# Drugs of natural origin

## Technological development in Pakistan

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**Technological development of drugs of natural origin is a multidisciplinary process, starting with the identification of commercially viable medicinal plants, proceeding to the development of commercially feasible processes, and culminating in the preparation of a successful marketing strategy for the product. This article summarizes some processes relating to the development of drugs of natural origin through the utilization of indigenous medicinal plants.**

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### Introduction

It is not possible to obtain a precise figure for the total number of species of higher plants existing on earth but estimates range from 250,000 to 750,000. Only about five to ten per cent of these species, however, have been acknowledged through scientific evaluation to have real therapeutic value. It has been reported by WHO that about 80 per cent of the world's population rely on medicinal plants for their primary health care. For example, in the People's Republic of China, the production, processing and practice of herbal drugs has developed into a pharmaceutical industry.

Plant-derived drugs are being widely used not only in developing countries but also in the most advanced countries. According to a report, 25 per cent of drugs used in the USA are of plant origin, and a large proportion of these are imported from developing countries. It has been estimated that the annual world requirement of herbal drugs exceeds US$ 11 billion.

### Herbal drugs in Pakistan

There are three main sources of drugs in Pakistan. Primarily they are imported as finished products. Secondly they are imported as raw materials and then formulated into tablets, capsules, syrups and others. Finally a large section of the population depends on traditional medicines derived from medicinal plants. Pakistan has been reported to possess about 1,500 species of medicinal plants.[1] Of these, about 300 are used by traditional practitioners (*hakims*) in remote areas, where lack of modern medicine and health care is critically felt.

A huge amount of foreign exchange is spent annually on the import of raw materials for synthetic drugs. In view of the therapeutic uses of medicines and their economic importance, what are needed are a systematic study of the cultivation and propagation of medicinal plants and the development of processes to isolate their active constituents, in order to collect the scientific data that would be a base for the establishment of basic drug manufacturing in Pakistan.

## Herbs as sources of drugs

Drugs derived from plants can be divided into two groups according to their sources:

- Drugs from cultivated plants; and
- Drugs from wild growing plants.

Originally herbal drugs were considered as mixtures of imprecisely defined ingredients. With technological advancement, however, this trend has completely changed. Every laboratory working on the preparation of pharmaceutical products of plant origin wants to know what is or are the active principles. Once they know the nature of the active constituent, they next aim to extract it in pure form and market the pure substance as a pharmaceutical product.

## R&D in drugs of natural origin

The Medicinal Botanic Centre, PCSIR, Peshawar, has undertaken research studies on the commercial exploitation of medicinal plants. During these investigations, conventional as well as advanced scientific techniques have been used for the extraction, characterization and biological evaluation of active constituents. Some of the processes developed are given below.

### Aescin pharmaceuticals

Aescin, an oedema-mobilizing anti-inflammatory principle of plant origin is a mixture of *triterpene glycosides*.[2] Aescin is commercially extracted from the seeds of *Aesculus hippocastanum L*. The plant is indigenous to Europe and Asia Minor but is not reported in Pakistan. However a related indigenous species is *Aesculus indica* (Wallex camb) HKf, which is abundantly available in the Hazara Division. The seeds of the plant are biodegradable and require careful post harvest treatment.[3] The seeds are often wasted and not utilized as a source of aescin. In view of the therapeutic and commercial significance of aescin, a simple and economical process for its commercial extraction from the carefully dried seeds has been developed.[4]

The identity and purity of the extracted compound was achieved through comparison with standard aescin, using UV, IR, NMR spectroscopy, mass spectrometry and potentiometric assay.

### Alpha aescin

Aescin occurs in nature in b-form. It is a crystalline material and is water-insoluble. Pharmacological studies have shown that b-aescin is very slightly absorbed from the gastro-intestinal tract, whereas amorphous a-aescin is consistently absorbed. Water-soluble or a-aescin is therefore used in the preparation of therapeutic agents required for oral administration. By destruction of the lattice structure, the crystalline b-aescin undergoes a transformation and is converted into an amorphous form. Under the influence of an organic base and with controlled heating, the crystalline aescin was converted into an amorphous water-soluble aescin (L. Khan, 1994).[5]

### Aescin polysulphate complexes

Complexes of aescin polysulphate sodium salt are used in the preparation of therapeutic agents used for topical therapy. These complexes possess good percutaneous absorption, and enhance oedema inhibiting and antithrombotic activity.

Partially derivatized glycosides polysulphate are often prepared in the presence of sulphating agents and electron-donating solvents. Due to the complex composition of aescin and the vigorous nature of sulphating agents, direct sulphation procedures are not attempted. Under anhydrous conditions and with the use of excess sulphur trioxide complex and pyridine, the sulphation of aescin has been achieved. The reaction mixture is not too acidic and thus no decomposition of aescin and subsequent formation of mixture of products has been observed (L. Khan, 2001).[6]

### Ruscogenins

Ruscogenins are steroid sapogenins, obtained from the rhizomes of *Ruscus* species. Ruscogenins are commercially extracted from *Ruscus aculeatus*. The plant is indigenous to Europe and is not reported in Pakistan. However a related indigenous species is *Ruscus hypophyllum L*., found in areas of North-West Frontier Province (NWFP).

