CHAPTER 1

Introduction
During the long history of mankind the importance of plants has been immense. Prehistorically, the detection of plants as sources of food, fabric, and medicine attested to human's curiosity driven in large part by a quest to survive and flourish. Traditionally people use a wide range of plants to maintain their health. Many such plants have been selected empirically for generations, a continuing experimental process still underway. Modern medicine has benefited from anecdotal results of these experiments by selecting needed plants and herbs for a currently inadequate pharmacopoeia to treat large number of diseases and symptoms.

Nature has bestowed enormous curative potential to plants. For centuries, therefore, mankind banked on the natural resources for the treatment of various kinds of disease. In the course of time, a large number of plants, which were brought into therapeutic use, were called as 'Medicinal plants'. From the modern scientific point of view, this classification seems ambiguous. Every plant, by virtue of its chemical constituents, excluding the highly toxic compounds, can find its utility in medicine, at one place or the other. However, for the sake of brevity, one may confine to the traditional system of classifying plants according to their common use.

The realm of modern pharmaceutical research lies in the creation of therapeutic, prophylactic and diagnostic substances having specific action and minimum contra indications. This has received great impetus from the study on the chemistry of natural products. Such studies have not only offered a fascinating variety of new and potent drugs, but have facilitated the design of prototype synthetic medicines.

Approaches to the study on the chemistry of medicinal plants have been multi-pronged, covering fields like structural elucidation of natural
products, their genesis and pharmacology. This resulted in perceptible progress in understanding the basis of their pharmacological properties and the mechanisms of their drug action. Further studies on the chemosystematic and chemotaxonomy have presented alternatives for a particular herbal drug.

Early searches for edible plants, must have turned down those that besides being non edible were also toxic and between these extremes, a large number of interesting plants which relieved pain or fought symptoms of diseases when used in small amounts. From these early findings, refined and extended as they were passed from generation to generation, sprang industries and technologies based on the products isolated from these plants and required by the developing needs of the civilized world. The use of these products, their analogs and semisynthetics reached a zenith in the late 19th century during a period of unprecedented growth and diversity of industrial phytochemistry only to recede under competition with synthetic organic chemistry during the 20th century. In many ways, human nurtured in the European culture and became antithetic to their prehistory or became increasingly independent of plants in every day life and as a consequence, they found little need to study them in any serious and rigorous way.

Assuming that this renewed interest in plants will continue and develop in the 21st century. Unfortunately, a new demand coincides with an accelerated destruction of tropical rain forests, where the majority of species grew, so that the annual loss of 20,000 species suggested by some individuals, over and above normal rates of extinction is clearly shrinking forever the world’s diversity of useful plants.

The plant kingdom has long served mankind as the veritable source of useful drugs. Classical examples such as the analgesic drugs: Morphine, anti-malarial, Quinine, anti-amoebic, Emetine, diphoretic, stimulatory, Ephedrine, enphoric, Cocaine, anti-hypertensive and tranquilizing, Reserpine; heart drug digitalis glycosides and the
anticancer agents Vinblastine, Vincristine and taxol serve to remind us of the debt that modern medicine owes to plant drug constituents. Each of these drugs has an interesting history of discovery and development, extending in some cases to several centuries, and often its application in modern medicine is predated by its use in traditional medicine. All these drugs have survived the test of time which again is a unique performance not found often in synthetic drugs.

Many users of herbal medicines believe that remedies from natural sources are more in harmony with the body's natural physiological laws than any other synthetic drug. This has prompted scientists and clinicians to renew their interest in phyto-pharmaceutical research. It is the current feeling that those concerned with new drug development should initiate effective programs to explore plants for biologically active substances that up till now have escaped the imagination of synthetic chemists.

The practical problems of plant drug research can be broadly divided into two parts, viz, the economic and the scientific. The first part of this problem constitutes the apathy on the part of established pharmaceutical concerns to provide funds for development of drugs from plants. The second part of the problem also is very potential. Medicinal plant research in chemical and pharmaceutical laboratories has been carried out only in bits and pieces without any coordination amongst the scientists. The number of higher plants that can be found growing on the surface of the earth is approximately 0.5 million. So far only about 5% of these plants have been investigated by chemists and biologists. The investigations have been carried out generally in search of particular class of low molecular weight plant metabolites e.g. Alkaloids, Phenolics, Steroids and related entities, for their structural elucidation.

In the first instance, a plant has an excellent method for elaborating big, complex and conspicuous molecules from carbon dioxide and water. Most of these have defied the efforts of organic chemists to
duplicate them in laboratory. Moreover, whenever such duplications have been attempted, the processes are mostly uneconomical to permit their commercialization. Secondly, within a plant, a natural product is elaborated with high degree of stereo-specificity. A laboratory synthesis, on the other hand, generally leads to the formation of stereo-isomers. Not only is their separation a difficult task but their therapeutic index also changes, because it is highly dependent upon the stereo-chemistry of a natural product. Sometimes a change in the stereo-chemistry makes a compound highly toxic.

