Introduction

INTRODUCTION

Medicinal properties of plants were known to Indian people as early as 4500-1600 B.C. when Rigveda was written. Rigveda contained mention of a number of medicinal plants. Atharvaveda, which was written later, also included mention of some more plants used for the cure of diseases. Eversince the publication of Ayurveda (written between 2000-600 B.C.), medicinal uses of plants spread to different parts of the world, which was highly instrumental in the generation of a perpetual interest and curiosity for identification and production of plants for natural compounds of medicinal value.

The eight divisions of Ayurveda were followed by two important works namely "Sushruta Samhita" and "Charaka Samhita", written during 1000 B.C. The former deals with comprehensive accounts on therapeutics and the latter contains a remarkable description of "materia-medica", as known to the ancient Hindus. Later, during the Buddhist period, considerable progress was made and medicinal plants were cultivated under the direction of highly qualified specialists.

The Hindu system of medicine suffered a set-back during 1300-1600 A.D. when the Muslims brought their own system of medicine known as "Unani" system, which also gave considerable emphasis on plants as sources of drugs. In fact, during later period, the two systems of medicines gained considerable knowledge from one another and a great amount of work pertaining to collection, description and standardization of botanical drugs were worked out. The practitioners of various Indian systems in different parts of the country tried to utilize the locally growing plants as far as possible and accepted those which were found useful after clinical trials.

With the beginning of European as well as Western influence during 16th-17th century, it was the Christian period of Indian history when our knowledge regarding indigenous drugs increased considerably by virtue of systematic and scientific research. The first pharmacopoeia in India was published in 1863 and was followed by publication of comprehensive work on Indian medicinal plants in the form of "Pharmacographica India" by Dymok, Warden and Hooker (1890-1893),

which described the therapeutics used both in Eastern and Western systems of medicines. A summary of all previous works, combined with the most up-to-date account of medicinal plants was published in "Dictionary of Economic Products of India" by Sir George Watt (1889-1904). Consequently, physiological, biochemical, ecological and pharmacological aspects of plants began to be probed systematically which led not only to further broadening of our knowledge on medicinal plants but also opened up new vista of study of medicinal plants.

Due to varied soil and climatic conditions as well as altitudinal ranges, India has a very rich floral wealth, the vascular plants only being more than 15,000 species; out of which about 2,500 species are known to possess medicinal and aromatic properties . It is to be noted, however, that only three percent of the above has been recognised by Indian Pharmacopoeia for the use in medical therapy.

Medicinal plants are abundant in the tropical, temperate and alpine zones of Eastern and Western Himalayas of India. Of late, a few species are also being commercially cultivated in different parts of the country. The Directorate of Cinchona and other Medicinal Plants of West Bengal has been especially spearheading the cultivation of medicinal plants in Darjeeling Hills. Some of the important species presently being cultivated are cinchona (Cinchona ledgeriana, C. robusta, C. succirubra), ipecac (Cephaelis ipecacuanha) and dioscorea (Dioscorea composita, D. floribunda and D. prazeri). Ipecac, the "Green Gold", called both for its unique medicinal property and high economic potentiality, is one of the most important plants being cultivated in the lower foot hills of Darjeeling in India.

The drug ipecac or ipecacuanha is the dried root of Cephaelis ipecacuanha (Brotero) A. Richard belonging to the family Rubiaceae. Ipecaucuanha is the Portugese name derived from Brazilian-Indian "Ipe-kas-guena" meaning "a creeping plant causing vomitting" (Habib and Harkiss, 1969). There are two principal commercial varieties of this drug, each named after the locality from where it was originally collected. They are : (i) Rio or Mattogrosso and Minas from Brazil; and (ii) Cartagena, Nicaragua, Panama and Savanilla from Nicaragua and Columbia.

Rio ipecac : Rio ipecac, also known as Mattogrosso and Minas variety, grows as wild undershurb in the moist, dense tropical forest in Brazil and Bolivia. At present it is also cultivated in the Indies and Federation of Malaya where it yields the commercial variety known as Johore ipecac. Rio ipecac root is reddish brown to dark brown and somewhat tortuous. Some roots are wiry and annulated; others are smooth and slender. The Minas variety closely resembles the Rio but the average alkaloid content is lower.

Cartagena ipecac : It is mainly obtained from plants growing in the damp and dark forests of Columbia, Nicaragua, Panama and Venezuela and is also known as Nicaragua, Panama and Savanilla ipecac. It closely resembles the Rio ipecac but is reported to be somewhat thicker roots with less pronounced annulations and larger starch grains.

