

Review

Plants as source of drugs

S.M.K. Rates

Laboratory of Pharmacognosy, Department of Production of Raw Material, School of Pharmacy, Federal University of Rio Grande do Sul, Av. Ipiranga, 2752 Porto Alegre CEP 90610-000, Brazil

Received 16 November 1998; accepted 26 April 2000

Abstract

This work presents a study of the importance of natural products, especially those derived from higher plants, in terms of drug development. It describes the main strategies for obtaining drugs from natural sources, fields of knowledge involved, difficulties and perspectives. It also includes a brief discussion of the specific situation in Brazil regarding the use of, trade in, and research into therapeutic resources of natural origin and the general lack of awareness of the use of potentially toxic plants, mainly in folk medicine. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: Medicinal plants; Phytomedicinal products; Natural products; Toxic plants

1. Introduction

The use of natural products with therapeutic properties is as ancient as human civilisation and, for a long time, mineral, plant and animal products were the main sources of drugs (see historical review by De Pasquale, 1984). The Industrial Revolution and the development of organic chemistry resulted in a preference for synthetic products for pharmacological treatment. The reasons for this were that pure compounds were easily obtained, structural modifications to produce potentially more active and safer drugs could be easily performed and the economic power of the pharmaceutical companies was increasing. Furthermore, throughout the development of human culture, the use of natural products has had magical-religious significance and different points of view regarding the concepts of health and disease existed within each culture. Obviously, this approach was against the new *modus vivendi* of the industrialised western societies, in which drugs from natural resources were considered either an option for poorly educated or low income people or simply as religious superstition of no pharmacological value.

However, even if we only consider the impact of the discovery of the penicillin, obtained from micro-organisms, on the development of anti-infection therapy, the importance of natural products is clearly enormous. About 25% of the drugs prescribed worldwide come from plants, 121 such active compounds being in current use. Of the 252

drugs considered as basic and essential by the World Health Organisation (WHO), 11% are exclusively of plant origin and a significant number are synthetic drugs obtained from natural precursors. Examples of important drugs obtained from plants are digoxin from *Digitalis* spp., quinine and quinidine from *Cinchona* spp., vincristine and vinblastine from *Catharanthus roseus*, atropine from *Atropa belladonna* and morphine and codeine from *Papaver somniferum*. It is estimated that 60% of anti-tumour and anti-infectious drugs already on the market or under clinical trial are of natural origin (Yue-Zhong Shu, 1998). The vast majority of these cannot yet be synthesised economically and are still obtained from wild or cultivated plants. Natural compounds can be lead compounds, allowing the design and rational planning of new drugs, biomimetic synthesis development and the discovery of new therapeutic properties not yet attributed to known compounds (Hamburger and Hostettmann, 1991). In addition, compounds such as muscarine, physostigmine, cannabinoids, yohimbine, forskolin, colchicine and phorbol esters, all obtained from plants, are important tools used in pharmacological, physiological and biochemical studies (Williamson et al., 1996).

In recent years, there has been growing interest in alternative therapies and the therapeutic use of natural products, especially those derived from plants (Goldfrank et al., 1982; Vulto and Smet, 1988; Mentz and Schenkel, 1989). This interest in drugs of plant origin is due to several reasons, namely, conventional medicine can be inefficient (e.g. side

effects and ineffective therapy), abusive and/or incorrect use of synthetic drugs results in side effects and other problems, a large percentage of the world's population does not have access to conventional pharmacological treatment, and folk medicine and ecological awareness suggest that "natural" products are harmless. However, the use of these substances is not always authorised by legal authorities dealing with efficacy and safety procedures, and many published papers point to the lack of quality in the production, trade and prescription of phytomedicinal products.

It is estimated that, in 1997, the world market for over-the-counter phytomedicinal products was US\$ 10 billion, with an annual growth of 6.5% (Soldati, 1997). The WHO considers phytotherapy in its health programs and suggests basic procedures for the validation of drugs from plant origin in developing countries (Vulto and Smet, 1998; OMS, 1991). Eastern countries, such as China and India, have a well-established herbal medicines industry and Latin American countries have been investing in research programs in medicinal plants and the standardisation and regulation of phytomedicinal products, following the example of European countries, such as France and Germany. In Germany, 50% of phytomedicinal products are sold on medical prescription, the cost being refunded by health insurance (Gruenwald, 1997). In North America, where phytomedicinal products are sold as "health foods" (Brevoort, 1997; Calixto, 2000), consumers and professionals have struggled to change this by gathering information about the efficacy and safety of these products, and new guidelines for their registration are now part of FDA policy (Israelsen, 1997). In 1997, the North American market for products of plant origin reached US\$ 2 billion (Brevoort, 1997).

Thus, the modern social context and economic view of health services, the needs of the pharmaceutical market and the recognition that research on medicinal plants used in folk medicine represents a suitable approach for the development of new drugs (Elisabetsky, 1987a; Calixto, 1996) have led to an increase in the number of publications in this field, and private and governmental institutions are now financially supporting research programmes worldwide.

The NCI (National Cancer Institute, USA) has tested more than 50,000 plant samples for anti-HIV activity and 33,000 samples for anti-tumour activity. In 1993, the International Program of Co-operation for Biodiversity (IPCB) was launched in order to promote natural products in Latin America and Africa, linking universities, industries and governments in a multidisciplinary programme for the sustained development and preservation of the environment (Rouhi, 1997). Large pharmaceutical companies, such as Merck, CIBA, Glaxo, Boehringer and Syntex, now have specific departments dedicated to the study of new drugs from natural sources (Reid et al., 1993).

However, the potential use of higher plants as a source of new drugs is still poorly explored. Of the estimated 250,000–500,000 plant species, only a small percentage

has been investigated phytochemically and even a smaller percentage has been properly studied in terms of their pharmacological properties; in most cases, only pharmacological screening or preliminary studies have been carried out. It is estimated that 5000 species have been studied for medical use (Payne et al., 1991). Between the years 1957 and 1981, the NCI screened around 20,000 plant species from Latin America and Asia for anti-tumour activity, but even these were not screened for other pharmacological activities (Hamburger and Hostettman, 1991).

2. Fields of knowledge

Research into, and development of, therapeutic materials from plant origin is a hard and expensive task (Borris, 1996; Turner, 1996; Williamson et al., 1996). Each new drug requires an investment of around US\$ 100–360 million and a minimum of 10 years of work, with only 1 in 10,000 tested compounds being considered promising and only 1 in 4 of these being approved as a new drug. Up to 1992, the NCI had only found 3 plant extracts active against HIV out of 50,000 tested, and only 3 out of 33,000 plant extracts tested were found to have anti-tumour activity (Williamson et al., 1996). Quantitative considerations regarding the average yield of active compounds and the amount of starting crude plant material required for the discovery, development and launch of a new drug on the market were presented by McChesney (1995): 50 kg of raw material are necessary to provide 500 mg of pure compound for bioassays, toxicology, and "in vivo" evaluation; full pre-clinical and clinical studies can require 2 kg of pure compounds obtained from 200 ton of raw material.

