fitochimica (SIF, <http://www.phytosif.org/>) has over 100 academic members, and is currently headed by Cosimo Pizza (University of Salerno). The Società Italiana di Farmacognosia (SIPHAR) and the Gruppo Italiano per lo Studio delle Piante Medicinali (SBI) are also active in academia. Conversely, most members of the Società Italiana di Fitoterapia (SIFIT, <http://www.sifit.org/>) are pharmacists and physicians. Finally, the Società Italo-Latinoamericana di Etnomedicina (SILAE) has been fostering collaboration on ethnomedicine and medicinal plants between Italy and South America, organizing a joint symposium every year since 1992.

Despite a growing interest in natural products by medicinal chemists, and in natural remedies and herbalism by consumers, a certain downsizing of pharmacognosy has been taking place over the years in the Italian Pharmacy curricula. Hopefully, the joint efforts of the many phytochemists active in Italy will reverse this trend and secure a brilliant future to what has traditionally been one of the most successful areas of research in Italy.

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Fifty Years of Natural Products Research in Japan: An Historical Perspective

Jun'ichi Kobayashi

Graduate School of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

While traditional medicines have been used in Japan since the early 1800s, natural products research started late in the century. This historical research survey covers epoch-making discoveries of many bioactive natural products from microorganisms, medicinal plants, and marine organisms, as well as their biosynthetic studies in Japan.

Microorganisms: Japan has a strong tradition in discovering useful products isolated from microorganisms. T. Yabuta reported the structure of kojic acid from *Aspergillus oryzae* (1916), and he and Y. Sumiki isolated gibberellins A and B from *Gibberella fujikuroi* as plant growth hormones (1938). As regards antibacterial antibiotics, the macrolides, leucomycins, were isolated by T. Hata (1953), an aminoglycoside, kanamycin, by H. Umezawa (1957), and the first monobactam type β -lactam, sulfazecin, by A. Imada (1981). Ivermectin, a leading antiparasitic macrolide antibiotic discovered and developed by S. Ōmura and the Merck group in 1979, is used widely as a potent nematocide and an invaluable tool for global initiatives to eliminate

human onchocerciasis and lymphatic filariasis. Many anticancer antibiotics were discovered in Japan, including mitomycins (T. Hata, 1956 & S. Wakaki, 1958), bleomycin (H. Umezawa, 1962), and zinostatin (N. Ishida 1965). Compactin, an inhibitor of HMG-CoA reductase, was isolated by A. Endo (1976); its derivative, pravastatin, is widely used for hyperlipemia. An immunosuppressant, tacrolimus, was isolated at Fujisawa Pharmaceutical Co (1987). Other discoveries include a fatty acid synthesis inhibitor, cerulenin, (T. Hata, 1960); a protease inhibitor, leupeptin (T. Aoyagi, 1969); an *N*-linked glycosylation inhibitor, tunicamycin (A. Takatsuki, 1971); a histone deacetylase inhibitor, trichostatin A (N. Tsuji, 1976); a protein kinase inhibitor, staurosporine (S. Ōmura, 1977); an Hsp90 inhibitor, herbimycin A (S. Ōmura, 1979); a nuclear protein export inhibitor, leptomycin B (T. Hamamoto, 1983); a chitinase inhibitor, allosamidin (S. Sakuda, 1986); and a proteasome inhibitor, lactacystin (S. Ōmura, 1991).

Medicinal Plants: Outstanding achievements in the history of phytochemistry in Japan relate to studies on alkaloids, phenolics, and triterpene saponins. Alkaloid studies started with the isolation of ephedrine from *Ephedra* sp. by N. Nagai (1887), followed by aconitine from *Aconitum carmichaelii* by his protégés. Phenolics from lichens were extensively studied by Y. Asahina. S. Shibata determined the structure of unique bis-anthraquinones, luteoskyrin and rugulosin, constituents of rice infected with fungi which caused liver disorders. He also isolated the triterpene saponins, ginsenosides, as the principal components of *Panax ginseng*, which has a long history of use as an oriental medicine. The isolation of epigallocatechin gallate from green tea (1930) led to the study of tea polyphenols worldwide in cancer prevention. Other investigations include the steviosides, sweet constituents of *Stevia* sp. by O. Tanaka (1970s); the isolation of the ginkgolides from *Ginkgo biloba* (K. Nakanishi, 1967); ptaquiloside from *Pteridium aquilinum* (K. Yamada, 1983); and studies of phototropism in higher plants by S. Yamamura. Chemical studies on traditional herbal medicines were carried out by I. Kitagawa and M. Yoshikawa, while the scientific evaluation of kampo medicines was performed by Y. Ogiwara, and T. Furuya and T. Yoshikawa succeeded in the isolation of secondary metabolites from calluses of medicinal plants.

Marine Organisms: Japanese scientists have excelled in studies on marine toxins. Kainic acid was isolated from a red alga, *Digenea simplex*, by T. Takemoto (1953). The structure of tetrodotoxin was independently reported by three groups (O. Tsuda, Y. Hirata, and R. B. Woodward, 1964), and the synthesis of D,L-tetrodotoxin was completed by Y. Kishi (1972), followed by its asymmetric synthesis by M. Isobe (2003). Y. Hirata and D. Uemura isolated palytoxin from *Palythoa tuberculosa*, and the structure was elucidated (1982, simultaneously by R. Moore); its total synthesis was achieved by Y. Kishi (1994). The structures of brevetoxins A and B were reported by Y. Shimizu and J. Clardy (1986) and K. Nakanishi (1981), respectively, while the structure of ciguatoxin was elucidated by M. Murata and T. Yasumoto (1997), and its total synthesis completed by M. Hirama (2001). The structure of maitotoxin was assigned by T. Yasumoto (1996), and the isolation of okadaic acid, a protein phosphatase inhibitor, from a sponge *Halichondria okadai*, was reported by K. Tachibana and P. Scheuer. Many bioactive marine natural products have been discovered by Japanese researchers. Halichondrin B was isolated from a sponge *H. okadai* by D. Uemura (1986) and synthesized by Kishi (1998); E7389, a synthetic analog of halichondrin B, has recently progressed to phase III clinical trials for cancer. Manzamine A, a potential antimalarial agent from a sponge, was isolated by T. Higa (1986) and many manzamine congeners by J. Kobayashi. The althohyrins/spongistatins, highly cytotoxic macrolides, have been isolated from sponges by I. Kitagawa and M. Kobayashi, and N.

Fusetani, respectively, amphidinolides, a series of cytotoxic macrolides, from dinoflagellates by J. Kobayashi, and a variety of saponins and glycolipids from echinoderms by I. Kitagawa, T. Komori, and R. Higuchi.

