CHAPTER - 1
INTRODUCTION

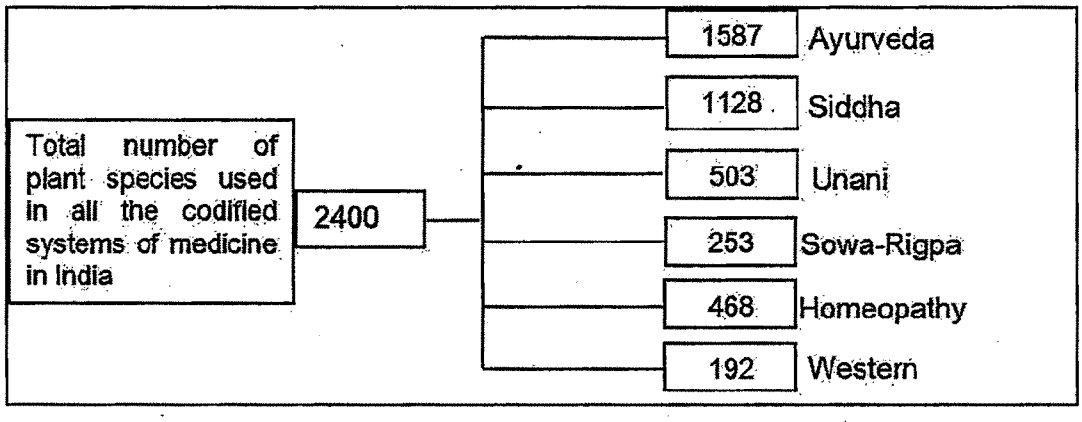
1.1 Traditional herbal medicines

Traditional medicine in India has its ancestry in the very rich and assorted health care practices that include the codified systems like Ayurveda, Siddha, Unani on one hand and the largely oral folk traditions on the other. These traditions, having evolved in the lap of nature, rely mainly on natural resources available in the environment with plants forming the major resource.

"*Jagatyevamanoushadham na kinchit vidyate dravyam vasatnanartha yoga yoh*"

- Jivaka (Astanga Hriday SU. 9-10)

It literally means "there is no plant in the world which is non-medicinal or which cannot be used as medicine". Even narrowing down this definition to the more practical one that categorizes only those plants as 'medicinal', there are such 6,000 odd higher plants (Foundation for Revitalisation of Local Health Traditions (FRLHT) Database) recorded in the country; estimates of this figure vary from 2,500 to 7,500. A consolidated checklist contains 2400 botanical identities used in various codified Indian systems of medicine & western systems.



Herbal cures are very important part of the Ayurvedic tradition. The people of ancient India identified and relied on the use of a large number of medicinal plants, concocting them from wide range of herbs. The Charaka-samhita cites 500 medicinal plants, while the Sushruta-samhita cites 760 various remedies ranging from milk of certain animals, minerals (sulfur, arsenic, lead, copper, sulfate, gold), and drugs made from various plants. Ayurvedic medicine is notable for its belief in

the slow and steady cure rather than the instant cures promised by modern day antibiotics and analgesics. The herbal remedies used in Ayurvedic medicine are of a type that registers gradually within the body, and in the process, they set off fewer side effects. Among them are a good number that make sense to pharmacists today. Senna was used then and still is used as a laxative.

In spite of such a long history and heritage, there was a decline in the use of herbal medicines from the early 20th century with the development of synthetic drug industry. This was especially so in the developed countries, but in the developing countries traditional herbal medicines continued to play an important role, running parallel to modern medical practices. Traditional herbal medicines are prescribed widely in these countries because of their relatively low cost and also their time-tested effectiveness. Moreover the traditional uses of medicinal plants frequently are coherent with the pharmacological effects of the main active principles of the respective plant sources. This ethnopharmacology knowledge, its holistic systems approach supported by experiential base can serve as an innovative and powerful discovery engine for newer, safer and affordable medicines (Patwardhan, 2005). Globally, in the last few decades there has been an increasing interest in the studies on medicinal plants, which is evident by numerous publications and reports.

Even though these traditional claims on medicinal plants are direct clinical clues, very often they are unscientifically exploited and/or improperly used. These medicinal plants deserve detail studies in the light of modern science and also need efficacy assessment in terms of their chemical composition and bioactivity profile. An exhaustive such study on medicinal plants may fabricate;

1. Interesting leads obtained on the novel chemical structure of active principles isolated from plants.

2. Possibility of deriving new knowledge on the mechanism of action of therapeutic agents which, in turn, may help in better understanding of the etiopathogenesis and the course of various disorders and diseases.
3. Possibility of preventing/minimizing complications of disorders and diseases by the judicious use of selected natural compounds, based on their mechanism of action.