The process is multi-disciplinary (De Pasquale, 1984; Verpoorte, 1989). The basic sciences involved are botany, chemistry and pharmacology, including toxicology. Any research into pharmacological active natural compounds depends on the integration of these sciences. The way they are integrated and the extent of integration depend on the objectives of the study. In any case, a particular discipline should not be seen as secondary to another; quite the opposite, as each step must be carried out considering the theoretical and technical background of each of the sciences involved, otherwise the results may not be robust enough and may lead to breakdown of the process.

Other fields of knowledge may also be involved if the long path from plant to medicine is taken into account. Anthropology, agronomy, biotechnology and organic chemistry can play very important roles. In addition, pharmaceutical technology is fundamental to the development of any drug, including drugs of plant origin (Petrovick et al., 1997; Sharapin, 1997).

Concerning drugs of plant origin, it is important to bear in mind certain conceptual distinctions. Plants can be used as therapeutic resources in several ways. They

can be used as herbal teas or other home made remedies, when they are considered as medicinal plants. They can be used as crude extracts or “standard enriched fractions” in pharmaceutical preparations, such as tinctures, fluid extracts, powder, pills and capsules, when they are considered as phytopharmaceutical preparations or herbal medicines. Finally, plants can be subjected to successive extraction and purification procedures to isolate the compounds of interest, which can themselves be active and used directly as a drug, examples being quinine, digoxin and ergotamine, or they can be used as precursors (e.g. diosgenin) in hemisynthetic processes or as models for total synthesis, with well-defined pharmacological activity or structure–activity relationship studies determining a prototype drug (e.g. morphine).

According to the OPS (Arias, 1999) a *medicinal plant* is (1) any plant used in order to relieve, prevent or cure a disease or to alter physiological and pathological process, or (2) any plant employed as a source of drugs or their precursors. A *phytopharmaceutical preparation* or *herbal medicine* is any manufactured medicine obtained exclusively from plants (aerial and non-aerial parts, juices, resins and oil), either in the crude state or as a pharmaceutical formulation. A *medicine* is a product prepared according to legal and technical procedures that is used for the diagnosis, prevention and treatment of disease and has been scientifically characterised in terms of its efficacy, safety and quality (WHO, 1992). A *drug* is a pharmacologically active compound, which is a component of a medicine, irrespective of its natural, biotechnological or synthetic origin.

3. Selecting a plant

The approach for drug development from plant resources depends on the aim. Different strategies will result in a herbal medicine or in an isolated active compound. However, apart from this consideration, the selection of a suitable plant for a pharmacological study is a very important and decisive step. There are several ways in which this can be done, including traditional use, chemical content, toxicity, randomised selection or a combination of several criteria (Ferry and Baltassat-Millet, 1977; Soejarto, 1996; Williamson et al., 1996).

The most common strategy is careful observation of the use of natural resources in folk medicine in different cultures; this is known as ethnobotany or ethnopharmacology. Information on how the plant is used by an ethnic group is extremely important. The preparation procedure may give an indication of the best extraction method. The formulation used will provide information about pharmacological activity, oral versus non-oral intake and the doses to be tested. However, certain considerations must be taken into account when the ethnopharmacological approach of plant selection is chosen. For instance, each ethnic group has its

own concepts of health or illness, as well as different health-care systems (Elisabetsky and Posey, 1986). The signs and symptoms should be translated, interpreted and related to western biomedical concepts, thus allowing a focused study of a particular therapeutic property.

Selection based on chemical composition uses phylogenetic or chemotaxonomic information in the search, mainly in certain genera and families, for compounds from a defined chemical class with known pharmacological activity (Gottlieb and Kaplan, 1993; Souza Brito, 1996).

The search for highly specific potent drugs for therapeutic use and, more precisely, as a investigation tool in biological research has been quite productive in toxic plants. A number of important compounds now used in research came from toxic plants and several examples have been mentioned earlier (Williamson et al., 1996). Observation of the plant's environment has led to the isolation of active compounds, mainly anti-bacteria and anti-insect drugs (Harmburger and Hostettman, 1991). Another method of selecting a plant is that the investigator decides on a well-defined pharmacological activity and performs a randomised search, resulting in active species to be considered for further study. The search for anti-tumour drugs is a good example of the use of this strategy.

Finally, it is possible, and often desirable and inevitable, to use a combination of several criteria. Furthermore, apart from the chosen strategy, searching databanks and the scientific literature is crucial in finding active and/or toxic compounds that have already been identified, and can also be used as a criterion for choosing plants, e.g. if the purpose is to find a new source.

However, the choice of a biological material to be screened for active compounds and the subsequent development of a drug must take into account that the exploration of natural resources should meet global and regional needs for new efficient and safe drugs, while preserving natural diversity and the environment. The present situation of exploitation of the world's vegetation may lead to the extinction of some species, which means not only the loss of interesting chemical compounds as potential drugs, but also the loss of genes, which could be of use in plant improvement or in the biosynthesis of new compounds. It is, therefore, crucial, both for the development of areas with rich flora, such as Asia and Latin America, and for the pharmaceutical industry, to protect and promote the rational exploitation of biodiversity as a source of chemical compounds that have direct biological activity or can be used for the rational planning of new drugs. By following this principle, a new understanding of sustained development emerges, involving preservation of the environment while searching for new drugs, especially in developing countries which, by coincidence, have the largest natural resources on the planet (Soejarto, 1996; Brito and Nunes, 1997; Rouhi, 1997). Sensible use of these resources must be based on the amounts available, ease of access, the possibility of preservation and replanting and the establishment of priorities in relation to a desirable pharmacological activity.

If possible, consideration should be given to the use of cultivated plants, which allows the production of homogeneous material, thus guaranteeing chemical homogeneity, and the use of plants from genetic enhancement projects, which preserve species threatened with extinction (Labadie, 1986).

The search for drugs active against tumours, viruses and cardiovascular and tropical diseases is a priority. The largest research fields, as defined by the number of publications describing bioactive plant-derived compounds in the last few years, are anti-tumour drugs, antibiotics, drugs active against tropical diseases, contraceptive drugs, anti-inflammatory drugs, immunomodulators, kidney protectors and drugs for psychiatric use (Hamburger and Hostettman, 1991).