The plant and its rhizomes are often wasted and not utilized as a source of Ruscogenins. In view of the therapeutic and commercial significance of ruscogenins, however, studies on the indigenous plant have resulted in the development of a simple process for the extraction of the drug.

### Ephedrine hydrochloride

Ephedrine, a sympathomimetic amine occuring in the species Ephedra has been widely used for the relief of congestion in colds, allergic disorder and hypertensive states. The drug is extracted from the Ephedra herb.

An Ephedrine molecule contains two asymmetric carbon atoms and exists in four optically active forms and two racemic mixtures. Of the four forms the D(-) isomer has the greatest therapeutic activity and this is the isomer that occurs in the species of Ephedra. However, as a result of depletion of cultivated areas, the existing technology is not yielding enough ephedrine to fulfil the needs of the indigenous pharmaceutical industry.

In view of the constraints faced by the manufacturing industry, a biochemical process for the preparation of the active isomer, involving a microbiological conversion, was evolved. For biochemical synthesis of D(-) ephedrine hydrochloride, during the fermentation phase, the enzyme-catalyzed condensation of benzaldehyde and molasses in the presence of *Saccharomyces cerecvisiae* yielded acetylphenylcarbinol. The active precursor was condensed with monomethylamine and the resultant intermediate reduced in the presence of colloidal platinum. Concentration of the reaction mixture and treatment with dilute HCl yielded the desired product.

### Silymarin

*Silybum marianum,* a medicinal herb, has been used in European traditional medicine. Extracts prepared from the seeds are used in the treatment of liver diseases, and in disorders of the bile duct and spleen. Silymarin, the purified compound of the seeds, and its major isomer silybin are used in the manufacture of therapeutic agents administered for liver diseases, jaundice and gallstones. The seeds of the indigenous species have not been used as a source of silymarin or its isomers silybin, silydianin and silychristin. A simple and economically viable process has been perfected for its commercial extraction and resolution from the carefully treated seeds.

The identity and purity of the extracted compound and its isomers was achieved through comparison with standard samples, using UV, IR, NMR spectroscopy and 2, 4, dinitrophenylhydrazone assay.[7,8]

### Herbal drugs for regulating bowel functions

Herbal drugs belong to a diverse group of products, ranging from plant parts through crude extracts to purified constituents. Herbal preparations for regulating bowel functions and acute and chronic constipation are prepared from Isphagul husk, plantago ovata seeds and senna pods.

Their action is based on vegetable mucilages, which swell up on contact with water, and thus ensure pain free evacuation. As alternatives to these imported herbal drugs, seeds of Tinnevelly senna pods, Isphagul husk and Plantago ovata seeds have been blended and transformed into pellets for sugar coating.

### Vegetable pigments

Chemically, these are regarded as mixtures of hydrocarbons and their oxygenated derivatives, synthesized and accumulated in plant tissues. General classification splits pigments of natural origin into:

1. Chlorophyll;
2. Carotenoids;
3. Flavonoids;
4. Benzoquinone;
5. Naphthaquinone;
6. Anthraquinone;
7. Coumarins; and
8. Tannins.

Generally these are edible, harmless and easily prepared as compared to synthetic pigments. On account of their good compatibility with food items, pharmaceutical products, textile, leather and colour coating materials, indigenous plant materials have been utilized for new and novel plant pigments.

### Essential oils

They are regarded as mixtures of odourless and steam-volatile hydrocarbons and their oxygenated derivatives and are generally extracted from plants. Given the economic importance of essential oils, indigenous plant species like *Rosa demascena*, *Matricaria chamomilla*, *Cymbopogon citratus*, *Mentha piperata* and others have been successfully cultivated and commercially exploited (L.Khan1992).[9]

### Glycyrrhizinic acid and ammonium glycyrrhizinate from licorice

The roots of *Glycyrrhiza glabra*, commonly known as licorice, are most frequently used for the production of Licorice syrups, long employed as flavouring agents, demulcents, mild expectorants and most recently in the treatment of gastric ulcers. The sweetness of licorice is due to the presence of triterpenoid saponins and glycyrrhizic acid, which is present as calcium and potassium salts called glycyrrhizin. It is 50 times sweeter than sucrose. Its sapogenin, glycyrrhizinic acid, has been shown to possess strong anti-inflammatory and anti-tussive and cough depressant action.

### Seabuckthorn oil from *hippophae rhamnoids*

Seabuckthorn (*Hippophae rhamnoids*) grows wild in the northern areas of Pakistan. The berries of seabuckthorn are so rich in vitamins and fatty acids that they have been used in the traditional Chinese system of medicine. The medicinal value of seabuckthorn is associated with its apparent ability to promote regeneration of the skin and the mucous membrane. Seabuckthorn oil preparations are widely used to promote recovery from various skin ailments, including eczema, burns, bedsores and skin-damaging effects of the sun. Cosmetic and skin care products made of seabuckthorn are valued for their rejuvenating, restorative and anti-aging action. A simple method has been developed for the large-scale extraction of this oil from the seed powder.