Biosynthetic Studies: Biosynthetic studies on natural products in Japan were pioneered by S. Shibata on plant and microbial metabolites using radioisotope labeled precursors. Application of ^{13}C double label technology first developed by H. Seto revealed biosynthetic pathways of many microbial polyketides. Such NMR technology was applied to direct or indirect ^2H detection methods, which were used for biosynthetic studies (*e.g.*, aminocyclitol) by K. Kakinuma. S. Okuda used *in vitro* studies to determine the stereochemical course of fatty acid biosynthesis, while enzymological studies were carried out on prenyltransferases (K. Ogura), fungal metabolites (U. Sankawa & A. Ichihara), and plant metabolites (Y. Yamada & M. Tabata). After production of the first hybrid antibiotic, “mederrhodin”, by genetic engineering by S. Ōmura, many biosynthetic studies at the gene level have been carried out on microbial and plant metabolites, including cloning of the avermectin biosynthetic gene cluster by Ōmura, and establishment of the non-mevalonate pathway by H. Seto. Studies on microbial type III polyketide synthase were initiated by S. Horinouchi, and structure-based engineering of plant type III polyketide synthases led to the production of unnatural novel products by I. Abe. Integrated analysis of the plant metabolome and transcriptome by K. Saito identified genes involved in anthocyanin accumulation.

Prospects: Many important clinical drugs from natural products have been discovered in Japan over the last half century. Japanese researchers will continue to contribute greatly to the field of natural products research, including chemical biology, during this coming century.

Pharmacognosy in Korea

Byong-Kak Kim and Eun-Bang Lee

College of Pharmacy, Seoul National University, Seoul 151-742, Korea

The American Society of Pharmacognosy directly encouraged professors of pharmacognosy in Korea, who had held bimonthly “botanical drug seminars” in Seoul in the 1950s, to consider ideas for the founding of an independent society of pharmacognosy. On December 27, 1969, they eventually established the Korean Society of Pharmacognosy (KSP) which has the following five objectives: to pursue originality of the pharmacy field in Korea by the advancement of pharmacognosy; to lead the cooperation between academia and industry for promoting the production, distribution and utilization of botanical drugs; to scientifically modernize Korean ginseng and its products; to scientifically improve plant drugs that are extensively used in the treatment and prevention of diseases in Korea; and to promote cooperation with foreign societies of pharmacognosy. As part of this cooperation, the KSP holds joint symposia with the corresponding Societies in Japan (JNP) and China (CCTCNM), and the 4th KSP-JSP-CCTCNM Joint Symposium on Pharmacognosy was held at the KIST Gangneung Institute, Gangwon-do, Korea in June, 2008. In the area of publications, KSP published the first quarterly issue of the *Korean Journal of Pharmacognosy* in March 1970, and since 1995 a new journal, *Natural Product Sciences*, has been published entirely in English every other month.

In its first edition, the *Korean Pharmacopoeia* described only 62 botanical drugs, but the current ninth edition now lists 160 such drugs. Because plant and animal drugs are being extensively used in Korea, the Ministry of Health and Welfare issued the first edition of the *Korean Herbal Pharmacopoeia* in 1984, which listed 152 articles on plant and animal drugs; after revision in December, 2007, however, the current edition lists 299 such articles.

In 1978, with the financial support of the World Health Organization, Professor Norman R. Farnsworth initiated the program of investigation on folk medicines in Southeast Asia, with a particular interest in the plant drugs having anti-fertility activity. Since Korea was one of its member countries, he selected the Natural Products Research Institute, Seoul National University as the Center of the WHO Program in Korea, and allocated a part of the budget to the Center and the College of Pharmacy. The Center organized seminars and workshops on the study of folk medicines, which were attended by scientists of the member countries for purposes of information exchange and training. The continuation of the WHO Program for ten years resulted in significant upgrading of the level of pharmacognosy in that region.

The extensive use of botanical drugs in the pharmacy field in Korea certainly requires its pharmacists to gain the knowledge of pharmacognosy. Therefore pharmacognosy is one of the twelve major subjects in the national examination for a pharmacist license. In the twenty colleges of pharmacy in Korea, pharmacognosy is an independent and active department and maintains itself as one of nine major fields in advanced graduate courses.

Ginseng is one of the unique, native medicinal plants of Korea. Three of the pharmacognosy professors in Korea played a major role in founding the Korean Society of Ginseng on September 26, 1975. The *Journal of Ginseng Research* is published quarterly by the Society. In September 2005, the Society celebrated its 30th anniversary at the Natural Products Research Institute, Seoul National University. (Its homepage, <http://www.ginsengsociety.org>)

One of the active research areas is the study of constituents of local medicinal plants. Eupatilin has been identified as one of the constituents of *Artemisia* species and was recently developed as a new drug for gastritis. In its tablet form, it is one of the most frequently prescribed drugs for the treatment and prevention of gastritis in Korea, and, moreover, is being exported to other countries.

The Korean Society of Pharmacognosy will celebrate the 40th anniversary of its founding in December 2009. (<http://www.ksp.or.kr>). (Written on Thomas Jefferson Day, 2008)

Pharmacognosy in Mexico at the Third Millennium

Rachel Mata and Rogelio Pereda-Miranda

Facultad de Química, Universidad Nacional Autónoma de México, Mexico City, 04510

The modern era of important natural products chemistry emerged in Mexico from 1940 to 1960 during the boom of steroidal sapogenins from Mexican yams as a source of progesterone. Indeed, this was the cornerstone of the Syntex Company.¹ Then, starting with the description of the structures of mexicanins from *Helenium mexicanum* (Asteraceae) in 1959, more than 30 years of key discoveries in sesquiterpene lactone chemistry flowed from the Institute of Chemistry of the National Autonomous University of Mexico (UNAM).² The best testimony to the importance of this work are the numerous publications in the *Journal of the American Chemical Society*, the

Journal of Organic Chemistry and other prominent international journals. Many Mexican natural product chemists figured in this golden age, but Jesús Romo Armeria and Alfonso Romo de Vivar merit special mention. Their academic legacy is beyond doubt.

During the early 1960s, the Instituto Mexicano de Plantas Medicinales (IMEPLAM) was founded for the multidisciplinary study of those plants most widely used in the country for treating common illnesses.¹ This governmental institution was the cradle for many researchers who now serve in a multitude of Mexican academic and health venues including the Instituto Mexicano del Seguro Social (IMSS), which became the first Latin-American health organization to include a research program on medicinal plants. The study of such plants in Mexico is relevant because so much of the population relies on herbal drugs for primary health care. This practice dates at least to early pre-Hispanic civilizations in Mesoamerica, which according to 16th century accounts in the likes of the Badianus and Florentine Codices possessed a rich medicinal flora.

These three developments have been the most influential in shaping Mexican pharmacognosy over the last two decades, and in determining its present course in the new millennium. Against this background, the tendency in research has been to focus on flowering medicinal plants, with some attention being given to microorganisms, although a wide range of research interests is characteristic of the Mexican pharmacognocist community. Multidisciplinary research has become the norm. Informed by orthodox ethnobotanical and anthropological considerations, classic pharmacological and clinical methods are applied to the search for new lead molecules that might be useful in developing new drugs. To a lesser extent, the efforts seek to establish procedures for preserving and exploiting herbal drugs, while assuring their quality and evaluating both possible drug interactions and safety. A wide range of *in vitro* or *in vivo* bioassay systems has been used to test extracts and guide the isolation of their active principles. Efforts have focused significantly on trying to discover agents that might be useful in the treatment of gastrointestinal disorders, diabetes, cancer and inflammatory diseases which are major health problems in Mexico.