The Indian ipecac is of Brazilian origin but it has assumed distinct characters probably due to the effect of different environmental factors prevalent in the region where the plant has been under continuous cultivation since many years. Brazilian ipecac is, by far, the most desirable source of the drug because of its highest emetine content which comprises the major portion of its alkaloid fraction.

History and nomenclature

Till 17th century when ipecac was unknown to the people of other parts of the world, the natives of Brazil used it for the treatment of diarrhoea and dysentery under the name "Igpecaya, Pecaya and Poaya" (Anonymous, 1971). The first European to become acquainted with the plant was Manoel Tristao - a Portuguese who, from 1589 to 1617, had been a pharmacist at different hospitals in Brazil.

In 1672, Le Gras, for the first time, brought ipecac root to Europe and introduced it as a medicine. But he could not work out the proper dosage. Jean Adreine Helvetius, son of a Dutch quack, learnt about ipecac root from a merchant named Garnier. In 1686, after working out proper dosage, Helvetius began to sell it as a secret remedy for dysentery. Later, the fame of this wonder drug reached the French court. After successful cure of the dauphin with Helvetius'

remedy, Louis XIV declared it a public property and offered money and honours to Helvetius for his wonder remedy (Anonymous, 1971).

When Hans Sloane of England and Leibnitz of Germany recommended the plant for dysentery in 1696, it became popular by the name Radix antidysenterica. After thirty years, Thomas Dover of Great Britain mixed ipecac powder with opium to produce the popular "Dover's diaphoretic powder". In 1788, both ipecacuanha and Dover's powder, for the first time, appeared in Pharmacopoeia Londinensis (Anonymous, 1971).

Ipecac was included in the critical list of drugs during the period of American Revolutionary War. According to the Army General Andrew Craigie, on December 2, 1775, there was only one pound of ipecac available for the entire army personnel. Therefore, John Morgan, the then Director General of Continental Army, had to send Barnabas Binny to Philadelphia in search of more ipecac but only 10 pounds of ipecac, that was available, could be purchased by him (Anonymous, 1971).

The actual source of the wonder drug ipecac remained a subject of dispute till the end of 18th century. In 1800, Antonio Bernandino Gomez, a physician in the Portuguese Navy, brought authentic specimens of the plant from Brazil to Lisbon where it was identified by another Portuguese, Felix de Avellav Brotero as Calicocca ipecacuanha (Fisher, 1973). In 1820, ipecacuanha was made official in the First United States Pharmacopoeia. In 1831, John Redman Coxe, M.D. described Cephaelis in American Dispensatory as Calicocca ipecacuanha (Griffenhagen, 1971). According to him the term "ipecacuanha" in South America implies "vomitting roots".

In due course ipecac plant was described as Cephaelis ipecacuanha in the United States and British Pharmacopoeias and the same name was accepted by International Code of Botanical Nomenclature (Fisher, 1973).

It was Sir George King who introduced the plant to India in 1866. He brought the plant from Kew, England to Royal Botanic Garden, Calcutta. But in 1870-71,

lack of follow-up care resulted in total mortality of the plants. The credit for the successful acclimatization and long-term cultivation of this plant in India goes to Dr. T. Anderson (Watt, 1972).

Three plants which had been sent from Kew to Rongbee Plantation of Sikkim in 1868 grew rather better. The population was increased to 300 by August, 1871 through root-propagation method. Trials were also conducted in Botanic Gardens at Barliar in Tamil Nadu by Mr. Mclivor in 1870 which succeeded fairly well. Three consignments of plants numbering 370 were received from Scotland in 1871-72, besides a smaller number from Royal Gardens, Kew. With these collections, the propagation had been so extensive that on 31st April, 1873, there were altogether 6719 young ipecac plants in Sikkim and 500 in Calcutta.

In Assam, the first trial of ipecac cultivation was undertaken sometime in 1949-50 at Nongpoh in United Khasi and Jayantia Hills at elevations of 450 to 820 m which was found to suit the species.

Ipecac was introduced to Mungpoo in 1871. However, its commercial cultivation took a long time for a successful beginning. In 1953, the cultivation of this valuable plant was undertaken by the then Medicinal Plants Committee of West Bengal. The foot hills of Rongo in Darjeeling District proved to be the best site for its cultivation and it was started there in 1957. Large-scale cultivation of ipecac soon began at Mungpoo, Munsong and Latpanchor at elevations of 500 to 900 m during the 1970s. Further extension of ipecac cultivation was speeded up in the subsequent years. The total area under ipecac cultivation in Darjeeling District at present (as by 1988) would be more than 100 hectares.

