PHARMACEUTICAL PLANTS (PLANTS USED IN PHARMACEUTICAL PREPARATIONS)

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Summary

The beginning of the pharmaceutical industry dates back to the eighteenth century when developments of chemistry, isolation, purification and structural elucidation of natural compounds of plant origin started. The development of isolation techniques facilitated the production of compounds of high purity. Quinine (*Cinchona spp*.) was the first pharmaceutical molecule to be produced on an industrial scale, for its use against malaria. The importance of poppy (*Papaver somniferum*) alkaloids (morphine, codeine etc.) increased continuously from the time of their isolation. In the last two decades the amount of morphine utilized annually, world-wide, increased from 160 to 313 tonnes. As a result of intensive research and development projects, a series of medicines of outstanding quality was developed from the toxic fungi ergot (*Claviceps purpurea*). To treat heart diseases foxglove (*Digitalis lanata*), with about 20 different glycosides (digoxin, digitoxin and the series of lanatoside C groups), has played a leading role in the past hundred years. More than 80 different alkaloids have been isolated from the periwinkle (*Catharanthus roseus*). Its main constituents, both vinblastine and vincristine are extremely valuable therapeutic agents for various form of cancer, used singly or in combination therapy. Pacific yew (*Taxus brevifolia*) is a new pharmaceutical discovery, having no historical precedence. A new anti-cancer drug made from it was registered in 1992 for treatment of ovarian cancer, and in 1994 for metastases. Pharmaceutical companies use thornapple (*Datura spp*.) and related species (*Duboisia spp*.) too, producing ready-made preparations containing hyoscine, atropine and their derivatives.

In spite of the enormous advances achieved by synthetic pharmaceutical chemistry and biotechnology, there are many compounds of plant origin, even today, which can be produced by using plants as a starting raw material.

1. Introduction

Until the beginning of the nineteenth century, many minerals and different products of plant and animal origin were used for medication. As a result of the rapid development of chemistry, isolation, purification and structural elucidation of natural compounds were started. Sugar and different acids (citric, gallic acid, etc.) were the target of the first series of investigations. Morphine purified from opium by Sertürner (1806) was the first alkaloid, with high biological efficacy. It was followed by isolation of many other alkaloids including strychnine from *Strychnos nux-vomica*, emetine from *Ipecacuana*, and quinine from *Cinchona spp*. As a result of the enormous development of chemistry and biochemistry, the chemical structure and biological efficacy of thousands of plant compounds were identified. The development of isolation techniques made possible the production of compounds of high purity. The administration of pure compounds facilitated the investigations necessitated by the development of registration procedures for the new medicines. In some cases, because of the complex pharmacological action of the plant constituents, a mixture of chemicals were processed, as happens even today, as in the case of *Silybum marianum, Chrysanthemum parthenium* ,and *Ginkgo biloba*. Parallel with the progress achieved in chemistry, the ability to produce natural compounds by semi or total chemical synthesis was developed by pharmaceutical industry. More recently the production of natural compounds by biotechnological methods has become a focus of interest. In spite of the enormous advances achieved by the pharmaceutical chemistry and biotechnology, there are many compounds of plant origin, even today, which can be produced by using plants alone as the starting raw material.

2. Species processed by pharmaceutical industry

The plant spectrum utilized by pharmaceutical factories is wide and variable from country to country. There are plant species, which are processed in large quantities, while others are used in restricted amounts. The list of species, which are processed in a relatively large-scale, is given in Table 1. The main pharmaceutical actions of the species and their active agents are also indicated.

Common names	**Scientific name**	**Active agents**	**Pharmacological action**
Red peppers	Capsicum annuum	capsaicin	local blood circulation, rheumatism
Hops	Humulus lupulus	humulone, lupulone	sedative
Senna	Cassia senna	sennoside A sennoside N, rhein	laxative
Milk thistle	Silybum marianum	silybin, silymarin	liver protection, antioxidant
Yam	Dioscorea spp.	diosgenin	source of steroids
Foxglove	Digitalis lanata	lanatoside C, digoxin	heart muscle activity, cardiac arrhythmias