Taxol is both an example of the importance of natural products and of the complexity and necessity of finding alternative routes by which it can be obtained. It is the most important natural product-derived diterpene with anti-tumour activity found in recent years. Taxol is isolated from *Taxus* (*T. brevifolia* and *T. bacata*). However, the biggest obstacle to its clinical use is obtaining the material. In order to produce 2.5 kg of taxol, 27,000 tons of *T. brevifolia* bark are required and 12,000 trees must be cut down. Due to the high demand, this species of *Taxus* will soon be extinct if no alternative source of taxol can be developed. An economically possible and technically realistic alternative is its partial synthesis, in considerable yield, from an analogue found in other species of *Taxus*, as well as the production of other hemi-synthetic analogues (Hamburger and Hostettman, 1991; Wall and Wani, 1996).

4. Preparation of the plant material and isolation of the active compounds

Once the plant is chosen, the next step is its collection and botanical identification, then it should be submitted to a stabilisation process. It is important that plant recollection involves a professional botanist who is able to correctly identify the species and prepare part of the material for herbarium preservation in order to have a reference material ("voucher specimen"). Preferably, the place and date of recollection should be recorded and the information retained for further collection, if necessary. Stabilisation is usually by drying the material at ambient temperature in a shady place, but can also be carried out in an oven with controlled airflow and temperature. When the stability of the compounds is unknown or if they are known to be unstable, the fresh plant should undergo a stabilisation process consisting of freezing, lyophilisation, use of alcohol vapour, etc (Williamson et al., 1996).

The dried or stabilised plant material should then be powdered and subjected to a suitable extraction process. When the chemical nature of the compounds involved is

known (once again, chemotaxonomic information and data-bank consultation are crucial), extraction methods should be directed at obtaining these compounds in as high a yield and purity as possible. When the chemical composition is unknown, the extraction procedure can be based on how the plant is used in folk medicine, or several extractions with solvents of increasing polarity can be performed (Williamson et al., 1996).

To obtain isolated active compounds, the plant extracts are first qualitatively analysed by thin layer chromatography (TLC) and/or other chromatographic methods and screened to determine the biological activity or to obtain a general evaluation of biological activities. For purification and isolation, the active plant extracts are sequentially fractionated (Verpoorte, 1989), each fraction and/or pure compound being subjected to bioassay and toxicity evaluation in animals (Fig. 1). This strategy is called bioactivity-guided fractionation. Bioassays can be performed using microorganisms, molluscs, insects, cellular systems (enzymes, receptors, etc), cell culture (animal and human), and isolated organs or in vivo (mammals, amphibians, birds, etc) (Hamburger and Hostettman, 1991; Souza Brito, 1996). All these methods have advantages and disadvantages and the appropriate method must be carefully selected at each step of any biological study aimed at the development of a drug or the understanding of the biological basis of a particular pathology or even the discovery of the mechanism of action of already known drugs.

In general, a plant extract contains low concentrations of active compounds and a large number of promising compounds, requiring the use of sensitive bioassays suitable for the wide chemical variety and small amounts of the tested samples. Tests must be simple, reproducible, fast and cheap (Souza Brito, 1996; Brito and Nunes, 1997). Furthermore, new techniques that can fulfil different needs and be adjusted to the classical pharmacological study of natural compounds should be sought. There is also a need for the improvement and establishment of experimental models not yet extensively used in the evaluation of natural products.

After verifying the purity of an isolated active compound, the structure is determined by spectroscopic methods (UV, IR, mass spectrum or NMR) (Verpoorte, 1989). Once the chemical structure is defined, total or partial synthesis and preparation of derivatives and/or analogues can be considered, and modulation of the biological activity and definition of the structure–activity relationship can be carried out. After completing all these steps, large-scale isolation (it may necessary to collect the plant again) or partial or total synthesis is required for pharmacological evaluation in pre-clinical, clinical and toxicological trials aimed at future therapeutic use (Hamburger and Hostettman, 1991; Borris, 1996). As mentioned above, the final result of this strategy, the drug, is expensive. However, the study of medicinal plants also allows their use "*in natura*" and/or in pharmaceutical formulations obtained

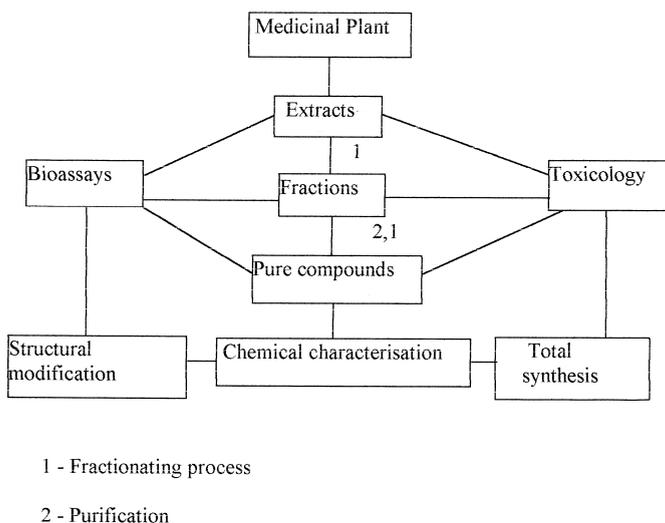


Fig. 1. Methods for obtaining active substances from plants.

from them, called *phytomedicines* or *herbal remedies*. This approach also requires efficacy and toxicity studies, but these are less time-consuming, as the steps of fractionation, purification and bioassay are basically not required or are far less complex (Fig. 2) (Elisabetsky, 1987b).

The Traditional Medicine Division of the WHO recognises that the centuries-old use of certain plants as therapeutic resources should be taken into account as proof of their efficacy (Gilbert et al., 1997). However, the total acceptance of plant-derived drugs and phytotherapy in scientific medicine and western health systems can only occur if these products fulfil the same criteria of efficacy, safety and quality control as synthetic products (Cáceres and Giron, 1997; Wagner, 1997). Moreover, knowledge of the main pharmacologically active plant compounds is an essential requirement for the standardisation and analysis of formulations. In the last decade, considerable effort, e.g. the Ibero-American Program, CYTED, ESCOP (European Scientific Cooperative of Phytotherapy) and Commission E (an independent committee on herbal remedies of German Federal Institute for Drugs and Medical Devices), has been made in trying to obtain clinical proof of efficacy, to standardise procedures for obtaining herbal remedies and to define chemical composition in order to replace crude products with modern pharmacological formulations. However, there is a long way to go! Lack of knowledge of chemical composition, geographical distribution and environmental impact on chemical biodiversity and plant variability makes it difficult to obtain a consistent quality. Furthermore, knowledge of the effect of production methods and adjuvant compounds on the pharmacological properties of products derived from medicinal plants is still a huge research field (Petrovick, 1997; Petrovick et al., 1997).