Mexico's astounding biodiversity as a source of bioactive compounds remains largely unexplored, but the results obtained so far have clearly indicated that there is great potential for the discovery of new or known substances that have valuable biological properties and significant structural or biogenetic interest. And the research into medicinal natural products helps ordinary people benefit from their nation's natural resources and aids conservation efforts. The most important research groups in the quest to develop new medicinal agents are at UNAM, Universidad Autónoma Metropolitana, Centro de Investigaciones Científicas de Yucatan (CICY), Universidad Autónoma del Estado de Morelos, Universidad Autónoma del Estado de Querétaro, Universidad Autónoma del Estado de Nuevo León (UAENL), Universidad Autónoma de Baja California Sur and IMSS.

Studies of the efficacy of medicinal plants using then-state-of-the-art pharmacological models were already notable by the beginning of the 20th century at the Instituto Medico Nacional. This important medical-research institution was founded by Mexican President Porfirio Díaz in 1877, but closed during the Mexican Revolution in 1914. The pharmacological investigation of medicinal plants did not resume until research started at IMEPLAM in the 1970s. In the past 20 years or so, interest in determining the efficacy of the most widely used medicinal plants through pharmacological and clinical studies has increased notably. This probably reflects factors that include the worldwide resurgence in the use of medicinal plants, changes in the legal

requirements for registering phytopharmaceutical products, and the growth in global trade in medicinal plants. Renewed attention has been given especially to plants used in medicines through the ages for a variety of diseases. Efficacy studies, most often performed by the same key research groups, are providing an institutional framework for subsequent clinical studies. Studies of medicinal plant material using a variety of analytical methods also are ongoing to define procedures for quality control of herbal drugs, mostly at UNAM and UAENL. Significant work on medicinal plants with a focus on the chemistry of natural products has also been done by a few research groups, notably by those headed by the late Prof. Lydia Rodríguez-Hahn at UNAM and Prof. Pedro Joseph-Nathan at the Centro de Investigaciones Avanzadas of the Instituto Politecnico Nacional in Mexico City. The latter group also has achieved the synthesis of important bioactive natural products. Regarding research on microorganisms, most of the work is oriented to the biotechnological field due to the legacy of Arnold Demain who trained many Mexican researchers in this area, but only two groups have exploited their potential as sources of new biodynamic compounds.

On the occasion of the 50th anniversary of the American Society of Pharmacognosy, the authors wish to take note of the stimulation derived from conversation and the exchange of ideas with ASP members from around the world, and acknowledge its importance to the progress of natural product research in Mexico.

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Pharmacognosy in the Netherlands 1946 - 2008

Annette I. Bierman^a and Teris A. van Beek^b

^a *Rotterdamse Rijweg 138a, 3042 AS Rotterdam, The Netherlands*

^b *Natural Products Chemistry Group, Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*

1. The early period

Just after the Second World War one could study pharmacy at four Dutch universities: in Amsterdam, Groningen, Leiden and Utrecht. At that time, the topic of pharmacognosy was still an important part of the pharmaceutical curriculum. In the fifties of the previous century the pharmacognosy professors at the last three universities had not only to teach pharmacognosy, but also taught the preparing of Galenicals and prescriptions. Much attention was given to microscopic identifications of medicinal plants and titrations. All the pharmacognosy professors were pharmacists. Only Amsterdam was different in this respect; Professor van Herk and his successor Professor Stegwee were biologists and their teaching commitment was plant physiology and pharmacognosy.

2. The sixties and seventies

In the sixties, pharmacognosy in Groningen, Leiden and Utrecht became booming business. In Groningen Henk van Os introduced chromatography in the analysis of medicinal plants; the main topics of research were *Digitalis* glycosides, essential oils and their constituents, and

pharmacopoeia monographs. Van Os was an enthusiastic member of the European Pharmacopoeia Committee and for many years Chairman of the Dutch Society of Medicinal Plant Research (NVGO). In Leiden, Robert Hegnauer concentrated on plant chemistry. In 1961, the first volume of *Chemotaxonomie der Pflanzen* was published, and he completed his magnum opus 40 years later with the publication of Volume 13. Without doubt, he is the most famous Dutch pharmacognosist, and he was an honorary member of many learned societies, including the American Society of Pharmacognosy. In 1962, Hegnauer's teaching order was changed to Experimental Plant Taxonomy. His successor, Anders Baerheim Svendsen, expanded plant chemistry and created a successful pharmacognosy section in Leiden in which isolation, analysis and identification of natural vegetable substances, in particular, essential oils were topics. He was president of the Gesellschaft für Arzneipflanzenforschung (GA).

3. The eighties and nineties

As successor of Otto Uffellie in Utrecht, Rudi Labadie started new research in the fields of ethnopharmacognosy and immunopharmacognosy. He had a strong interest in medicinal plants from Sri Lanka. In the 1980s, pharmaceutical higher education in The Netherlands was concentrated, and only Groningen and Utrecht were allowed to educate pharmacists. Pharmacy in Amsterdam came to an end, but pharmacognosy had already ceased to exist there. In Leiden a new research institute was established, with a new educational direction leading to an M.Sc. in biopharmaceutical sciences. Pharmacognosy played a successful role in this study under the guidance of Rob Verpoorte, who succeeded Anders Baerheim Svendsen in 1989. Initially he was mostly interested in the structure elucidation of alkaloids, but already in the 1980s he pursued plant cell biotechnology as a new line of research. In 1999, he organized in Amsterdam with others the largest joint ASP/GA/PSE/AFERP meeting ever with over 1100 participants. Pharmacognosy remained very fruitful and vibrant in The Netherlands from a scientific point of view; however its role in the education of pharmacists gradually became smaller and smaller. After the death of Theo Malingré in 1993 and the retirement of Rudi Labadie in 1999, no successors were appointed in Groningen and Utrecht, respectively.

4. The final period

In Groningen the name of the department was changed to Pharmaceutical Biology, and under the new professor, Wim Quax, the research was changed to enzyme engineering. In Utrecht some staff members remained, but pharmacognosy no longer exists as a separate entity. In 2008, there is only one full professor in pharmacognosy left in The Netherlands, Robert Verpoorte, who is now working at the Biology Institute Leiden, Metabolomics section. He still leads a sizeable group that nowadays uses NMR for the rapid identification of plant secondary metabolites, but after his retirement in 2011 most likely he will not be succeeded, and thus no Professor in - Pharmacognosy will remain in The Netherlands. This is sad, as with the renewed interest in drugs from plant origin, e.g. Traditional Chinese Medicine, the declining rain forest, the advent of Systems Biology, and new powerful analytical methods for metabolomics, there are fantastic opportunities for the emergence of a new style Pharmacognosy. Probably it will survive, but at least in The Netherlands, no longer under its original name.

Table 1 Professors in Pharmacognosy in The Netherlands, 1945-present

AMSTERDAM		LEIDEN	
Adriaan Willem Hendrik van Herk (1904 - 1966)	1946 - 1966	W.A. Goddijn (1884 - 1960)	1934 - 1952
Durk Stegwee (b. 1925)	1967 - 1975	Robert Hegnauer (1919 - 2007)	1952 - 1962
		Anders Baerheim Svendsen (1920-2004)	1964 - 1989
		Robert Verpoorte (b. 1946)	1989 - present
GRONINGEN		UTRECHT	
Frederik Hendrik Lucas van Os (1907 - 2001)	1946 - 1975	Otto Frederik Uffellie (1906 - 1992)	1946 - 1977
Theo M. Malingré (1929 - 1993)	1980 - 1993	Rudi Paul Labadie	1982 - 1999

Pharmacognosy in the Nordic countries

Lars Bohlin

Division of Pharmacognosy, Department of Medicinal Chemistry, Uppsala University

In society today there is a renewed interest in environmental aspects, green chemistry and the sustainable use of natural products. With modernization and renewal, the venerable, proven science, Pharmacognosy, as one of several scientific disciplines, has a strategic position in bridging chemistry and biology. This multidisciplinary subject is important for discovery of novel unique molecules having drug potential, and in revealing new targets, by studying the evolutionary structure-activity optimization in Nature.