Wormwood	Artemisia annua	artemisinin	cerebral malaria
Feverfew	Chrysanthemum parthenium	parthenolide	migrene, menstrual disorders
Ginkgo	Ginkgo biloba	ginkgolides	cerebral circulation, loss of memory
Thornapple	Datura stramonium Datura metel	hyoscyamine, atropine, hyoscine	depressant of nerve endings, control of motion sickness
Henbane	Hyoscyamus niger	hyoscyamine, hyoscine	sedatives, secretion
Deadly nightshade	Atropa balladonna	hyoscyamine, atropine, scopolamine	depressant of nerve endings, control of motion sickness
	Duboisia myoporoides Duboisia leichhardtii Duboisia hopwoodii	hyoscyamine, hyoscine	sedatives, secretion
Ephedra	Ephedra sinica Ephedra equisetina Ephedra gerardiana Ephedra intermedia Ephedra major	ephedrine, pseudoephedrine	relief of asthma and fever, anti-inflammatory
Opium poppy	Papaver somniferum.	morphine, codeine, narcotine, papaverine	Pain relief, hypnotics, allaying coughing, narcotic antagonists
Ergot	Claviceps purpurea	ergocristine, ergocornine, ergocryptine, ergometrine	migraine, autonomic nervous system, adrenaline antagonist, action on blood vessels
	Rauwolfia serpentina	reserpine, rescinnamine, ajmaline	hypertension, neuropsychiatric disorders, cardiac arrythmas
Quinine	Cinchona succirubra Cinchona officinalis Cinchona ledgeriana Cinchona calisaya	quinine, quinidine	antimalarial, cardiac arrhythmias, cardiac depressant
Periwinkle	Catharanthus roseus	vincristine, vinblastine	Hodkin,s disease, nonHodgkin,s lymphomas, leukaemia in children
Pacific yew	Taxus brevifolia	taxol, baccatin, 10-deacetylbaccatin,	ovarian cancers, breast cancers, head and neck cancers
Rue	Ruta graveolens	rutin	antihaemorrhagic, emmenagogue, hypotensive
Ipecac	Cephaëlis	emetine, cephaëline,	amoebic dysentery,

	ipecacuanha	psychotrine	expectorant, antitumor action,

Table 1. Species processed by pharmaceutical industry on a large scale

3. Characterization of the species of main importance

3.1. Quinine

History

According to historical data, Central and South American Indians before the arrival of Europeans knew the plant and its utilization. Its curing effect was a secret until about 1630, when the first application of the brown bark by European people was recorded. Eight years later, when the wife of the Mexican governor-general, princess Cinchona became ill, the bark powder was applied, and resulted in complete recovery. The tree which the brown bark was collected from, in honour of the princess, was given the name Cinchona. The introduction of the plant to Europe took place around 1640. In 1742 Linnaeus established the genus *Cinchona* and in 1753 described *Cinchona officinalis*. From 1820 expeditions were organised to Peru by Dutch and British governments to obtain propagation material of high alkaloid content. After initial problems, the introduction to Java and establishment of plantations by the British in India (see Figure 1) and Ceylon were successful.