1.2 Bitters

In Ayurveda, for the highest heat, fever and pitta conditions- bitter, fire purging and heat dispelling herbs are used i.e., bitters (Tridosha is an Ayurvedic philosophy, the three doshas are Vata - a force conceptually made up of elements ether and air; Pitta - a force created by the dynamic interplay of water and fire; and Kapha - the conceptual equilibrium of water and earth, together they govern all metabolic activities of the body). Bitters are the strongest herbs for cooling pitta, for sedating, detoxifying liver and for reducing deep-seated heat/fever in the interior of the body. Bitters also increase agni (fire) by their drying action; in addition they do not aggravate pitta (Lad and Frawley, 1986).

In European system, bitters ('amara') are subdivided into three groups: amara tonica, amara aromatic and amara acria. Amara tonica are pure bitter substances supporting the secretion of digestive liquid and showing a basically tonic effect. Therefore, they are applied to treat indigestion and debility. Amara tonica plants are yellow gentian (*Gentiana lutea*) and centaury (*Centaurium erythraea*). Amara aromatica are bitter drugs additionally containing a considerable amount of essential oils. These like amara tonica take effect on the stomach but also on the intestines, on liver and bile; and are slightly antiseptic. Amara aromatica plants are motherwort (*Artemisia vulgaris*), angelica (*Angelica archangelica*) and yarrow (*Achillea millefolium*). Amara acria are bitter drugs, which additionally contain acrid agents. These improve blood circulation. Amara acria plants are ginger (*Zingiber officinale*) and galanga (*Alpinia officinarum*).

Bitter taste is the most common one found among medicinal plants. It has been suggested that the bitter taste is generally unpleasant because it warns of potentially toxic ingredients. These toxins are strong medicines, and it is because of this that they become common among the ingredients of herbal medicines. Alkaloids, which often affect the nervous system, are consistently bitter, and glycosides, which usually affect the circulatory system, are frequently bitter; so are flavonoids, which have broad beneficial health effects if taken in sufficient quantities. There are two basic qualities associated with bitter taste;

- According to the five element systematic correspondence, the bitter taste is associated with the heart system. The alkaloids and glycosides commonly found in bitter plants help explain this relationship.
- According to the taste/action dogma, bitter herbs have a cleansing action (removing heat and toxin). The cleansing action of bitters mainly refers to their antimicrobial and anti-inflammatory effects, which are found with alkaloids, glycosides, and flavonoids. The bitter herbs also dry dampness, and this refers mainly to reduction of mucous membrane secretions; we can recognize today that increased mucoid secretion is usually secondary to inflammation and infection.

According to contemporary knowledge, bitters are a group of botanicals with predominantly bitter in taste, due to the presence of chemical constituents like alkaloids, monoterpenes (iridoid and secoiridoids), sesquiterpene lactones, diterpenes, triterpenes, rarely flavanones, acyl phloroglucides and steroids (pregnane type) (Wagner and Bladt, 1996). Bitters stimulates the gastric reflex, increases the flow of digestive juices from the pancreas and duodenum, increases the nerve tone of the entire digestive tract muscles and enhances liver in better assimilation of nutrients. Bitters produce diuretic effect and also regulate the secretion of the pancreatic hormones (insulin and glucagon) that regulate blood sugar. Bitters can also be supportive in reducing stress, anxiety and regenerating

the nervous system. The intensity of all these effects is considered directly proportional to the strength of its bitterness.

1.3 Bitters and hypoglycemic effect

Momordica charantia (Cucurbitaceae) is a very common folklore remedy for diabetes. Several earlier and recent studies have indicated the hypoglycemic activity of various parts of this plant. Charantin, a steroidal saponin, obtained from *Momordica charantia* is known to have an insulin-like activity, responsible for its hypoglycemic effect (Ng et al., 1986). Charantin stimulates the release of insulin and blocks the formation of glucose in the bloodstream, which may be helpful in the treatment of diabetes, particularly in non-insulin dependent diabetes.

Citrullus colocynthis (Cucurbitaceae) is an annual herb found in wild as well as cultivated throughout India in the warm areas. The fruit of this plant is traditionally used as anti-diabetic. Several studies have shown the hypoglycemic effect of various extracts of the plant. It is reported to exert an insulinotropic effect (Abdel-Hassan at al., 2000; Nmila et al., 2000).

Aloe vera (Liliaceae) has long been used all over the world for their various medicinal properties. Hypoglycemic effect of aloes and its bitter principle is mediated through stimulation of synthesis and/or release of insulin from the β-cells of Langerhans (Ajabnoor, 1990).

Andrographis paniculata (Acanthaceae) is an erect annual herb commonly known as Kalmegh or 'King of Bitters'. Number of studies have shown that *Andrographis paniculata* extract can exert potent antihyperglycemic activity. Andrographolide, a diterpenoid lactone, obtained from *Andrographis paniculata* was found to possess significant hypoglycemic activity (Borhanuddin et al., 1994; Yu et al., 2003).

Swertia chirayita (Gentianaceae) is a traditional Ayurvedic herb commonly known as Chirata. Different extracts as well as swerchirin (1,8-dihydroxy-3,5-

dimethoxyxanthone), an active constituent isolated from the hexane fraction of the plant have been studied in various animal models of diabetes and found to exert potent hypoglycemic activity (Saxena et al., 1993). The bitterness, antihelmintic, hypoglycemic and antipyretic properties are attributed to amarogentin, swerchirin and swertiamarin.