On the other hand, bioactivity-guided fractionation,

essential when trying to isolate an active substance, may exclude plants or compounds with relevant pharmacological activities. This can occur when the effect is not caused by a single compound, but by a combination, as a result of pharmacodynamic synergism or pharmacokinetic influences. A good example of this is *Panax ginseng* in which the whole plant or its saponin fractions are more active than the isolated compounds (Hamburger and Hostettman, 1991). In addition, when only one activity is considered in pharmacological screens, it is not possible to detect other potentially useful activities. *Catharanthus roseus* was initially studied for its anti-diabetic activity described in folk medicine, but it also contains a powerful anti-tumour compound, currently in clinical use (Williamson et al., 1996). Ginkgolides are another example of the difficulties encountered in determining an active compound (Hamburger and Hostettman, 1991). *Ginkgo biloba* has been used for centuries in Chinese medicine to treat asthma and cough. The clinical efficacy of *Ginkgo biloba* extract was, for many years, attributed to its phenolic compounds (flavonoids and biflavonoids). The first pharmaceutical formulations of *Ginkgo* extracts were marketed in 1960, but, only a few years ago, it was found that the “standardised extract” inhibits platelet aggregation factor (PAF)-induced platelet aggregation. The compounds responsible for this effect were later isolated and identified as ginkgolides A, B, C and M. Interestingly, these compounds were already known, their isolation having been described in 1932 and their chemical structure determined in 1967, but they were considered not to have any activity.

The low yield of material, the physico-chemical characteristics of the final compound and subsequent problems, such as solubilisation of extracts and fractions in solvents compatible with the animal system, are difficulties which must be resolved in the pharmacological evaluation of

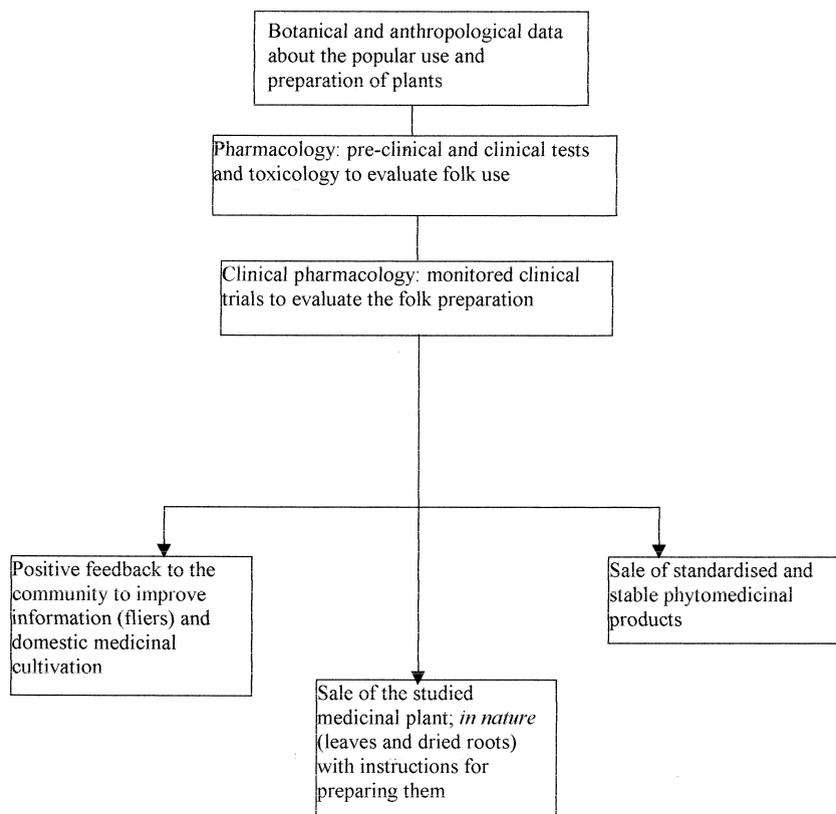


Fig. 2. Methods for pharmacological validation of the popular use of medicinal plants.

natural products. These problems, in fact, can invalidate the entire study because of false negative results, interference from compounds with unspecific or cytotoxic activity, poor absorption through natural biological barriers and poor bio-availability of the products.

The limitation on the amount of material that can be obtained has been gradually overcome by the use of modern extraction, purification and isolation methods, and the development of highly specific sensitive bioassays. Auxiliary substances, such as alcohol, Tween[®] 80, NaHCO₃, carboxymethyl cellulose, citric acid, DMSO, propylene glycol, polyethylene glycol and preparation of salt derivatives, are currently used to dissolve extracted materials and isolate compounds. There is an urgent need for the development and improvement of technologies for the extraction and preparation of “enriched fractions” of suitable solubility in biological fluids.

In summary, research into medicinal plants and the search for plant-derived drugs require a multidisciplinary approach with integrated projects, financial and technical support, and a very carefully planned strategy. The aims should consider demands in terms of public health, preservation of Biodiversity and the technical qualification of each laboratory or research group involved. Finally, advances in technology and knowledge of natural products must be viewed not

merely from the perspective of drug development, but also as a special tool for the understanding of biological phenomenon in order to contribute to the well-being of humanity.

5. When herbal remedies become poisons: toxic accidents with plants

As already discussed, phytomedicines are freely marketed and, in underdeveloped or developing countries, the use of medicinal plants is widely accepted. This can result in toxic accidents resulting from the use of plants as food or for therapy or from accidental ingestion by children or animals. Toxicity can result from highly concentrated doses or from the state of conservation of plants and the form of use.

Among the various types of registered cases, it is possible to point out (Pereira, 1992; Gilbert et al., 1997; Simões et al., 1998; Schenkel et al., 2000):

Accidents due to mistakes of botanical identification: The use of a wrongly identified plant is common, as is the substitution of different plants for the same indication. In Brazil, mainly in the North and Northeast regions, it

is common to use certain plants (bark, root or seeds) to prepare infusions used as substitutes for coffee (*Coffea arabica*), some common examples being tea made from “cha-de-bugre” or “café-do-diabo” (*Casearia sylvestris*), “café-do-mato” (*Cordia coffeoides*), “café-dos-navegantes” (*Mucuna pluricostata*) and “fedegoso” (*Cassia occidentalis*). Because of this, intoxication occurs as a result of incorrect identification. A number of deaths have occurred, mainly in the south of Pará, because of the use of *Hura crepitans* bark (Euphorbiaceae), also known as “açacu”, another coffee substitute; this plant contains a toxic lectin, as do other plants such as “mamona” (*Ricinus communis*) and “jequiriti” (*Abrus precatorius*). Another example from Brazilian folk medicine is the use of a plant called “quebra-pedra” as a diuretic and in the treatment of gallstone problems. The correct plant is *Phyllanthus nirurii*, which is commonly confused with species from the *Euphorbia* genus, which are potentially toxic.