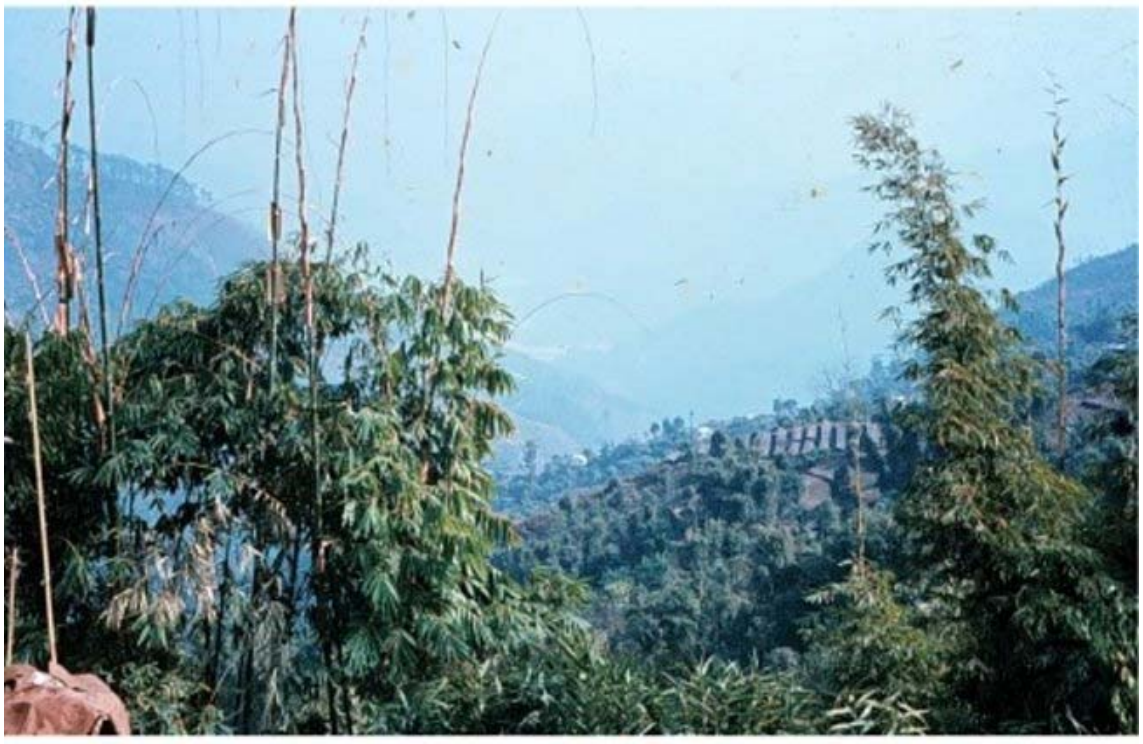

Figure 1. Large scale production of *Cinchona spp*. (quinine) in the Darjeeling region of India
(photo Bernáth, J.)

The demand for quinine was rather stable for a century. After the Second World War plantations in other regions were established. In addition to Java (now part of Indonesia), India and Sri Lanka (Ceylon), plantations were established in South American and African countries, and even in Australia and Hawaii.

Distribution

The taxonomic situation with the genus *Cinchona* is rather confusing. Its original distribution is in the Bolivian and Peruvian rain forests. Because of the large morphological and chemical diversity, hundreds of species names have been proposed and published. However, the majority of names proved to be only synonyms. Of course there are some differences in distribution of the related taxa. For instance *C. calisaya* (Weddel) and *C. ledgeriana* (Moens) occur in southern Peru and Bolivia at 1200 to 1700 m; *C. officinalis* (L.) is found from Columbia to northern Peru at higher altitudes and *C. succirubra* (Pavon ex Klotzsch), being a very tolerant species, occurs in a wide range of altitudes from Costa Rica to Bolivia. However, as a result of the worldwide introduction procedure, the species are grown in wide range of ecological conditions. The main countries where production is going on are as follows: Indonesia, India, Guatemala, Costa Rica, Mexico, Jamaica, Reunion, Martinique, Puerto Rico, Brazil, Bolivia, Peru, Ivory Coast, Nigeria, Congo, Uganda, Tanzania, Kenya, Madagascar, Hawaii and Australia.

Description

There are about 40 different species of *Cinchona* found in the tropical regions of Central and South America. The species are evergreen shrubs or trees, which grow up to 20 to 24 m high. *C. ledgeriana* reaches only 6 m. The main species from the point of view of the production are as follows:

C. calisaya (yellow Cinchona) has oblong-lanceolate, glabrous leaves of 7.5 to 15 cm, shiny above. The flowers are pale flesh-colored, arranged in a terminal pyramidal panicle, the lower branches in the axis of leaves. Corolla is 8 to 17 mm long, rose-colored with lanceolate lobes. The capsule is ovoid-oblong and 8 to 17 mm long.

C. ledgeriana (ledger Cinchona) has similar leaves of that of *C. calisaya*. Its yellowish white flowers are strongly scented. Corolla is 8 to 13 mm long, tubes are pentagonous, and the lobes are the same color as the tube and are fringed with very long white hairs. Capsule is ovoid-lanceolate of 8 to 13 mm long.

C. succirubra (red Cinchona) is a large tree, attaining 24 m high. Leaves are soft pubescent or tomentose, elliptic, acute at both ends with blades of 15 to 30 cm long. Flowers are rose-colored, with compact cymes in a large pyramidal thyrsus. Corolla is 1.3 to 2.0 cm. Capsules are large (2.5 to 3.2 cm) oblong, and narrowed towards the appex.