The logical starting point of this short overview of natural product research with emphasis on pharmacognosy in the Nordic countries is Linnaeus and his interest in, and holistic view of Nature. His famous book *Materia Medica* (1749) focused on combining botany with medicine, aimed at discovering the medical potential of nature. After the tenure of his successors, Thunberg and Wahlenberg, a part of the chair changed in 1852 to cover the subject “pharmacognosy, pharmacy, physiological and pathological chemistry”. Following several further professorial appointments, the chair changed to “general and experimental pharmacodynamics with pharmacognosy” in 1893, and Henrik Victor Rosendahl was appointed. He became later the first professor of botany and pharmacognosy in 1901 at the Royal Institute of Pharmacy (RIP) in Stockholm. Up to the mid-1950s, education and research in pharmacognosy focused on the botanical aspects of the identification and control of crude drugs, but with the appointment (1954) of Finn Sandberg (a medical doctor) working in close collaboration with Gunnar Samuelsson, it changed dramatically towards pharmacological and phytochemical properties of natural products. In 1968, the RIP moved to Uppsala to become the Faculty of Pharmacy at Uppsala University, still the only one in Sweden. During the past 50 years research has focused on natural products with pharmacological activity by using and developing modern bioassays, and 46 doctoral theses have been produced covering a broad area from traditional medicine, biosynthesis and metabolism, to peptide research, marine pharmacognosy and studies of methods of selection. Following a long tradition, professors have authored text books, with the first by

Rosendahl (1897) followed by Westling (1927), and Gunnar Samuelsson (*Drugs of Natural Origin*, 5th edition, 2004). New courses on bioactive natural products have created interest among medical and science students, and there is a demand for highly educated students in pharmacognosy in areas such as pharmacy, medical product agencies and the drug industry.

Pharmacognosy in Finland started in 1761 with the appointment of a professor in natural history and pharmacy at Regia Academia Aboensis in Turku which moved to Helsinki in 1827, and later became the University of Helsinki, where it has always been part of the pharmacy curriculum. It was the first discipline in pharmacy to implement research and international connections in the 1970s under Max von Schantz (1922-2007), a longtime GA board member, who was succeeded by Raimo Hiltunen, and later, Heikki Vuorela. The first doctoral thesis in pharmacy was awarded in 1960, and the first in pharmacognosy in 1963, followed by 37 thereafter. With the change of the Department of Pharmacy to the Faculty of Pharmacy in 2004, the Division of Pharmacognosy was renamed the Division of Pharmaceutical Biology, having incorporated pharmaceutical microbiology in 1995. It includes two professors (currently Faculty Dean and Vice-Dean), three university lecturers and one assistant, and about ten Ph.D. and M.Sc. students. The Drug Discovery and Development Technology Center, DDTC, founded in 2000, has bioactivity screening of natural products as one of its main focuses, and works in close cooperation with pharmacognosy. Pharmacy teaching in Swedish has been ongoing for 50 years at Åbo Akademi University in Turku, where one of the two professors has a background in pharmacognosy, whereas at the University of Kuopio, pharmacognosy is not an independent discipline.

Pharmacognosy in Denmark can be traced back to 1772, when the first Pharmacopoeia with some 500 herbal drugs was published. In 1863, the chair in pharmacognosy was established at the University of Copenhagen, but soon afterwards it was decided to establish a dedicated college for pharmacy education, and the Royal Danish School of Pharmacy was founded in 1892. At the same time, the original donation from the pharmacist Alfred Benzon initiated the Pharmacognostic Collection, which has been greatly expanded over the years and serves today as the witness to the history of pharmacognosy in Denmark, used for education and historical studies alike. In 2004, the Royal Danish School of Pharmacy became The Danish University of Pharmaceutical Sciences. In 2007, the University merged with the University of Copenhagen and became the Faculty of Pharmaceutical Sciences. The Faculty is still the only site of pharmacy education in Denmark, including education in pharmacognosy and natural products. The first Ph.D. degree in the area of pharmacognosy/natural products was awarded in 1954, and currently two degrees are granted on average per year. The first teacher in pharmacognosy was docent S. Rützou (1892-1901), followed by B. Gram (1902-1927), F. J. Mathiesen, M. Wellendorph, and U. Nyman. Helmer Kofod became professor in the chemistry of natural products in 1958, followed by J. W. Jaroszewski in 1997. While the original focus of the research in pharmacognosy was botany and plant anatomy, chemistry and biological activity of natural products assumed an increasingly dominant position from the mid 1970's. Today, the research and teaching in natural products and pharmacognosy is being conducted within the framework of the Department of Medicinal Chemistry of this faculty. Current research areas comprise natural product-based drug discovery, bioassay development, hyphenated NMR used as a dereplication and metabolomics tool, and syntheses of natural product analogues. This work is being conducted by 25-50 researchers, including 8 faculty members

Systematic education in Pharmacy in Norway started in 1932 when the Institute of Pharmacy at the Blindern Campus was opened. A degree took 4 years including a middle one year period in a pharmacy. As more active ingredients were identified, botanical aspects including microscopic identification were de-emphasized to focus on quantitative control of plant drugs based on active constituents, and spectroscopic, electrophoretic, chromatographic and enzymatic methods were introduced as important parts of the course. Advances in the knowledge of the biosynthesis of important natural products led Arnold Nordal to introduce this topic. From 1973 the curriculum was extended to five years to include a one year's master thesis, and advanced courses in natural products chemistry and biology. During the 1980s, phytotherapy research emerged, textbooks came on the market, and the use of herbal remedies exploded amongst the population. Courses that included phytotherapy as well as quality control of herbal remedies on the market were developed. In 2003 a new integrated curriculum was introduced at School of Pharmacy in Oslo with a focus on different drug classes and uses of drugs, and thus herbal remedies, natural products and compounds are now taught as an integrated part with medicinal chemistry and pharmacology in such a way that the students get a better overview of the total types of compounds available for the treatment of the different ailments.

Pharmacognosy research in Iceland was started some 30 years ago by Kristin Ingolfsdottir (present Rector of University of Iceland) at the Faculty of Pharmacy, University of Iceland when she started to investigate natural compounds from Icelandic plants, and in particular from Icelandic lichens. Gradually the natural products research group expanded and strengthened to include a number of scientists and collaborators, both in Iceland and abroad. Apart from teaching pharmacognosy and natural products chemistry, the group is conducting research on natural products from Icelandic plants, especially lichens and lower plants like clubmosses and liverworts, involving both M.Sc. and Ph.D. students. This group is still the only group in Iceland doing research in pharmacognosy.