Botany

It is a perennial, straggling evergreen herb (Plate I) growing upto 60 cm in height. The roots of a luxuriantly grown mature ipecac plant measure upto 40 cm in length and 0.4 to 0.6 cm in diameter. The roots are in tufts, the secondary roots are also frequently branched. They have a thick yellowish-brown bark with a number of deep transverse incomplete furrows imparting a characteristic annulated appearance. The main stem is hard, sparingly branched,

Plate I. **Cephaelis ipecacuanha - habit.**

marked with leaf scars, green when young and brown when mature. Leaves are rich green in colour, simple, coriaceous, opposite-decussate, entire, elliptic-ovate, acute, with cuneate base. Stipules are interpetiolar, bilobed, lobes fimbriate, persistent. The petioles are short.

When about 10-month to 1-year old, the plant starts flowering in the month of March-April (Plate II). The inflorescence is cymose head borne at branch apices. The peduncle is brownish-green, more or less pubescent and somewhat horizontally oriented. The flowers are interspersed with an involucre of bracts which are foliaceous and arranged in two or more rows. The outer bracts are larger, slightly pubescent and elliptic-ovate. The midrib of the bract is grooved and the apex is reflexed. Inner bracts are smaller, linear-lanceolate, alternating with the outer ones. The flowers are small, scentless, erect, sessile, bisexual, actinomorphic, isostemonous, typically pentamerous but the number of floral parts vary very often. The flowers are dimorphic, showing heteroanthy and heterostyly. Calyx is regular, gamosepalous, persistent with green tube. Calyx limb is usually 5-lobed but the number varies from 4 to 9, the lobes are brownish green and has an acute apex. Corolla is regular, gamopetalous, nearly rotate, limbs curved outwards and white in colour. The number of petal is usually 5, often 6, but varying from 4 to 9. Corolla is erect, lanceolate, sparsely pubescent and the neck is hairy. Stamens are white, epipetalous and antisepalous, attached to the neck of corolla tube. Two types of stamen are found, one with long filament and the other with short filament. Anther is white, introrse, dorsifixed and bilobed, lobes unequal. Dehiscence of the anther is apical. Pollens are more or less round. Pistil is bicarpellary and has three morphological types (one with short, one with mid and the third with long style). Style is white, filiform, glabrous, glandular. Stigma is bifid with recurved tip but in short styled pistils it is straight. Ovary is inferior, enclosed within the calyx tube, ellipsoidal, elongating with maturity, 2-chambered with single ovule in each chamber, placentation axile.

By November-December, the fruits ripen, becoming dark magenta in colour. Each ripe berry contains two cream-coloured seeds, each of which is enclosed in a hard stony, straw-coloured pyrene which is flat on the inner side and convex

Plate II. *Cephaelis ipecacuanha* plants in bloom.

on the outer side. Seeds need a post-ripening period of 40-60 days.

Cytology

Young root-tip squash studies have shown that the diploid chromosome number of ipecac is 22. The chromosomes are, in general, very small in size and have a length of 3 to 4 µm. 4 pairs have median and 6 have sub-median constriction while the remaining one pair is of a comparatively larger size with prominent secondary constriction.

Biochemistry

The medicinal properties of ipecac is due to the presence of the alkaloid, *emetine* which is the principal alkaloid obtained mainly from the roots of this plant. Besides emetine, the other major alkaloid is cephaeline. It is a phenolic alkaloid and very toxic, but can be converted into emetine by methylation of the phenolic hydroxyl moiety. Besides emetine and cephaeline, a few other minor alkaloids like psychotrine, O-methyl psychotrine and emetamine have also been reported from ipecac root.

Emetine : Emetine ($C_{29}H_{40}O_4N_2$) was discovered in 1817 by Pelletier and Magendie. It is colourless amorphous powder which is bitter in taste. It is sparingly soluble in water and light petroleum, slightly soluble in benzol and readily soluble in alcohol, ether and chloroform. It turns brown on exposure to light; softens at 70°C and melts at 74°C.

Emetine hydrochloride ($C_{29}H_{40}O_4N_2$, 2HCl, $7H_2O$; M.W. : 679.7) has been crystallised from water in which it tends to form supersaturated solution and separates amorphously. This salt usually occurs as heptahydrate form and appears colourless to slightly yellow. It is odourless, bitter in taste, amorphous, freely soluble in water, ethanol (95%) and chloroform. Emetine hydrobromide is the *stage usually employed during the purification of emetine hydrochloride.* The hydroiodide and the nitrate can be crystallised from either water or alcohol whereas its sulphate is highly soluble in water.