Intoxication by popular remedies: Popular remedies, made without legal authorisation and sold by herbalists or even prescribed by religious leaders for use in rituals, have often resulted in toxic symptoms immediately after ingestion or later. In Brazil, among many examples, the use of *Symphytum officinalis* (“confrei”) as a panacea and *Aloe* spp (“babosa”) and *Euphorbia tirucalli* (“aveloz”) for treating cancer is very common. Because of its high content of potentially hepatotoxic pyrrolizidine alkaloids, comfrey (“confrei”) is now legally prohibited for internal use (Portaria 10/SVS, 30.01.1992). Other plants with a high content of pyrrolizidine alkaloids are *Senecio brasiliensis* and *Lantana camara*, the latter also being legally prohibited for internal use in several states (“Resolução ESESA — PR, 10.03.1992). Currently, there are no reports of the toxicity of the mucilaginous gel obtained from “babosa”; however, consistent data about its efficacy in the treatment of cancer are unavailable and the presence of hydroxyanthracene glycosides makes “babosa” potentially toxic, one of its toxic effects being severe diarrhoea. The latex of “aveloz” is rich in phorbol esters. Several studies have confirmed the tumour-promoting activity of phorbol, and a correlation with Burkitt’s lymphoma and nasopharyngeal carcinoma and the occurrence of *E. tirucalli* in regions of Africa and China has been demonstrated (Osato et al., 1987). In addition, users report strong oesophageal irritation (Cataluña and Rates, 1999) due to an irritant and inflammatory effect of the latex, which is used as venom on arrow tips in Africa.

Accidents with cardiotoxic plants: Plants with a high content of cardiac glycosides, such as *Nerium oleander* (“espírradeira”), *Thevetia peruviana* (“chapéu-de-Napoleão”), *Gomphocarpus fruticosus* and *Calotropis procera*, are used as decorative plants and have caused a number of domestic accidents involving children and animals.

5.1. Plants that interfere with conventional pharmacological therapy

1. **Plants containing coumarinic derivatives:** These compounds can lead to haemorrhagical accidents because of their chronic use or synergistic effects with oral anti-coagulants, such as dicoumarol and the sodium coumarins. Among the coumarin-rich plants widely used in folk medicine as herbal medicines and to enhance flavour are *Mykania* spp (“guaco”), *Melilotus officinalis* (“trevo-doce-amarelo”) and *Dypterix odorata* (“fava-tonka”).
2. **Plants with a high tyramine content:** Tyramine is a phenylethylamine found in yeast products, such as cheese and wine, which can be responsible for hypertensive accidents in patients treated with monoamine oxidase inhibitors. Mushrooms and higher plants, such as *Portulacca* spp (“onze-horas”), *Phoradendron* spp and *Psittacanthus* spp (“erva-de-passarinho”), are also potentially dangerous.
3. **Plants containing oestrogenic compounds:** Gingseng (*Panax* spp), used world-wide as a panacea, can have important oestrogenic effects and its use in combination with steroid drugs is not recommended. This also applies to plants such as “inhame” (*Dioscorea* spp).
4. **Plants that cause irritation and allergic problems:** Allergic reactions caused by contact with plants via pollen, secretions or volatile substances are not uncommon. The folk literature reports many plants that cause irritation; these include all species from families such as Urticaceae (*Urtica urens*) (“urtigas, cansações e mucunãs”), Euphorbiaceae (*Croton* spp., *Jatropha* spp., *Cnidioscolus* spp.) and Leguminosae (*Mucuna pruriens*). Sesquiterpene lactones, found in Asteraceae, cause irritation, and plants otherwise considered harmless, such as camomille (*Matricharia recutita*) and “arnica” (*Arnica montana*), can cause dermatitis. Allergic reactions, caused by the roots of *Pfaffia* spp, are seen in workers in the herbal medicines industries, which use this plant as a substitute for *Panax* spp (Subiza et al., 1991).
5. **Plants containing photosensitive compounds:** Among the well-studied photosensitive compounds are the furocoumarins, present in plants used in folk medicine and as food. Furocoumarinic derivatives are found in *Psoralea corylifolia*, *Conilla glauca* (Leguminosae), *Ficus carica* and *Brosimum gaudichandii* (Moraceae) and in several species of *Citrus* (Rutaceae). The “mamacadela” (*Brosimum gaudichandii*), found in Brazil, is used for the treatment of vitiligo. In 1984, information spread by laymen was responsible for several serious accidents and deaths in Brazil because of the use of “cha-de-figo” (*Fucus carica*) as a tanner. Another plant containing photosensitive compounds is *Hypericum perforatum* (Gutifereae), used in phytotherapy as an anti-depressant drug, and it is possible that other plants of the same genus have similar photosensitive properties because of the presence of hypericin and analogues.

Among other toxic plants, we can mention “comigo-ninguém-pode” (*Difenbachia* spp), which is used as a decorative plant and in Afro-Brazilian religious superstition and has been responsible for several toxic accidents, mainly involving children, because of the presence of calcium oxalate raphides. Others include the “arruda” (*Ruta graveolens*), popularly known to cause abortion, and plants from the genus *Atropa*, *Brugmansia*, *Datura* and the decorative *Hyoscyamus*, which are cultivated to produce tropanic alkaloids. They are also used in folk medicine against asthma, but have toxic effects due to their content of yioscyamine, scopolamine and atropine, responsible for accidental or voluntary intoxication and causing atropinic hallucination. Other plants causing toxic effects in the CNS include *Chenopodium ambrosioides*, *Artemisia absinthium* and *Equisetum* spp. A well-known and very interesting example is the symbiosis between plants from the *Bacharis* genus (Asteraceae) and fungi, such as *Mycothecium verrucaria*, which produce mycotoxins. Plants from the *Bacharis* genus (Asteraceae) are popularly used as kidney protectors and diuretics, as well as in the herbal medicines industry in South America.

6. Research into, and use and marketing of, medicinal natural products in Brazil

In Brazil, medicinal plants are widely used in both rural and urban areas. Most are used according to folk tradition developed by natives or brought to the country by Europeans, Africans and Asians. The plants are used in formulations of home remedies, such as teas, decocts and other tinctures, syrups and powders, or, as a consequence of the current development of the national pharmaceutical company, less often in capsules and pills (Mentz and Schenkel, 1989; Matos, 1997). The list of plants employed by the phytopharmaceutical industry contains approximately 90 species. Considering the cultural and economic perspectives, phytotherapy plays an important role and its use is recommended by the official national health service (“Portaria 08/CIPLAN, 1988”).