This short summary of natural product research in the Nordic countries includes obviously the development of Pharmacognosy. However, there are also several research groups in natural products chemistry in the Nordic countries doing similar research. The study of the chemical and biological properties of secondary metabolites is a well-established branch of organic chemistry in Sweden. Here two groups are exemplified based on the research by the former famous professor Holger Erdtman in Stockholm and Börje Wickberg in Lund. Research in natural product chemistry at the Royal Institute of Technology (KTH) was continued by Torbjörn Norin and has during the last 30 years developed from separation and structural elucidation of new natural products mainly related to conifers (terpenoids, resin acids and phenolics) to the interdisciplinary research area of chemical ecology, with a focus on the function of chemical compounds (semiochemicals) produced by plants, insects and other organisms. The present head of the research is Anna-Karin Borg Karlsson who, in cooperation with biologists, has identified new moth and butterfly pheromones, as well as key attractive plant compounds, using chemical and electrophysiological methods. At the University of Lund the present principal investigator Olov Sterner did his Ph.D. studies with Börje Wickberg, who himself studied with Holger Erdtman. Examples of ongoing projects, besides the isolation and characterisation of biologically active secondary metabolites, are the following: Combinatorial semi-synthesis with natural products; endogenous conidiation factors in fungi; inhibition of STAT3 by galiellalactonoids; pharmacophore model of the benzodiazepine binding site of the GABA_A receptor, and SAR studies of capazepinoid bronchodilators.

In conclusion, natural products are involved in scientific issues important for a sustainable society, and a multidisciplinary subject like Pharmacognosy and natural product research in general will be important, not only in education and research in the future drug discovery process, but also to establish a secure and efficient use of herbal remedies in society.

Natural Products Chemistry in Russia

Valentin A. Stonik

Pacific Institute of Bioorganic Chemistry, the Far-Eastern Branch of the Russian Academy of Sciences, Prospect 100-letya Vladivostoka, 159, Vladivostok

The first chemical studies on natural products took place in Russia during the second half of the 19th – early 20th century, when the isolation and chemical transformation of plant secondary metabolites and the development of new isolation methods were carried out. It may be exemplified by the studies of E. Wagner (structure of α -pinene and so-called camphene rearrangements) and M. Tsvet, who first developed chromatographic separation and proposed the term chromatography. Later, in the former Soviet Union time, well known scientific schools under the leadership of Professors A. Orekhov (alkaloids), M. Shemyakin (antibiotics), L. Bergelson (lipids), I. Torgov (steroids), N. Kochetkov (carbohydrates), G. Elyakov (terrestrial and marine natural products) and others were successfully operating. During this period, the Academy of Sciences of the Soviet Union remained a bastion of the research activity in natural product chemistry. Now the Russian Academy of Science (RAS) plays the same leading role.

1. Microorganisms

Russia has strong traditions in the studies of microorganisms as sources of physiologically active natural products. During the Second World War, extensive and successful investigations on antibiotics had led to the isolation of gramicidin S (G. Gauze, 1942) and the organization of its industrial production. As a result, the lives of millions of wounded people were saved. Numerous structures of new antibiotics, as well as their total syntheses and chemical transformation were reported, for instance, structures of variamycin A (A. Shaskov, et al.), eremomycin and analogs (Ju. Dudnik, M. Preobrazhenskaya et al), synthesis of tetracycline (M. Kolosov et al.) and other antibiotics. Many new antibiotics were introduced into Russian medical practice following up the criterion of industrial strains and rational methods for industrial production. At the present time in the Far East of Russia, the wide search for new physiologically active metabolites from marine bacteria and fungi is carried out (V. Mikhailov and T. Kuznetsova) resulting in the discovery of many new taxa of marine microorganisms.

2. Medicinal plants and other terrestrial organisms

Important achievements in phytochemistry in Russia and the former Soviet Union concerned the studies on alkaloids, triterpene and steroid glycosides and various phenolic metabolites. S. Yunusov *et al.* described numerous alkaloids from *Vinca erecta*, *Allium giganteum*, *Talictrum* spp. and other Middle Asian higher plants. G. Elyakov's group (1964-1972) contributed to the structure elucidation of ginsenosides from *Panax ginseng* and other triterpene glycosides from the Far-Eastern Araliaceae as well as to phenolic metabolites from *Eleutherococcus senticosus*. At the present time alkaloids and oxylipins from higher plants growing in the European part of Russia (M. Yunusov, A. Grechkin), as well as the chemistry of glycyrrhizinic acid and different secondary metabolites from the Siberian plants (G. Tolstikov), are being developed. Toxins from spiders and other terrestrial biological sources are under investigation at the Institute of Bioorganic Chemistry, Moscow (E. Grishin *et al.*).

3. Marine Organisms

Russian scientists actively participate in studies on marine natural products. About 150 new sea cucumber triterpene glycosides, including so-called non-holostane ones were isolated and their physiological activities were investigated (S. Avilov *et al.*). Extremely potent immunostimulatory properties of these natural products were discovered and used to select pharmaceutical leads for further preclinical and clinical trials. Unexpected so-called two-headed sphingolipid sponge metabolites were found and studied (T. Makarieva *et al.*). About two hundred new steroid metabolites from echinoderms and sponges (A. Kicha *et al.*) were described. The first marine dioxin derivatives (N. Utkina), numerous new alkaloids such as the pibocins, new varacins, and ophiuroidin were discovered at the Pacific Institute of Bioorganic Chemistry (Vladivostok) and have made a substantial contribution to the chemistry of marine natural products.

4. Prospects

As a result of the long-term work of Russian scientists, many hundreds of new natural products were obtained. A series of drugs, based on natural products and their derivatives and/or analogs (Nicavir, Eremomycin, Histochochroms, Maxsar, and many others) have been elaborated and now are in clinical application in Russia.

Table. Some Russian natural product researchers and governmental institutions.

Anufriev V.F. (Pacific Institute of Bioorganic Chemistry of RAS, Vladivostok)	Syntheses of Natural Products
Dyatlovitskaya E.V. (M.M. Shemyakin, Ju. A. Ovchinnikov Institute of Bioorganic Chemistry of RAS, Moscow)	Sphingolipids
Grechkin, A. N. (Kazan Institute of Biochemistry, Kazan Scientific Center of RAS, Kazan)	Oxylipins from higher plants, structures and biosynthesis
Grishin E. V. (M.M. Shemyakin, Ju. A. Ovchinnikov Institute of Bioorganic Chemistry of RAS, Moscow)	Peptide toxins
Knirel Ju. A. (N.D. Zelinsky Institute of Organic Chemistry of RAS, Moscow)	Lipopolysaccharides from bacteria
Myasoedov N. F. (Institute of Molecular Genetics of RAS, Moscow)	Physiologically active oligopeptides
Ovodov Ju. S. (Institute of Physiology, Komi Scientific Center of RAS, Syktyvkar)	Plant carbohydrates
Preobrazhenskaya, M.N. (G.F. Gauze Scientific-Research Institute of New Antibiotics of RAMS, Moscow)	Antibiotics
Stonik V. A. (Pacific Institute of Bioorganic Chemistry of RAS, Vladivostok)	Marine natural products
Tolstikov G. A. (N.N. Vorozhtsov Institute of Organic Chemistry of RAS, Novosibirsk)	Phytochemistry and chemical transformation of natural products from higher plants
Usov, A. I. (N.D. Zelinsky Institute of Organic Chemistry of RAS, Moscow)	Structures and properties of algal polysaccharides
Vaskovsky, V.E. (Pacific Institute of Bioorganic Chemistry of RAS, Vladivostok)	Marine lipids
Yunusov, M. S. (Institute of Organic Chemistry of Ufa Research Center of RAS, Ufa)	Structures and chemical transformation of alkaloids and other metabolites from terrestrial plants