There is a bewildering group of diseases, such as Cancer, Leprosy, Arthritis and Asthma, for which there hardly exists any synthetically prepared therapeutic drugs. It has, therefore, necessitated the exploration of effective natural products. It would not be an exaggeration to claim that phytochemicals have, to a large extent, facilitated the management of most of such vulnerable diseases.

Primarily, the plant metabolites are divided into two categories, namely primary metabolites and secondary metabolites. The former includes compounds like carbohydrates, fats, vitamins and enzymes. These products are vital to the growth and maintenance of human body. The secondary metabolites incorporate compounds like Chalcones, Coumarines, Flavonoids, Chromones, Terpenoids, Steroids and Alkaloids. These serve as the therapeutic agents.

In any programme in which the end product is to be a drug, biological evaluation is necessary. There is no doubt that herbal medicines are also drugs and their pharmacological, toxicological, immunological and chemical evaluations must obviously be carried out. The search for specific activities often overlooks other useful activities, which are not detected, or are ignored, in the screening process. There is a real need for reliable general bioassays, which can detect a broad spectrum of pharmacological activities in higher plants and, yet can be employed by those who are interested in drugs from plants in house, at
low cost, to guide phyto-chemical screening and fractionation\(^2\). Some of the most active principles are toxic at elevated doses (There are exceptions, which may not be considered at this stage), a possible approach of developing an effective bioassay might be simply to screen substances that are toxic to zoological systems. One such simple assay method, utilising brine shrimp (Artemia salina Leach), is available for determination of toxicity of plant products\(^8\).

The failure to obtain reproducible pharmacological results from one lot of plant extract is another vexing problem. This is due to failure to collect the same specimen having the same degree of maturity, on separate occasions. The importance of documenting the collections is thus reiterated. Secondly, it is possible that a compound exhibits one type of activity at a lower dose and an appropriate activity at a higher dose (biphasic response) giving rise to abnormal dose response curve. Thirdly, false negative responses are occasionally produced in the pharmacological screens even though the extracts are chemically found to contain active compounds. A logical explanation for this negative response could be that the active compounds are present in insufficient quantity in the extracts to elicit any perceptible activity at the dose levels used. Another possibility is that, if the compounds are present in appreciable amounts, could it also be that there are pharmacologically antagonistic compounds. It may not be an easy task to efface these drawbacks. However, some of the following measures can be adopted. The extract can be fractionated into lipid soluble, water soluble, basic, acid, phenolic and neutral fractions and then subjected to pharmaceutical screen. Another alternative could be to isolate the different groups of substances present in the extract and to study their pharmacological effects separately.

Natural product chemists never consider active principles of medicinal plants in isolation when they examine the therapeutic efficacy of plants. The intimate association of medicinal plants with synergistic,
antagonists, and toxic principles *vis-à-vis* active principles are also considered at the time of investigation. However, it should be emphasised that manifestation of drug action of a medicinal plant is to be understood at molecular levels, since the drug receptor interaction is essentially a chemical phenomenon. Practitioners of traditional medicine believe that there are in-built antibodies in plant which neutralise the toxic effects, if any. It is also believed that plants contain ingredients, which modify the rate of digestion, absorption and assimilation of the herbal drug and impart a sobering effect on the toxicity. Each herbal drug preparation, single or compound, is to be subjected to detailed physical, chemical, pharmacological and toxicological analysis in order to obtain prima facie evidence if it can be tried in humans and finally, it is put to extensive clinical trials before endorsing the billing 'drug'.

Throughout the history, mankind has passed an information about efficacious and non-toxic medicinal plants by word-of-mouth and through various writings. As a result of this continual refinement of knowledge, about 20,000 plant species are now used for medicinal purposes around the world. Crude plant drugs became used as aqueous or alcoholic extracts and chemical work resulting in the isolation of their active principles began in earnest in the 19th century. The activity directed isolation of plant principles continues in many academic, government laboratories today wherein extracts exhibiting a particular biological activity or interest are purified chromatographically, guided by periodic evaluation with one or more bioassay systems, resulting in the eventual isolation of one or more biologically active constituents.

Observations made by local populations have played a large part in the development of plant derived drugs. Of the previously mentioned 119 important plant derived drugs reported by Farnsworth and Colleagues, 1987, 88 (74%) were judged as having their origin in traditional medicine. A good example of this is Digitoxin (1) which is the principal cardiac glycoside constituent of *Digitalis purpurea* L. (Purple foxglove),
and remains an important drug for the treatment of atrial fibrillation. The propensity of *D. purpurea* in treating dropsy (edema), mediated by heart failure, was first documented in 1776 by an English Physician, William Withering, after he had observed the folkloric use of the plant for this same disease state.