Obviously, the official use of these therapeutic resources in the national health service requires more than popular knowledge. Considering that the Brazilian flora is very rich, accounting for 22% of the higher plant species on the planet, (Elisabetsky and Costa-Campos, 1996), solid scientific knowledge is required for the transformation of medicinal plants into industrialised medicines. However, social, cultural and economical problems, lack of well-planned and integrated strategies and poor access to scientific information must still be dealt with in order to use the available resources for the modern concept of a drug. In terms of drug consumption, Brazil is the fifth most important country worldwide, but the national pharmaceutical industry is not developed and depends on external synthetic resources and technology. In fact, the national pharmaceutical industry in

Brazil is basically an “industry of transformation” (Korolkovas, 1989) and the market is controlled by foreign companies. In the natural product field, perhaps the most significant example is pilocarpine, produced by Merck from species of a Brazilian plant called *Pilocarpus*, the exploitation of which is cheap compared with market profits, even inside Brazil. By considering this approach, the pharmaceutical industry has an unequalled opportunity to grow in this field in Brazil (Calixto, 1996). The herbal medicines market makes profits of US\$ 40 billions per year (Calixto, 1996). However, herbal medicine companies basically consist of small businesses, which experience great difficulty to keep running. Research projects in this field have basically developed in university laboratories, supported by the now extinct “Central de Medicamentos (CEME)” and other governmental institutions involved in research. This activity is restricted to a small number of graduate students and their supervisors who use the chemistry and pharmacology of natural products to obtain an academic degree (Gottlieb and Borin, 1997), and, with few exceptions, does not involve any consistent integration with industry. As a result, very often the quality of the products sold does not meet minimal standards or even reach the level of WHO recommendations for products for traditional use. The most common problems are adulterated products, substitution, the lack of standards for chemical composition and the lack of scientific studies on pharmacological properties and therapeutic use (Liberalli, 1944; Oliveira and Akisue, 1973; Farias et al., 1985; Schenkel et al., 1986; Rates et al., 1993).

In 1995, the “Secretaria de Vigilância Sanitária” (SVS, MS) considered the critical situation of the market in Brazil and established a set of rules for the registration of phyto-medicinal products (Portaria no. 6 de 24.01.95, SVS-MS, Brazil, 1995a) and for the study of the toxicity of these products (Portaria no. 116 de 08.08.96, SVS-MS, Brazil, 1996). Recently, another set of rules, taking into account the traditional use and WHO, ESCOP and Commission E regulatory status, was published by the “Agência Nacional de Vigilância Sanitária” (Portaria no. 17/00 de 25.02.200, ANVS/MS, Brazil). By meeting these suggestions, the competitiveness of our industry will be guaranteed and a great advance in knowledge in the use of natural products as therapeutic resources will be made. To do so, links must be forged between pharmaceutical industry and the academic sector, since the universities are aware of scientific advances in this field, necessary for an industry, which currently sells its products in a restricted market that can be expanded to include the external market (Calixto, 1996). This is particularly important if we consider commercial agreements, such as NAFTA, ALCA and MERCOSUL.

On the other hand, industry, put under pressure by present legal requirements, is becoming organised and has set up several groups to study and improve the quality of its herbal medicine products and establish academic co-operation in order to subject them to scientific investigation. These

groups have proposed a list of plants for inclusion in the 4th edition of the Brazilian Pharmacopoeia and the future creation of the Phytomedicinals Products National Formulary (Sindusfarm, SP, 1995; Comissão, 1995).

There have been four editions of the Brazilian Pharmacopoeia. The first, in 1929, contained 300 monographs on medicinal plants, whereas the second, in 1959, and the third, in 1977, contained, respectively, only 94 and 26. In the first two editions, methods of analysis were restricted to describing the basic botanical identification, whereas the third edition contained physicochemical methods for analysis, such as TLC, and procedures for measuring active compounds, such as gravimetric and volumetric procedures and UV absorption. The second volume of the fourth edition, published in 1997, contains 10 revised monographs with methods of analysis compatible with the present technical ability of the national laboratories. The update of this edition will contain modern methods of analysis, while retaining methods suitable for small laboratories. Plants already mentioned in previous editions will be retained, since they meet the needs of the market and public health and requirements, such as adequate scientific data, which can ensure the quality control and the efficacy and safety of the final product (Henriques, 1997).¹

However, unfortunately it seems that these new marketing perspectives and governmental rules have not made significant changes in the quality of herbal medicinal products sold in Brazil. Recent work has shown that, overall, the quality of the product remains at the same level as in previous decades (Marques, 1996; Dias, 1997; Zuculotto, 1997; Zuculotto et al., 1999). Nevertheless, there are some signs of better days. As a result of the Medicinal Plants Project of the CEMÉ, launched in 1983, native plants, such as *Maytenus illicifolia* and *Phyllanthus* spp, are seen as real perspectives for the development of safe and effective phytomedicinals by the national industry. A few agreements between universities and industry are being strengthened with the support of agencies or institutions managed by industry. Research groups devoted to the pre-clinical pharmacology and chemistry of natural products are now relatively well developed in several regions of the country.

Recently, a special issue of “Ciência e Cultura Journal of the Brazilian Association for the Advancement of Science” (1997) on research into natural products in Brazil was published. The most important aspects of this field were presented as original contributions, rather than as the usual presentations. However, despite the effort of Brazilian scientists, most reports are restricted to the isolation and identification of chemical compounds or to the preliminary pharmacological study of crude extracts without identification of the chemical substances involved. The usual

presentation is still abstracts and short communications during conferences and symposia, such as the annual meeting of the Federação das Sociedades Brasileiras de Biologia Experimental (FESBE) and the Simpósio Bi-Annual of Plantas Medicinais (SBPM), both established for more than 10 years. Information in the databank of the Fundação Brasileira de Plantas Medicinais on the pharmacology of natural products suggests an increase in the number of species studied, with an annual growth of 10% (Souza Brito, 1996). The “SBMP 1996” (Souccar and Lapa, 1997) and the “SBMP 1998” contained around 500 and 300 reports, respectively, on pharmacological activity. However, the number of projects involving collaboration between more than one university or research institute or even interdepartmental projects is still low (Elisabetsky and Costa-Campos, 1996). International collaborations are being established and have increased, but vary considerably from year to year (Elisabetsky and Costa-Campos, 1996). Reports of university–industry collaboration are still rare. Souza Brito (1996) seems to be correct when she pointed out that it is untrue that the advance of pharmacological investigation of natural products is slow due to a lack of interest in this area. The fast growth of the pharmacology of natural products requires more than the interest of researchers and is dependent on political and institutional decisions. Government, universities and pharmaceutical industries must establish mutual agreements on the importance and possibility of developing natural products as a source of new drugs. This will be a very hard task for the future!