Pharmacognosy in South and South-East Asia

M. Iqbal Choudhary and M. Mosihuzzaman

*International Center for Chemical and Biological Sciences, (H. E. J. Research Institute of Chemistry, Dr. Panjwani Center for Molecular Medicine and Drug Research)
University of Karachi, Karachi-75270, Pakistan*

South and South East Asia have an unbroken tradition of the use of plants for medicinal purposes. A number of well-documented systems of medicine, Ayurveda and Unani, evolved over the years, and are still practiced in the region. As a result, pharmacognosy and natural product chemistry have been prominent as active areas of research in the region.

Research in the field of pharmacognosy began in the Indian sub-continent at the beginning of the 20th century when B. N. Dhawan and Salimuzzaman Siddiqui, started to work on the chemistry of Indian medicinal plants. A number of important molecules were discovered from plants such as *Rauwolfia serpentina* and *Azadirachta indica*. At this time, Calcutta University and Benaras Hindu University were already in the forefront in research on natural products chemistry, and with the development of the CSIR system, the drug discovery program was given a boost, centering around the laboratories of the Central Drug Research Institute (CDRI; Lucknow), the Regional Research Laboratory (Jammu), the Central Institute of Medicinal and Aromatic Plants (CIMAP) and the National Chemical Laboratory (NCL). In collaboration with a few other sister laboratories, they developed and commercialized a number of plant-based drugs, notably (i) Arteether, a blood schizontocidal antimalarial, developed from the plant *Artemisia annua* (Themis Chemicals Ltd; trade name E-Mal); (ii) Gugulipid, a hypolipidemic agent developed from *Commiphora mukul* (CIPLA Ltd; trade name Guglid); (iii) Isaptent, a cervical dilator for medical termination of pregnancy developed from *Plantago ovata* (Unichem Laboratories Ltd as Dilex-C); and (iv) Picroliv, a hepatoprotective agent comprising a mixture of iridoid glycosides obtained from *Picrorhiza kurrooa* (roots and rhizomes) that has completed Phase I and Phase II clinical trials. Besides these, several single- and multi-herbal formulations have been commercialized. In recent years, several laboratories, outside the CSIR system, have also initiated natural product research. These include the Indian Institute of Science (Bangalore), Jadavpur University, (Kolkata), and Jawaharlal Nehru University (Delhi). A second generation of Indian pharmacognosists is active at all these institutions, and scientists at CDRI and NCL have made major contributions to the field.

In Pakistan, Salimuzzaman Siddiqui, a veteran CSIR scientist, established a post-graduate research institute in University of Karachi in 1966, which was later named as the H. E. J. Research Institute of Chemistry. This institute under the leadership of Atta-ur-Rahman, a renowned natural product chemist, has worked on over 300 most important medicinal herbs of Pakistan, resulting in the identification of thousands of secondary metabolites. As an academic research institute, H. E. J. has trained hundreds of natural product chemists and pharmacognosists who are serving in top institutions of the world. Studies on *Catharanthus roseus* and *Azadirachta indica* have attracted world attention. This institute, now working under the Directorship of Iqbal Choudhary, is continuing the legacies of Siddiqui and Atta-ur-Rahman, although now research is largely focused on molecular aspects of disease and their treatments by novel natural products. The main emphasis has been on the scientific evaluation of medicinal plants used in the Unani (Greco-Arab) system of medicine.

Systematic studies on natural products chemistry in Sri Lanka began largely under the leadership of M. U. S. Sultanbawa at the University of Peradeniya from the late 1960s to the early 1980s, initially on the chemistry of forest trees and endemic plants funded by the US Department of Agriculture, and later on plants which could help in fertility regulation funded by the WHO. Research in applied areas, largely on essential oils, was initiated at the Ceylon Institute for Scientific and Industrial Research, under the leadership of R. O. B. Wijesekera. Early studies on medicinal plants were conducted by L. B. de Silva at the Medicinal Research Institute. Currently, groups involved in the study of medicinal plants are active at the University of Sri Jayawardenapura (A. M. Abeysekera), University of Colombo (E. D. de Silva and W. D. Rathnasooriya), Industrial Technology Institute (ITI; L. Arambewala) and Institute of Fundamental Studies, Kandy (H. R. W. Dharmaratne and L. Jayasinghe), while the University of Kelaniya has established itself as a leader in chemical ecology (N. Gunawardena). The University of Kelaniya (P.A. Paranagama) and the ITI (R. Samarasekera) have also been investigating the use of natural products in pest control.

In Bangladesh, pharmacognosy has remained mainly within the University of Dhaka (DU). During the last two decades, extensive work has been done on antidiabetic and anticancer plant materials in the Department of Chemistry (M. Mosihuzzaman and Nilufar Nahar). A large number of known and new compounds, some with significant bioactivity, have been isolated. The Pharmacy department of DU, and Rajshahi and Jahangirnagar Universities have also made some contributions to pharmacognosy.

In Thailand, pharmacognosy has evolved as a strong area of research largely at the Chulabhorn Research Institute (Bangkok). HRH Princess Chulabhorn Walailak and her group, as well as V. Reutrakul's team (Mahidol University), have worked on plants of tropical rain forests, and have recently expanded into the study of marine organisms and microorganisms. Natural products research is augmented by strong programs in medicinal and synthetic chemistry

The earliest investigations of Malaysian plants can be traced back to the research of Nakanishi and Amarisingham in the 1950s, followed by that of K. C. Chan and S. W. Goh in the 1960s. A vigorous expansion of natural products chemistry was clearly observed in the 1980s, after the return of a large number of foreign-trained postgraduates to their respective jobs at several universities and research institutions in Malaysia. Currently, pharmacognosy is one of the major research areas in most universities and research institutions. For example, of the Laboratory of Natural Products, University Putra, Malaysia, has been studying the antioxidative, cytotoxic and anti-inflammatory principles of locally used plant groups from the genera *Hedyotis*, *Garcinia* and those of the Zingiberaceae family; recently he reviewed his work on *Hedyotis* species. The group in the University of Science Malaysia, led by Chan Kit Lam, is working on pharmacological aspects of medicinal plants especially those having antimalarial activity, including clinical studies of the active constituents. Another group at the National University of Malaysia led by Ikram Said, has been strongly involved in mitragyna indole alkaloids for use as potential sedatives. An important major achievement is the development of infrastructure and research capacity in natural products and its allied areas such as pharmacology, biotechnology and organic synthesis.

Research at the Marine Science Institute at the University of the Philippines, Diliman, is aimed at generating basic and applied information to promote the optimal and sustained use and conservation of the country's marine environment and its resources. Dr. Gisela Concepcion leads

programs directed at the discovery of novel bioactive agents from marine invertebrates, including turrif snails and sponge-associated microorganisms. Dr. Montañó studies algal polysaccharides and other marine natural products extracted from indigenous marine species for alternative food additives and medicinal products, thus providing the Filipino people with alternative sources of livelihood.