C. officinalis (pale Cinchona) has glabrous, lanceolate or ovate-lanceolate leaves wit blades of 7.5 to 15.0 cm size. Flowers are red and formed in short corymbiform compound cymes. Corolla-tubes are 1.7 to 2.0 cm long with white adpressed hairs. The capsule is ovoid-oblong and 1.7 to 2.0 cm long.

Active agents

The bark of all species accumulates up to 16% (mostly 6 to 10%) total quinoline alkaloids including quinine, quinidine, cinchonine and cinchonidine. Other alkaloids, which have limited importance, are epiquinine, epiquinamine, hydroquinidine, hydroquinine and quinamine. Accumulation of tannins, quinic acid, resin, wax etc. is also reported.

Utilization

The bark is used chiefly for the extraction of alkaloids. Some of the alkaloids, especially quinine hydrochloride and quinine sulfate are listed in the Food Chemical Codex and used as a bitter in tonic waters and alcoholic drinks. The extract of bark is used in frozen foods, baked goods, condiments and relishes.

Pharmacological activity

The alkaloids of *Cinchona* have anti-malarial and anti-pyretic properties. Quinine is the most important alkaloid and is used as its salts, sulfate, bisulfate, hydrochloride and dichloride for the prevention and treatment of malaria. Quinidine and quinine have cardiac depressant properties, too. Quinidine, particularly its sulfate is used for treating cardiac arrhythmia.

Cultivation

The cultivation of quinine is conducted in different countries and under the different ecological conditions of three continents (America, Asia and Australia). The plant can be propagated by seed and by vegetative methods as well. Seedlings are transferred from seedbeds to nursery beds and are planted out when they are 20 to 40 cm high and 12 to 18 months old. About 1500 plants have to be planted to one hectare. Half of the trees are thinned out in the fourth or fifth year of the plantation. The bark of the thinned trees can be used for extraction. The trees being left may be harvested when they are six or seven years old. The bark is stripped from trees that have been uprooted or felled. The felling is done above ground level to permit shoots to grow from the stump and these yield very fine quills for a number of years. When the shoots weaken, the stump is uprooted. The root bark is very rich in alkaloids. The harvested bark is dried gradually, preferably in the shade. In some places artificial drying is employed. The bark is extracted by various methods. It is very common when the finely powdered bark is mixed with slaked lime and 5% aqueous solution of sodium hydroxide. The mixture is extracted with hot petroleum or toluene. The petrol extract is treated with hot, dilute sulfuric acid to convert the alkaloids into their sulfates. The quinine sulfate crystalizes out on cooling and is recrystalized from hot water. To separate other alkaloids the mother liquors has to be extracted by solvents.

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Biographical Sketch

Prof. Dr. Jenő Bernáth was born in Rimaszombat in 1944. He received his academic qualification at the University of Agriculture, Gödöllő in 1966. Between 1967 and 1992 he was employed by the Research Institute for Medicinal Plants (Budakalász, Hungary), at first as a research worker and later as scientific director. In 1989 he was invited to be an honorary professor of the University of Szeged and in 1992 the full professor of the Faculty of Horticulture, Department of Medicinal and Aromatic Plants (BKA University, Budapest). On the basis of his scientific activity he was awarded a Doctor Degree of the Hungarian Academy of Sciences in 1985 (Budapest).
His scientific activity is demonstrated by his publishing 32 books and book-chapters, 239 scientific articles and about 150 scientific lectures. Between 1974 and 2004 he acted as the editor of the international journal of Herba Hungarica and Acta Horticulturae (ISHS - International Society of Horticultural Sciences) and the editor of Newsletter of Medicinal and Aromatic Plants (supported by FAO). He was invited to be a member of the editorial board of Journal of Spices, Herbs and Medicinal Plants (USA). He has contributed to the creation of 11 new medicinal plant cultivars, two of them registered in Germany.
Between 1974 and 2004 he took positions as president of the medicinal plant working groups of the International Pharmaceutical Federation (FIP), International Society of Horticultural Sciences (ISHS), and European Co-operative Programme of Crop Genetic Resources Networks (ECP/GR). He also became a member of the presidency of the International Council of Medicinal and Aromatic Plants (ICMAP).