Finally, the great diversity of the Brazilian flora has been a major issue and many people have demonstrated against abuse of the tropical forest by international interests. Legal approaches are being studied to avoid loss of resources and germoplasm extinction. This is particularly important, said Gottlieb and Borin (1997), because “any lasting social benefit depends not only on the adequate exploitation of our biodiversity, but also how it is exploited, the aim being auto-sustainable development, with preservation”. There is specific regulation for the collection of natural resources for scientific purposes (Decreto-Lei no. 98930 of 15.01.1990). Recently, the National Law of Patents (Decreto-Lei no. 9279 of 14.05.1996) was approved, the result of intense discussion in the academic sector. However, it is too early to evaluate the impact of this legislation on trade and drug development from natural resources. This will certainly increase the interest of multi-nationals in the country, but arguments against the protection of patents for natural resources in general and drugs in particular are hampered by fear of the consequences, such as an increase in the price of drugs and the collapse of the national pharmaceutical industry, which would lead to unemployment and market evasion, expropriation of the national genetic resources and an increase in commercial and technological dependency. On the other hand, favourable aspects, such as the preservation of indigenous knowledge,

¹ Personal communication, Dr Henriques A.T., Co-ordinator for the Sub-Committee of Medicinal Plants, Brazilian Pharmacopoeia, 1997.

can be pointed out. Questions such as intellectual property are also crucial. In general, ethnic-pharmacological research should involve collaboration of native communities. Secrets from ancient traditions are often reported in scientific meetings, many scientific studies are published and important substances are developed as a result of these studies, while the native population, which has the original knowledge and is in need of better care, does not benefit.

References

- Arias, T.D., 1999. Glosario de Medicamentos: desarrollo, evaluación y uso. Washington: Organización Panamericana de La Salud. Organización Mundial de La Salud, p. 171.
- Borris, R.P., 1996. Natural products research: perspectives from a major pharmaceutical company. *Journal of Ethnopharmacology* 51 (1/3), 29–38.
- Brasil, 1995. Portaria n° 6, de 31 de janeiro de 1995. Diário Oficial da República Federativa do Brasil, Brasília, n. 26, 1523–1524. 6 fev. Seção 1.
- Brasil, 1996. Portaria n° 116, de 8 de agosto de 1996. Diário Oficial da República Federativa do Brasil, Brasília, n. 155, 15199–15200. 12 ago. Seção 1.
- Brevoort, P., 1997. The current status of the US botanical market. In: World Congress On Medicinal And Aromatic Plants For Human Welfare, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-42.
- Brito, A.R.M.S., Nunes, D.S., 1997. Ethnopharmacology and the sustainable development of new plant-derived drugs. *Ciência e Cultura, Journal of the Brazilian Association for the Advancement of Science* 49 (5/6), 402–408.
- Cáceres, A., Giron, L., 1997. Multidisciplinary needs for quality control and regulation of phytotherapy. In: World Congress on Medicinal and Aromatic Plants For Human Welfare, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-51.
- Calixto, J.B., 1996. Fitofármacos no Brasil: agora ou nunca! *Ciência Hoje* 21 (123), 26–30.
- Calixto, J.B., 2000. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). *Brazilian Journal of Medical and Biological Research* 33 (2), 179–190.
- Cataluña, P., Rates, S.M.K., 1999. The traditional use of the latex from *Euphorbia tirucalli* Linnaeus (Euphorbiaceae) in the treatment of cancer in south Brazil. *Acta Horticulturae* 501, 289–295.
- Comissão De Homeopatia E Fitoterapia Do Sindusfarm — SP, 1995. Lista de Plantas SINDUSFARM, São Paulo: SINDUSFARM, 9–13.
- De Pasquale, A., 1984. Pharmacognosy: the oldest modern science. *Journal of Ethnopharmacology* 11, 1–16.
- Dias, T., 1997. Produtos fitoterápicos a luz da legislação vigente e confiabilidade de suas indicações terapêuticas. Porto Alegre: UFRGS, Faculdade de Farmácia. Trabalho de conclusão.
- Elisabetsky, E., 1987a. Pesquisas em Plantas medicinais. *Ciência e Cultura* 39 (8), 697–702.
- Elisabetsky, E., 1987b. Etnofarmacologia de algumas tribos brasileiras. In: Ribeiro, D. (Ed.). *Suma etnológica Brasileira*, vol. 8. Petrópolis, Vozes, pp. 135–138.
- Elisabetsky, E., Costa-Campos, L., 1996. Medicinal plant genetic resources and international cooperation: the Brazilian perspective. *Journal of Ethnopharmacology* 51, 110–120.
- Elisabetsky, E., Posey, D.A., 1986. Ethnopharmacological research and natural resources of humid tropics: the case of Kayapó indians and its implications for medical science. *Anais do 10 Simposio do Trópico Úmido* 2, 85–93.
- Farias, M.R., Schenkel, E.P., Bergold, A.M., Petrovick, P.R., 1985. O problema da qualidade dos fitoterápicos. *Caderno de Farmácia* 1 (2), 73–82.
- Ferry, S., Baltassat-Millet, F., 1977. La prospection des plantes medicinales. *Lyon Pharmaceutique* 28 (3), 257–260.
- Gilbert, B., Ferreira, J.L.P., Almeida, M.B.S., Carvalho, E.S., Cascon, V., Rocha, L.M., 1997. The official use of medicinal plants in public health. *Ciência e Cultura. Journal of the Brazilian Association for the Advancement of Science* 49 (5/6), 339–344.
- Goldfrank, L., et al., 1982. The Pernicious Panacea: Herbal Medicine. *Hospital Physician* 10, 64–86.
- Gottlieb, O., Kaplan, M.A., 1993. Das plantas medicinais aos fármacos naturais. *Ciência Hoje* 15 (89), 51–54.
- Gottlieb, O., Borin, M.R. de M.B., 1997. Natural products research in Brazil. *Ciência e Cultura. Journal of the Brazilian Association for the Advancement of Science* 49 (5/6), 315–320.
- Gruenwald, J., 1997. The market situation and marketing of herbal medicinal products (HMP) in Europe. In: World Congress on Medicinal And Aromatic Plants For Human Welfare, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-33.
- Hamburger, M., Hostettmann, K., 1991. Bioactivity in plants: the link between phytochemistry and medicine. *Phytochemistry* 30 (12), 3864–3874.
- Israelsen, L.D., 1997. United States regulatory status of botanical preparations. In: World Congress on Medicinal And Aromatic Plants for Human Welfare, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-44.
- Korolkovas, A., 1989. Planejamento de Fármacos. *Ciência e Cultura* 41 (6), 528–537.
- Labadie, R.P., 1986. Problems and possibilities in the use of traditional drugs. *Journal of Ethnopharmacology* 15, 221–230.
- Liberali, R.P., 1944. Atitudes e rumos da indústria farmacêutica. *Revista Brasileira de Farmácia* 25 (3), 122–133.
- Marques, L.C., 1996. Avaliação do mercado de fitoterápicos em relação às exigências em vigor da Portaria SVS No 06/95. In: Simpósio de Plantas Medicinais do Brasil, 16. Programa e Resumos. Florianópolis, UFSC, p. 61.
- Matos, A.F.J., 1997. Living pharmacies. *Ciência e Cultura. Journal of the Brazilian Association for the Advancement of Science* 49 (5/6), 409–412.
- McChesney, J.D., 1995. The promise of plant-derived natural products for the development of new pharmaceuticals and agrochemicals. In: Seidl, P.R., Gottlieb, O., Kaplan, M.A.C. (Eds.). *Chemistry of the Amazon. Biodiversity, Natural Products, and Environmental Issues*, ACS Symposium Series No. 88. American Chemical Society, Washington, DC.
- Mentz, L.A., Schenkel, E.P., 1989. A coerência e a confiabilidade das indicações terapêuticas. *Caderno de Farmácia* 5 (1/2), 93–119.
- Oliveira, F., Akisue, G., 1973. O problema da adulteração de drogas. *Revista Brasileira de Farmácia* 54 (2), 71–83.
- OMS — Organización Mundial de la Salud. Pautas para la evaluación de medicamentos herbáricos. Ginebra, 1991.
- Osato, T., Mizuno, F., Imai, S., 1987. African Burkitt's lymphoma