Swiss Natural Products Chemistry and Pharmacognosy. Historical Aspects

Otto Sticher

Prof. emeritus, Institute of Pharmaceutical Sciences, ETH Zurich

Natural products chemistry has been an important part of Swiss chemical and pharmaceutical research for the last century, with Richard Martin Willstätter (1872-1942) and Hermann Staudinger (1881-1965) (ETH), and Paul Karrer (U. Zurich) providing the impetus to the research in the first two decades of the 20th century, and Nobel laureates, Leopold Ruzicka (1887-1976; ETH), Vladimir Prelog (1906-1998; ETH), Paul Karrer (1889-1971; U. Zurich) and Tadeus Reichstein (1897-1996; ETH / U. Basel) leading during the later “golden decades”.

ETH Zurich: Willstätter (Prof., 1905-1912) and Arthur Stoll worked on plant pigments (carotenoids, chlorophyll, anthocyanins), and Staudinger (Prof., 1912-1926) started his independent research on rubber and cellulose. Both moved to chemistry chairs in Germany, and both received Nobel Prizes, Willstätter in 1915, and Staudinger in 1953. In 1929, Staudinger’s Ph.D. student/assistant, Ruzicka, became professor in organic chemistry. His research focused on the chemistry of terpenes and steroids, and investigation of the highly valued insecticide, *Pyrethrum cinerarifolium*, led to the chemistry of monoterpenes, higher terpenes and male sex hormones, resulting in strong support from the Swiss pharmaceutical and perfumery industry. He was awarded the Nobel Prize in 1939, and after 1950, he studied terpene biosynthesis, publishing a hypothesis entitled “Biogenetic isoprene rule.” Coworkers at the ETH were Reichstein (see below) and Prelog who succeeded Ruzicka, and performed extensive research on the stereochemistry of alkaloids, antibiotics, enzymes, and other natural compounds, making major contributions to the understanding of stereoisomerism, and with R. Cahn and C. Ingold, developing a nomenclature system describing the stereochemistry of complex organic compounds (Cahn-Ingold-Prelog system). He was awarded the 1975 Nobel Prize, and it is due to his and Ruzicka’s work that the ETH became one of the most prominent centers of organic chemistry in the 20th century. Major contributions to the chemistry of many classes of natural products were made later by P. Plattner, W. Keller-Schierlein, E. Hardegger, O. Jeger, and A. Vasella, and in bioorganic chemistry by D. Arigoni (biosynthesis/enzyme-catalyzed reactions) and A. Eschenmoser (structure elucidation and synthesis/biosynthesis/biochemical reactions).

University of Zurich: Karrer, (Prof., 1918-1956), noted for his research related to plant pigments, particularly the yellow carotenoids, showed that some of these substances are transformed in the body into vitamin A, and in the 1930s, he established the correct constitutional formula of β -carotene. He later confirmed the structure of ascorbic acid (vitamin C), extending his research to the fields of vitamin B₂, E and K, flavins and the curare alkaloids. He was awarded the Nobel Prize in 1937, and his textbook *Lehrbuch der Organischen Chemie* was published in thirteen editions and translated into seven languages. Later important

contributions were made to the chemistry of many classes of natural products by Hans Schmid, Manfred Hesse, Conrad Hans Eugster, André Dreiding, and Max Viscontini.

University of Basel: Reichstein (Prof., 1938-1967) made major contributions to the synthesis and mass production of vitamin C using *Acetobacter suboxydans*, the isolation of cortisone and the discovery of its therapeutic value in the treatment of rheumatoid arthritis (together with E. C. Kendall and P. S. Hench), the isolation of aldosterone, and the isolation and structure elucidation of various cardenolides. Reichstein, Kendall and Hench were jointly awarded the 1950 Nobel Prize in Physiology and Medicine. After Reichstein's retirement in 1967, Christoph Tamm made substantial contributions in the field of microbial metabolites.

Pharmaceutical Industry: Switzerland has long had a strong pharmaceutical industry concentrated around Basel [e.g., Hoffmann-La Roche, Ciba-Geigy and Sandoz (today Novartis)]. Of the many researchers, space only allows mention of Arthur Stoll and Albert Hofmann, formerly of Sandoz. Stoll (1887-1971) left Willstätter's laboratory in 1917 to become Director of the newly founded pharmaceutical department at Sandoz. Together with Hofmann, he studied ergot alkaloids, cardenolides from many sources (scillaren A, lanatosides, *D. purpurea* glycosides, k-strophanthoside), sennosides, and *Allium sativum* (alliin, allicin), and they can be largely credited with the successful development of many new drugs from natural sources at Sandoz. Hofmann (Ph.D. under Karrer) investigated the active ingredients in medicinal plants and ergot, isolated lysergic acid (1938), synthesized LSD and detected its hallucinogenic activity (1943), and later isolated other psychoactive compounds (e.g., psilocybin and psilocin). He wrote *LSD: mein Sorgenkind* ("LSD: My Problem Child"), and in 2007, readers of the *Guardian* (England) chose him as one of the "world's top 10 living geniuses". Other important naturally-derived drugs developed by Swiss companies include reserpine, etoposide, various antibiotics and the immunosuppressants, cyclosporine A, everolimus and mycophenolic acid. Important research was also performed in fragrance chemistry (Firmenich, Givaudan, Geneva).

Pharmacognosy is included in the Swiss pharmacy curriculum. Pharmacy schools remain at ETH and U. Basel and U. Geneva, but those at U. Bern and U. Lausanne have closed. Originally, pharmacognosy focused on the description and identification, history, commerce, collection, preparation and storage of botanical drugs. Famous early pharmacognosists were Carl Hartwich (1851-1917; ETH, 1892-1917) and Alexander Tschirch (1856-1939; U. Bern, 1890-1932), who respectively wrote the well-known reference books, *Die menschlichen Genussmittel* and *Handbuch der Pharmakognosie*. Their research focused on the classical botanical aspects, but that of Hans Flück (1901-1985; ETH, 1935-1971), former assistant of Tschirch, clearly shows the enormous development of pharmacognosy, beginning in the 1920s with microscopic work on medicinal plants, followed by increasing emphasis on active plant constituents, including their biogenesis, and research on quality control. Since the 1970s the name, pharmacognosy, changed to "pharmacognosy and phytochemistry", and is now called "pharmaceutical biology".

University of Bern: E. Steinegger [1915-2004; Prof., 1954-1981) was the first pharmacognosist to include phytochemistry in his research, contributing substantially to structure elucidation and to the quality control of phytopharmaceuticals. R. Brenneisen (b. 1949) continued research and teaching from 1981 until 1996, and is now a member of the department of clinical research studying phytopharmacology, bioanalytics and pharmacokinetics, mainly of psychoactive drugs.

ETH: Otto Sticher (Prof., 1972-2002) focused on the chemistry and biological screening of a range of natural products, ethnopharmacology, quality control of phytomedicines, and the

development of new technologies for isolation and separation. The research of his successor, Karl-Heinz Altmann is at the interface between chemistry and biology, focusing on the chemical synthesis and the biological and pharmacological profiling of active natural products and their synthetic and semi-synthetic analogs (e.g., anticancer agents; e.g., epothilones).