![Digitoxin (1)](image)

Although plants have a long history of use in the treatment of cancer^9, many, if not all, of the claims for the efficacy of such treatment should be viewed with some skepticism because cancer, as a specific disease entity, is poorly defined in terms of folklore and traditional medicine^10. Amongst the best known are the so-called *Vinca* alkaloids, Vinblastine^11 (2) and Vincristine^12 (3) isolated from the Madagascan Periwinkle, *Catharanthus roseus*. This plant was used by various cultures for the treatment of diabetes, and these compounds, together with two other related active alkaloids, Vinleurosine and Vinsosidine, were isolated during an investigation of the plant as a source of potential oral hypoglycemic agents. Therefore, the discovery of the initial two compounds may be indirectly attributed to the observation of an unrelated medicinal use of the source plant.

The parent compound of the two clinically active agents Etoposide^13 (4) and Teniposide^14 (5) is epipodophyllotoxin. This is the naturally occurring epimer of podophyllotoxin^15 (6) which was isolated as the active anti tumour agent from the roots of various species of the
genus *Podophyllum*. These plants possess a long history of medicinal use by early American and Asian cultures, including the treatment of skin cancers and warts.

![Chemical structure of Vinblastine and Vincristine]

Although podophyllotoxin was investigated at length by the National Chemical Laboratory (NCL), Poona as a potential anti tumor agent it was shelved due to intractable toxicity problems.  

![Chemical structures of Etoposide and Teniposide]
Podophyllotoxin (6)

Camptothecin (7) was isolated from the Chinese ornamental tree *Camptotheca acuminata*, by Wani and Wall contemporaneously with the initial discovery of taxol. As the sodium salt camptothecin was advanced to clinical trials by NCL, Poona in the 1970s, it was however dropped because of severe bladder toxicity\(^{17,18}\).

Camptothecin (7)

Latter on it was modified by National Cooperative Drug Discovery Group involving Johns Hopkins University and the then Smithkline Beckman. From these studies eventually came the modified camptothecin, Topotecan\(^{19}\) (Hycamptin), which was approved for use in the USA in 1996.

The complex diterpene Taxol\(^{20}\) (Paclitaxel) initially was isolated from the bark of *Taxus brevifolia*, collected in Washington state as part of a random collection programme by the United States Department of Agriculture for the National Cancer Institute\(^{21}\). Historically, parts of the
Yew tree (*T. brevifolia* and other *Taxus* species) had been used by several native American tribes for the treatment of some non-cancerous conditions and leaves of *T. baccata* are used in the traditional Asiatic Indian (Ayurvedic) medicinal systems, with one reported use in the treatment of cancer.

![Chemical structure of Taxol](image)

**Taxol (6)**

Paclitaxel, along with several key precursors (the baccatins), occurs in the leaves of various *Taxus* species and the ready semi-synthetic conversion of the relatively abundant baccatins into paclitaxel, as well as to active paclitaxel analogy, such as Docetaxel\(^{22}(9)\), has provided a major, renewable natural source of this important class of drugs.

![Chemical structure of Docetaxel](image)

**Docetaxel (9)**

The flavone, flavopiridol\(^{23}(10)\) is currently in Phase I/II clinical trials against a broad range of Tumors, while flavopiridols is totally synthetic, the basic for its novel structure is the natural product
rohitukine (11) isolated from *Dysoxylum binectariferum*\textsuperscript{24}. Flavopiridol has a very interesting mechanism of action in that it is an inhibitor of cyclin dependant kinases. Flavopiridol is not the only CDK inhibitor discovered from a natural source which is then extended to give semi synthetic and synthetic compounds with a variety of potencies and specificities.

![Flavopiridol (10)](image1)

![Rohitukine (11)](image2)

Although Epinephrine\textsuperscript{25} (adrenaline) was discovered from natural sources. The Chinese had known of the potential of the plants *Ephedra sinaica* and *E. equisetina* for millenia\textsuperscript{26} as treatment for asthmatic and other bronchial conditions and then in 1923, Chen et al obtained pure Ephedrine\textsuperscript{(12)} from *E. sinaica* and demonstrated that its physiological actions were very similar to adrenaline, causing elevation of blood pressure, plus inotropic and chronotropic actions on the heart. Following regulatory, approval, it became the first in a very long time of bronchodilators /cv agents.

![Ephedrine (12)](image3)
India is a veritable emporium of aromatic and medicinal plants. About three fourth of the drugs mentioned in various pharmacopoeias grow wild in the country. In her northern region the state of Jammu and Kashmir is a superb botanical garden of these plants and, therefore, offers a great deal for fruitful research. A wide range of flora, particularly, the flora of alpine regions, of this state remains chemically uninvestigated. It is well known that trace constituents influence pharmacological properties of a plant, to a large extent. For obvious reasons, detailed studies on the chemical composition of many plant species, of this region, which have been previously investigated for their major components, alone have to be undertaken. Since, the state is industrially underdeveloped and its forest wealth extends ample opportunities for setting up plant based chemical industries, the basic data for commercialization of medicinal plants has to be compiled, before studying the process of development.

The present work, was, therefore, undertaken to study the detailed chemical composition of four plants, namely Lavaterea cachmiriana, Salvinia natans, Inula racemosa and Aralia cachemirica. The pharmacological activity of some of the compounds, isolated during the present investigation and their synthetic derivatives has also been carried out.
REFERENCES