Test for emetine hydrochloride :

i) When 10 mg of emetine hydrochloride is dissolved in 2 ml of hydrogen peroxide solution and heated with 1 ml of hydrochloric acid, an orange colour is produced.

ii) When 5 mg of emetine hydrochloride is sprinkled on the surface of 1 ml of a 5% w/v solution of ammonium molybdate in sulphuric acid, a bright green colour is developed.

Cephaeline : Cephaeline ($C_{28}H_{38}O_4N_2$) melts at 115°-116°C. It crystallises from ether in chloroform and forms colourless needles. It is sparingly soluble in water, ether and light petroleum and readily soluble in acetone, alcohol, chloroform and aqueous alkali solutions. The hydrochloride or hydrobromide is more crystalline compared to corresponding salts of emetine while its sulphate, hydroiodide and nitrate are amorphous.

Psychotrine : Psychotrine ($C_{28}H_{36}O_4N_2$) melts at 120-138°C. It crystallises from dilute acetone-alcohol. It is soluble in acetone, chloroform and alcohol but sparingly soluble in ether and benzol.

O-methyl psychotrine : O-methyl psychotrine ($C_{29}H_{38}O_4N_2$) melts at 123-124°C. It can be isolated from the mother liquors of emetine in the form of its acid oxalate. It crystallises as acid oxalate together with emetamine from which it can be separated by treating in chloroform with dilute H_2SO_4.

Emetamine : Emetamine ($C_{29}H_{36}O_4N_2$) is soluble in alcohol, benzol and chloroform and sparingly soluble in ether and insoluble in alkalies. When regenerated from salt in ether, it crystallises forming colourless needles with melting point 138°-139°C and from ethyl acetate it forms colourless needles with melting point 153°-154°C.

Colour reactions of the alkaloids

Emetine gives a greenish-yellow colour with concentrated sulphuric acid and molybdic acid, but its hydrochloride produces a green colour under similar

conditions. Emetine assumes an intense and permanent yellow colour with solution of chlorinated lime and a little acetic acid. Calcium chloride in hydrochloric acid gives a deep yellow colour with emetine and cephaeline. Cephaeline with a mixture of sulphuric acid, molybdic acid and a trace of hydrochloric acid gives a dull greenish-blue colour. Both emetine and cephaeline give precipitates with mercuric chloride, platinic acid, phosphotungstic acid, Mayer's reagent, potassium bismuth iodide and potassium iodide. When bleaching powder is added to a solution of the alkaloids in dilute hydrochloric acid, orange colouration is developed. Cephaeline gives a bright blue colour with Froede's reagent and hydrochloric acid. Psychotrine gives a green colour with sulphuric acid and molybdic acid, a green colour with Froede's reagent and hydrochloric acid. O-methyl psychotrine and emetamine gives an emerald-green colour in sulphuric acid and vanadium oxide.

Besides these alkaloids, a few other compounds are also present in the root. A crystalline yellow colouring matter which forms a purple red compound with alkaloid has been identified as erythrocephaeline along with choline. A colourless glucoside ipecacuanhin, a phytosterol together with large amount of starch, tannins, maleic acid, citric acid, saponins, resin and fat have also been reported in ipecac root.

Pharmacological uses of emetine

The principal and specific therapeutic use of emetine lies in the treatment of amoebiasis. Injection of emetine hydrochloride decisively controls the disease. The causal organism, Entamoeba histolytica is readily killed by the salt especially when it is embedded in the intestine and not free-swimming. In bacillary dysentery, however, emetine is totally without effect. In diarrhoea and some cases of dyspepsia, especially when associated with functional derangement or torpidity of the liver as well as in chronic constipation, it acts beneficially (Watt, 1972).

In large doses, it is emetic and removes indigestible matters from the stomach. Therefore, in earlier times, the most common use of ipecac was as emetic

in stomach poisoning. Ipecac acts directly on vomiting reflex centre in the brain to cause vomiting (Anonymous, 1981). In small dose it acts as expectorant and also used in catarrhs, chronic bronchitis, asthmatic emphysema, tuberculosis and disorders of lungs and early stages of whooping-cough. When mixed with opium, it also acts very satisfactorily as diaphoretic. It has also been beneficially used in hydrocephalus.