### Guar gum from *Cyamopis tetragonolobus*

Guar gum is the powdered endosperm of the seed of *Cyamopsis tetragonolobus*. The crude gum contains 84 per cent of D-mannose and 16 per cent of D-galactose. The gum hydrates in cold water and is found suitable in acidic formulation. The plant is indigenous and reported to occur in many parts of the country. At present the fruits are not utilized for the preparation of guar gum, but instead are used as cattle feed. Guar gum is extensively used in pharmaceuticals as a thickening agent and as a tablet binder and disintegrator.

### Aloe gel from *Aloe vera*

*Aloe vera* contains a clear, colourless, practically odourless and tasteless viscous hydrocolloid, consisting essentially of polyhexosanes. The raw gel removed from the leaf remains unstable. After isolation, discolouration takes place and the gel loses its utility and beautifying properties. Therefore for cosmetic preparation the natural gel must be sufficiently purified and the substances responsible for degradation removed. In view of the therapeutic and commercial significance of the *Aloe vera* gel, value addition studies on the raw material abundantly available in the country were performed.

### Tragacanth from *Astragalus gummifer*

Tragacanth is the dried gummy exudation from *Astragalus gummifer* or other Asiatic species of *Astragalus*. The gum develops through injury to the stem and accumulates in the pith and medullary rays. Absorption of water causes the gum to swell and exude through the incision. Tragacanth consists of the calcium, magnesium and potassium salts of bassoric acid, known as bassorin. It is used as a suspending agent for insoluble powder, an emulsifying agent for oils and resin and a binding agent

in pills and tablets. Indigenous species of *Astragalus* will be exploited for obtaining the desired colourless gum tragacanth.

## Standardized extracts

It is essential to estimate the nature, constituents and potency of herbal extracts used for human consumption. The use of crude extracts present a number of hazards, so it is necessary to evaluate them to pharmacopoeial standards of quality, purity and safety. Moreover, any studies on the constituents of the crude extracts, which could elicit their pharmacological effects, can help in understanding their structure and activity relationships. Standardized extracts of the following herbs have been prepared:[10]

- *Tribulus terrestris*
- *Withania somnifera*
- *Mucuna pruriens*
- *Asparagus adscendens*
- *Lepidium sativum*
- *Artemesia annua*
- *Stevia rebaudiana*
- *Opuntia monocanta*
- *Gallium aparine*

## R&D plans

- Resource management, conservation and development of commercially viable medicinal plants.
- Identification of sources of plant drug adulteration and variability and methods for their standardization and value addition.
- Phytochemical studies on the nature, sources and current importance of the major classes of natural products and their future demand for the country.
- Marketing strategies for raw materials, powdered herbal drugs, crude extracts and purified constituents.
- Procedure and design for collaborative research with related institutions on natural products.
- Technological development for drugs of natural origin.

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### Databases of traditional medicines in the Asia-Pacific region

**Alternative medicines in the Philippines**
*http://stuartxchange.com/AltMed.html*

The site provides information about 30 popular medicinal plants, with detailed information on their botanical description, habitat uses, etc., and about 108 other medicinal plants. In addition to this, the information on the time and method of collection, preparation and other therapies is also available on the site.

**APINMAP - An Asian medicinal plants database**
*http://www.nal.usda.gov/pgdic/Probe/v2n3/apinmap.html*

The Asian Pacific Information Network on Medicinal and Aromatic Plants (APINMAP) resources include an integrated database containing bibliographic and factual information on medicinal plants, and a list of research projects, institutions and personnels.

**China TCM Patent Database**
*http://www.sipo.gov.cn*

Established by the Patent Data Research & Development Centre, a subsidiary of the State Intellectual Property Office (SIPO) of China, this database contains >19,000 records and 40,000 formulas from 1985 to the present

**FRLHT Encyclopedia of Indian Medicinal Plants**
*http://www.medicinalplants.in/*

This online encyclopedia of Indian medicinal plants lists the information available on each medicinal plant species such as the number of vernacular names, distribution data, trade, propagation, agro-technique, seed storage, eco-distribution maps, pharmacology and pharmacognosy, and digital images.

**Indian System of Medicine**
*http://indianmedicine.nic.in/*

This website is a gateway to information on Indian systems of medicine and homeopathic medicine and provides useful links to education, R&D, institutions, pharmacopoeia, research councils, manufacturers, medicinal plants, acts and rules, eminent people and related sites to ISM.

**TCM Database System**
*http://www.cintcm.com*

A series of databases of traditional Chinese medicine, comprises 10 Chinese and 2 English databases, including TCMLARS (Traditional Chinese Medlical Literature Analysis and Retrieval System) and TCDBASE (Traditional Chinese Drug Database).

**Traditional Chinese Medicine (TCM) - Herbal database**
*http://www.rmhiherbal.org/ai/pharintro.html#herbdb*

This is a frames based on-line reference of clinical information about over 220 herbs of the TCM-materia medica. The database includes information about botanical classification, dosage, contraindications, preparation, physiological notes, and traditional Chinese clinical indications.