- and Epstein — Barr Virus — Enhancing plant *Euphorbia tirucalli*. *The Lancet*, 1257–1258.
- Payne, G., Bringi, V., Prince, C., Shuller, M., 1991. The quest for commercial production of chemicals from plant cell culture, *Plant Cell and Tissue Culture in Liquid Systems*, Oxford University Press, Oxford.
- Pereira, S.M.N., 1992. Ocorrência de acidentes tóxicos com plantas. *Infarma Nov/Dez*, 16–19.
- Petrovick, P.R., 1997. Development of new drugs from plant origin. In: *World Congress On Medicinal And Aromatic Plants For Human Welfare*, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-21.
- Petrovick, P.R., Ortega, G.G., Bassani, V.L., 1997. From a medicinal plant to a pharmaceutical dosage form. A (still) long way for the Brazilian medicinal plants. *Ciência e Cultura. Journal of the Brazilian Association for the Advancement of Science* 49 (5/6), 364–369.
- Rates, S.M.K., Von Poser, G.L., Gosmann, G., Apel, M., Rosa, A.M., Andrade, L., 1993. Avaliação da qualidade de produtos fitoterápicos comercializados em Porto Alegre — RS. In: *Congresso de Ciências Farmacéuticas del Cono Sur*, 2, 1993. Montevideo.
- Reid, W.V., Laird, S.A., Meyer, C.A., Gámez, R., Sittenfeld, A., Janzen, D.H., Gollin, M.A., Juma, C., 1993. Biodiversity Prospecting: Using Genetic Resources for Sustainable Development, World Resources Institute (USA).
- Rouhi, A.M., 1997. Seeking drugs in natural products. *C and EN* 7, 14–29.
- Schenkel, E.P., Gosmann, G., Farias, M.R., Santos, R.I., Vianna, R.M.J., Simões, C.M.O., 1986. O controle de qualidade de insumos vegetais e fitoterápicos na Faculdade de Farmácia da Universidade Federal do Rio Grande do Sul. *Caderno de Farmácia* 2 (2), 139–151.
- Schenkel, E.P., Zannin, M., Mentz, L., Bordignon, S.L., Irgang, B., 2000. Plantas Tóxicas. In: Simões, C.M.O., Schenkel, E.P., Gosmann, G., Mello, J.C.P., Mentz, L.A., Petrovick, P.R. (Eds.). *Farmacognosia: da planta ao medicamento*, vol. 35, UFSC/UFRGS, Porto alegre (pp. 755–788).
- Sharapin, N., 1997. Development of new drugs from plant origin. In: *World Congress On Medicinal And Aromatic Plants For Human Welfare*, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-38.
- Simões, C.M.O., Mentz, L.A., Schenkel, E.P., Irgang, B.E., Stehmann, J.R., 1998. *Plantas da Medicina Popular no Rio Grande do Sul*, 5th ed. UFRGS, Porto Alegre (173p.).
- Sindusfarm — Sindicato da Indústria de Produtos Farmacéuticos No Estado de São Paulo, 1995. Contribuição do Subgrupo de Fitoterápicos do Sindusfarm — SP à Estruturação da Fitoterapia no Brasil. São Paulo, pp. 1–8.
- Soejarto, D.D., 1996. Biodiversity prospecting and benefit-sharing: perspectives from the field. *Journal of Ethnopharmacology* 51 (1/3), 1–16.
- Soldati, F., 1997. The registration of medicinal plant products, what quality of documentation should be required? The industrial point of view. In: *World Congress on Medicinal and Aromatic Plants for Human Welfare*, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-48.
- Souccar, C., Lapa, A.J., 1997. Analgesic and anti-inflammatory screening of two Brazilian medicinal plants: a positive and a false-positive result. *Ciência e Cultura. Journal of the Brazilian Association for the Advancement of Science* 49 (5/6), 416–421.
- Souza Brito, A.R.M., 1996. How to study the pharmacology of medicinal plants in underdeveloped countries. *Journal of Ethnopharmacology* 54, 131–138.
- Subiza, J., Subiza, J.L., Escribano, P.M., Hinojosa, M., Garcia, R., Jerez, M., Subiza, E., 1991. Occupational asthma caused by Brasil ginseng dust. *Journal of Allergy and Clinical Immunology* 88 (5), 731–736.
- Turner, D.M., 1996. Natural product source material use in the pharmaceutical industry: the Glaxo experience. *Journal of Ethnopharmacology* 51 (1/3), 39–44.
- Verpoorte, R., 1989. Some phytochemical aspects of medicinal plant research. *Journal of Ethnopharmacology* 25, 43–59.
- Vulto, A.G., Smet, P.A.G.M., 1988. In: *Dukes, M.M.G. (Ed.). Meyler's Side Effects of Drugs*, 11th Ed.. Elsevier, Amsterdam, pp. 999–1005.
- Wagner, H., 1997. Guidelines for quality control of phytomedicines. In: *World Congress On Medicinal And Aromatic Plants For Human Welfare*, 2, 1997. Abstracts. Mendoza: ICMPA/ISHS/SAIPOA, p. L-4.
- Wall, M.E., Wani, M.C., 1996. Camphothecin and taxol: from discovery to clinic. *Journal of Ethnopharmacology* 51 (1/3), 239–254.
- WHO — World Health Organization, 1992. Quality control methods for medicinal plant materials, Geneva.
- Williamson, E., Okpako, D.T., Evans, F.J., 1996. *Selection, Preparation and Pharmacological Evaluation of Plant Material*, Wiley, Chichester.
- Yue-Zhong Shu, 1998. Recent natural products based drug development: a pharmaceutical industry perspective. *Journal of Natural Products* 61, 1053–1071.
- Zuccolotto, T., 1997. Análise qualitativa de produtos fitoterápicos e insumos vegetais comercializados em Porto Alegre — RS. Porto Alegre: UFRGS, Faculdade de Farmácia. Trabalho de conclusão.
- Zucolloto, T., Apel, M., Rates, S.M.K., 1999. Análise de produtos fitoterápicos comercializados em Porto Alegre — RS. *Revista do Instituto Adolfo Lutz* 58 (2), 25–31.