Emetine is highly irritating to gastric mucosa. Large doses injected subcutaneously or intravenously act as depressant on the motor and respiratory centres. It has been used in haemophilia and hepatic abscesses. In haemorrhages, especially in uterine cases and menorrhagia, it has proved to be an effectual remedy. It is also used as counter-irritant. The powder moistened and made into a paste is applied locally to control the stings of venomous insects. In such treatment, it allays the pain and irritation in a remarkable manner.

Action of cephaeline is, to a large extent, similar to that of emetine but it is more toxic and irritant whereas psychotrine is considered to be non-toxic, but inactive.

In recent times emetine hydrochloride is being pre-eminently used in cancer chemotherapy. The toxicity limits of this alkaloid have already been worked out in Cancer Chemotherapy National Service Centre, National Institute of Health, U.S.A. With correct dosage, emetine hydrochloride can prove to be one of the safest chemotherapeutants for certain types of cancer (Fisher, 1973).

Agronomy

Ipecac is a shade-loving plant and it is sensitive to direct exposure to sun and to high as well as low temperature. Cultivation is done under artificial shade (Plate IV). The plants require moist climate and steady temperature ranging from a minimum of 18-20°C to a maximum of 36-38°C and annual rainfall of 150 to 500 cm.

The plants are normally raised from seeds; though stem, leaf and even root

cuttings can serve good sources of propagules. The nursery beds prepared under shade are divided into a number of compartments, locally known as 'kamras'; each kamra has an area of 3.34 sq. m (2.74 x 1.22 m). The beds are built on slopy area to avoid water stagnation and are usually raised 15-20 cm above the level of the ground. Three-fourth of the depth of the bed-soil comprises of leaf mould which increases fertility, improves moisture-retention and facilitates proper growth of roots.

Seed sowing : Seeds are soaked in water for 24 hours and light, non-viable seeds are discarded. The viable seeds are then sown on raised seed beds under artificial shade at the rate of 100 g per kamra. One has to be very careful regarding the season of seed sowing. Taking into consideration of some relevant factors, the best time for seed sowing is the middle of February to early March. Proper and judicious watering is very important. Seed germination depends on different factors like temperature, light, pH and moisture content of the medium. Germination is slow and starts about 80-90 days after seed sowing. The process of seedling emergence is very erratic and it takes a couple of months from the initiation of germination to complete the germination process. This exposes the seed bed to a high incidence of weed-growth. For the control of weeds and to facilitate earlier germination, mulching of beds with perforated black polyethylene sheet is generally practised (Plate III). Black polyethylene cover over the soil surface increases the ambient temperature, retains higher moisture level and speeds up germination process. Altitudinal placement of nurseries also affect the germinability and the rate of germination. A lower altitude favours better germination.

Transplanting : The seedlings are usually transplanted twice. The initial transplantation is done in the month of July at the spacing of 5 cm x 5 cm when the seedlings attain a height of 2.5 to 3.0 cm. The final transplanting is done at the spacing of 10 cm x 10 cm after 200 to 240 days of the first transplanting. Delayed transplanting results in poor survival and ultimately reduction in the yield of root biomass.

Maintenance : Ipecac plants need constant care for a good growth and satis-

Plate III. **Seed bed of Cephaelis ipecacuanha.**

Plate IV. **C. ipecacuanha plants growing under shade.**

factory yield. Weeding is done as and when necessary. The plants are watered daily and even more than once a day, in dry and hot spells of summer. Though the plants need high moisture-level, the beds have to be protected from being hit by direct rain as it would lead to the uprooting of young plants in their early stages of growth. Soil-working is done to facilitate increased aeration which thereby enhances proper growth of roots.

Harvesting : Though the stands on the bed can be maintained for more than 4-5 years, they are generally harvested at the age of 3 years. It has been established that with the increase of plant age, the emetine/cephaeline ratio decreases. For harvesting, the beds are forked and the plants are properly dug out. Whole plants are taken out of the soil; root portions are separated by cutting at the root-stem transition zone. The roots are then washed, dried and stored. Because of negligible alkaloid content, the upper portions of stem and leaves are generally discarded.

In Nicaragua where ipecac plants grow wild as common forest-floor species, these are combed by the native root-diggers every year. The plant thus gathered are not usually more than one or two-year old.

Yield and value : The average yield of dry root from a good plantation is 800-1000 g per kamra of 3.34 sq. m area. The dried roots are sold at $ 35-40 (Rs.440-500/-) per kg depending on their emetine content. It is remarkable that no synthetic drug or antibiotic has yet been able to replace this wonder drug. The international demand for the drug is quite high. Ipecac roots of Indian origin have earned an enviable market reputation and have already proved to be a valuable foreign exchange earner.