Universities of Lausanne and Geneva: Kurt Hostettmann (U. Lausanne, 1981-2004; U. Geneva, 2004-) studies bioactive plant metabolites, and he is pioneering the application of sophisticated separation methods such as LC-MS and LC-NMR to the isolation and analysis of natural products.

University of Basel: Matthias Hamburger's (2004-) main research areas include the chemistry and the development and validation of methods for the chemical and biological characterization of natural products.

UK Pharmacognosy and Phytochemistry - Past, Present and Future

Simon Gibbons

Centre for Pharmacognosy and Phytotherapy, The School of Pharmacy, University of London, 29-39 Brunswick Square, London WC1N 1AX, U.K.

While Nobel Laureates, Robert Robinson, Alexander Todd, John Cornforth and Derek Barton, were giants in exploring the biosynthesis and chemistry of natural products, this review¹ starts with the late Jeffrey Harborne FRS, a major figure in UK natural product science with broad interests, who was highly productive in flavonoid phytochemistry,² author of the popular texts *Introduction to Ecological Biochemistry*, *Phytochemical Methods* and Editor in Chief of *Phytochemistry*. Tony Swain was the previous Editor of *Phytochemistry* who with 'E.C.' Bate-Smith was very active in the structure elucidation and distribution of phenolic compounds. Together they set up the Plant Phenolics Group (PPG), which became the Phytochemical Society of Europe.³

In the 1950s at The School of Pharmacy, J. W. Fairburn transformed pharmacognosy with his work on anthraquinones, alkaloid metabolism⁴ and early studies on *Cannabis*. He was followed by F. J. Evans, who sadly passed away in 2007 but was responsible for much phytochemical and biological research, particularly on the irritant phorbol esters from the Euphorbiaceae.⁵ Perhaps one of his best achievements was the training of one Douglas Kinghorn, a PhD student 'exported' to the US. He was also founding Editor of *Phytotherapy Research*, currently under the Editorship of Elizabeth Williamson (U. Reading), author of many useful pharmacognosy texts including *Major Herbs of Ayurveda*. W. C. Evans, formerly Reader in Phytochemistry at U. Nottingham, is co-author and Editor of Trease and Evans *Pharmacognosy*, now in its 15th edition as an undergraduate text for pharmacy students. His former student J. G. Woolley (De Montfort U.) recently retired and has interests in tropane alkaloid and lignan biosynthesis.

J. David Phillipson⁶ has contributed greatly to UK phytochemistry and pharmacognosy, with interests in structure determination of alkaloids, antimalarial metabolites and the phytochemistry of herbal medicinal products. The 3rd edition of his text *Herbal Medicines*, co-authored with Linda Anderson (MHRA) and a former colleague, Joanne Barnes (now U. Auckland) is one of the most useful texts for healthcare professionals interested in the pharmacognosy of herbal medicinal products. He was fortunate to work with Norman Bisset under the then head of Pharmacognosy at Chelsea College (now King's College London), E. J. Shellard, an expert in alkaloid analysis who provided an excellent environment for them to flourish. One of his colleagues, Margaret Roberts (The School of Pharmacy) was an alkaloid biosynthesis researcher, with interests in enzymatic studies in the Papaveraceae. At the same time, E. Arthur Bell was

able to identify many polar water-soluble alkaloids e.g. castanospermine⁷, and demonstrate the presence of unusual amino acids in plants. Director of the Royal Botanic Gardens (RBG) Kew (1981-1988), Bell remained a keen attendee of seminars well into his 70's until his death in 2006. His Ph.D. students include Linda Fellows and Robert Nash, both of whom have been productive in research into polar alkaloids. Pharmacognosy remains strong at The School of Pharmacy; the permanent staff of the Centre for Pharmacognosy and Phytotherapy have diverse research interests: ethnobotany and anti-inflammatory natural products (Michael Heinrich), anti-protozoal and fatty acid synthesis inhibitors from plants and marine sources (Deniz Tasdemir), plant-derived antibacterials and efflux pump inhibitors (Simon Gibbons) and computational biochemistry and nutraceuticals (Jose Prieto-Garcia).

John Pickett FRS (Rothamsted Research) has a global reputation for research into chemical ecology, specifically interactions between insects and plants which are natural product mediated. The most productive UK phytochemist in recent times is Peter G. Waterman, formerly at the U. Strathclyde (now Emeritus Prof., Southern Cross Univ.), who since the 1970's carried out extensive phytochemical and chemosystematic studies on the Rutales⁸ and on biologically active natural products. His former colleague and Ph.D. student, Alexander Gray has also been very productive phytochemically with interests in Colombian medicinal plants, and Veronique Seidel, a new member of the Strathclyde team has interests in antibacterial plant natural products. From the Univ. Glasgow, J. D. Connolly has a considerable track record in phytochemistry, in particular, the structure determination of triterpenoids, and Marcel Jaspars (Univ. Aberdeen), 2003 ASP Matt Suffness awardee and co-author of the highly useful text *Organic Structure Analysis*, is Chairman of the Editorial Board of *Natural Product Reports* and is successful in marine natural product chemistry. Colin Wright (Univ. Bradford) is working on the synthesis and evaluation of ethnobotanically-derived antimalarial compounds, such as the alkaloid cryptolepine, while at the Univ. Ulster, Satyajit Sarker, a former student of Waterman, is engaged in phytochemical and chemotaxonomic research, particularly on iridoids.

One of the most successful UK groups is that at the Jodrell Laboratory of the RBG Kew, headed by Monique Simmonds, whose successful career covers many areas of natural product research including insect anti-feedants, chemical taxonomy and biological evaluation of plant natural products.⁹ This team includes Renée J. Grayer who has made significant contributions to chemosystematics, particularly in the use of flavonoids. Several exceptional phytochemists working at Kew, include Nigel C. Veitch (2003 Jack L. Beal awardee), Tetsuo Kokubun, Philip Stevenson and Geoffrey C. Kite. This team has been very productive in structure elucidation of many different plant metabolites in chemosystematic and herbal medicinal product research. From King's College London, Peter J. Houghton, an inspiration to many in our area, has broad interests in pharmacognosy, particularly in anti-Alzheimer's disease metabolites, and his colleague Peter J. Hylands, (phytochemistry of plant medicines) has recently become Head of Department; thus, pharmacognosy will continue to flourish at King's. UK Phytochemistry has also benefited from the move from S. Africa of Dulcie Mulholland, now Professor of Biological Chemistry (U. Surrey) and expert in the Hyacinthaceae

UK Pharmacognosy and natural product research will continue to flourish, despite the challenges faced with acquisition of research funding, because many UK researchers are working in topical areas requiring solutions which natural products can afford. Recent EU legislation on the quality and safety of Herbal Medicinal Products also offers opportunities for pharmacognosists who are truly interdisciplinary scientists. The launch of a new Pharmacognosy Journal, *Phytochemistry*

Letters is also evidence that the discipline in the UK has a bright future (<http://ees.elsevier.com/phytol/>).

- (1) Reviews of this type are by their nature incomplete and I apologise for omissions. An attempt has been made to review individuals and their accomplishments in UK pharmacognosy and phytochemistry.
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