Some of chemical entities isolated from bitters reported for antidiabetic activity are;

- Charantin, polypeptide-P (plant insulin), lanolin acid 3-O-glucuronide and momordin isolated from *Momordica charantia* L. (Cucurbitaceae),
- Potent natural α-glycosidase inhibitors such as kotalanol and salacinol isolated from the roots and stems of *Salacia reticulata* Wight. (Celastaceae),
- Andrographolide from *Andrographis paniculata* Nees (Acanthaceae),
- Swerchirin from *Swertia chirayita* (Roxb. ex Fleming) H. Karst (Gentianaceae) and
- Trigonelline and 4-hydroxyisoleucine from *Trigonella foenum graceum* L. (Fabaceae).

Considering the significance of bitters and their therapeutic value as antidiabetics, the proposed study was planned to explore some medicinal plants used traditionally as bitters.

1.4 Selection of plant materials

Selection of medicinal plants was based on their traditional claims as bitters and the scope they offered for further antidiabetic studies;

1. *Clerodendrum phlomidis* Linn. f. (Lamiaceae) (Syn. *Clerodendrum multiflorum* (Burm.f) O. Kuntze, *Volkameria multiflorum* Burm. f.)

2. *Nymphaea stellata* Willd. (Nymphaeceae) (Syn. *Nymphaea nouchali* Burm. f.)

1.5 Diabetes mellitus

Diabetes mellitus (DM) is considered as one of the five leading causes of death in the world. About 150 million people are suffering from diabetes worldwide, which is almost five times more than estimates ten years ago and this may double by the year 2030. India leads the way with its largest number of diabetic subjects in any given country. It has been estimated that the number of diabetes in India is expected to increase 57.2 million by the year 2025 (King et al., 1998). Current therapeutic strategies for investigations on diabetes are limited and involve insulin and four main classes of oral hypoglycemic agents that,

- Stimulate pancreatic insulin secretion (sulphonylureas and rapid-acting secretagogues/insulinotropics e.g., glibenclamide, glipizide, rapaglinide),
- Reduce hepatic glucose production (biguanides e.g., metformin),
- Delay digestion and absorption of intestinal carbohydrate (α-glucosidase inhibitors e.g., acarbose),
- Improve insulin action (thiazolidinediones (TZDs) e.g., pioglitazone, rosiglitazone).

Each of above agents suffers from generally inadequate efficacy and number of serious adverse effects. Thus, there are wide variety of newer therapeutic agents/strategies being examined for the treatment of diabetes.

Type 2 diabetes is a progressive disease characterized by insulin resistance in peripheral tissues and/or impaired insulin secretion by the pancreas. The resultant high blood glucose level, generally leads to several serious complications. The World Health Organization recently warned that type 2 diabetes has become a global pandemic (King et al., 1998). At the molecular level, the mechanism of insulin resistance in type 2 diabetes appears to involve defects in post-receptor signal transduction (Youngren and Goldfine, 1997; Montalibet and Kennedy, 2005; Vats et al., 2005). Although number of oral hypoglycemic agents are used in management of type 2 diabetes especially in controlling hyperglycemia, they show sometimes prominent untoward effects (Rang and Dale, 1991).

Many medicines such as insulin secretion agents, aldose reductase inhibitors, R-glycosidase inhibitors, and biguanides have been investigated to ameliorate diabetes or its complications, (Tripathi and Srivastava, 2006). Peroxisome proliferator-activated receptor (PPAR)-γ ligands have been developed as a target of type 2 diabetes mellitus. These medicines improve the condition of insulin resistance by inducing differentiation from preadipocytes to small adipocytes that can enhance glucose uptake with insulin stimulation (Okuno et al., 1998). More recently, PTP1B has emerged as an attractive therapeutic target for treatment of insulin resistance related to type 2 diabetes and obesity (Kenner et al., 1996). Since the knowledge of heterogeneity of type 2 diabetes is increasing, there is a need to look for more efficacious agents for treatment with lesser side effects and thus offer scope for the search of a better medicament.

World Health Organization (WHO) has recommended the traditional plant treatments for diabetes warrant further evaluation (WHO, 1980). Moreover, today it is necessary to provide scientific proof as to whether it is justified to use a plant or its active principles for treatment (Singh et al., 2000). Medicinal plants have always been an exemplary source of chemical entities used as drugs. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated consistent activity in the treatment of diabetes. Among these are alkaloids, glycosides, galactomannan gum, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, saponins, mucilages, glycopeptides, terpenoids, amino acids and inorganic ions.

Even the discovery of widely used hypoglycemic drug, metformin came from the traditional approach of using *Galega officinalis*, a plant known for several centuries to reduce the symptoms of diabetes mellitus. *Galega officinalis* is a natural source of galegine which is a prototype of metformin, now a very widely used oral hypoglycemic agent. Therefore, it is prudent to look in to traditional medicines as alternative resources for the treatment of diabetes.