CHAPTER 1

MEDICINAL PLANTS AND DIABETES
Chapter 1

1 MEDICINAL PLANTS AND DIABETES

1.1 INTRODUCTION

Medicinal plants are significant source of herbal drugs. Before the availability of synthetic drugs, man was completely dependent on medicinal herbs for prevention and treatment of diseases. The use of the medicinal herbs for curing diseases has been documented in the history of all civilizations. The drugs were used in crude forms like expressed juice, powder, decoction or infusion. Although the formulations mentioned in ancient texts are difficult to understand in terms of scientific parameters, but some of them are reputed for their curative values.

The use of plants as drugs by human beings has been prevalent since times immemorial (Anthony, 1997). This is because of the fact, that they have served the immediate personal needs, are easily accessible and inexpensive. During the thousands of years of early human existence many natural material were identified for combating human ailments either by instinct or intuition or trial and error. Natural products have played an important role throughout the world in treating and preventing human diseases. Natural product medicines have come from various source materials including terrestrial plants, microorganisms, marine organisms, vertebrates and invertebrates (Newman et al., 2000).

The WHO has emphasized the utilization of indigenous system of medicines based on the locally available raw material, i.e., medicinal plants (Ali, 1997). The famous statement, “one man’s aspirin is another man’s peptic ulcer” (Kitty, 1988) also led people to look for
alternatives. It has been estimated that up to 50% of the prescriptions presently dispensed in USA may contain one or more natural product drug (Douglas, 2000).

1.1.1 History of Medicinal Use of Plants in India

In India, the use of different parts of several medicinal plants to cure specific ailments has been in vogue from ancient times. The indigenous systems of medicine, namely Ayurvedic, Siddha and Unani, have been in existence for several centuries. These systems of medicine cater to the needs of nearly seventy percent of our population residing in the villages. Apart from India, these systems of medicines are prevalent in Korea, China, Singapore, West Asia and many other countries (Handa, 1991).

Indian traditional medicines are based on use of plant drugs (Patwardhan and Hooper, 1992). The earliest mention of the medicinal use of plants has been found in ‘Rig Veda’, written between 4000 and 1600 BC (Mukherjee, 2002). Indian Materia Medica includes about 2000 drugs of natural origin, out of these 400 are of mineral and animal origin while the rest are of vegetable origin.

India is a vast country where wide variations in climate, soil, altitude and latitude are available. Nature has bestowed on us a very rich botanical wealth and a large number of diverse types of plants grow wild in different parts of the country. Increased awareness about the potential of this group of interesting and useful plants has encouraged many innovative and progressive growers and entrepreneurs to take up their cultivation as a commercial enterprise. Apart from health care this enterprise provides means of livelihood to scores of people (Handa and Kaul, 1996).

India is endowed with more than 47000 known species of plants (Roghuram, 2002), of these about 15000-20000 plants have good medicinal value. However, traditional communities use only about 7000-7500 for their medicinal values. The Siddha system of medicine uses about 600, Ayurveda 700, Unani 700 and Modern medicines about 30. Effective Western style medicine is neither accessible nor affordable for millions of
people worldwide. Nowhere is this more true than in India, where in spite of the wide and rapid spread of Western medical practices throughout the country during past 150 years, majority of the populace still continues to rely on traditional medicine for their health care needs.

1.1.2 Drug Discovery from Natural Products

The importance of natural products in modern medicine has been discussed in recent reviews and reports (Newman et al., 2003; Koehn and Garter, 2005; Paterson and Anderson, 2005; Balunas and Kinghorn, 2005; Jones et al., 2006). The value of natural products in this regard can be assessed using 3 criteria:

1. The rate of introduction of new chemical entities of wide structural diversity, including serving as templates for semisynthetic and total synthetic modification
2. The number of diseases treated or prevented by these substances, and
3. Their frequency of use in the treatment of disease.

Plant based drugs can be used directly, i.e., they may be collected, dried and used as therapeutic agents (crude drugs), or their chief constituents/active principles separated by various chemical processes which are then employed as medicines. The active principles may be carbohydrates, glycosides, tannins, lipids and alkaloids. The active principles or compounds with similar structure and activity are manufactured chemically to produce the synthetic drugs used in allopathic or modern systems of medicine (Balandrin and Klocke 1988; Tyler et al., 1988).

Although interest in natural products as a source of new biologically active compounds decreased in the last few decades as synthetic chemistry programmes expanded, natural products continued to form a significant proportion of drugs in current use and of those under investigation. Plant secondary metabolites are not only useful as potential drugs in their natural unmodified form, but are also suitable as synthetic intermediate substances for the production of useful drugs, e.g., the readily available plant steroids, diosgenin
from Dioscorea species may be synthetically converted to steroids with anabolic, anti-inflammatory and oral contraceptive activity (Briggs, 1990).

It has been estimated that 56% of the lead compounds for medicines in the British National Formulary are natural products or derived from natural products (amoxycillin, cefaclor, ceftriaxone and lovastatin) and two others (captopril and enalapril) resulted from leads provided by a natural product (Hobden and Harris, 1992). In 1991, forty two new agents were introduced to medical practice, of these, sixteen were natural products or were derived from natural products. Similarly there were forty three new chemical entities introduced in 1992 and eighteen were natural products or their derivatives (Davis, 1993).

Several technological developments in the last few decades offer traditional possibility for the discovery of drugs from the plants. During recent years phytochemists have been able to isolate a number of active constituents from these plants, which may be attributed to combination of the wisdom of ancient sages and use of modern techniques such as UV, IR, HNMR, HPLC, HPTLC, DCCC, GLC, 2D-NMR, C-NMR and mass spectroscopy. These techniques have led to enormous growth in phytochemistry.

1.1.3 Bottlenecks in the Research and Utilization of Medicinal Plants

An analysis of the origin of the drugs developed between 1981 and 2002 showed that natural products or natural product derived drugs comprised 28% of all new chemical entities (NCEs) launched onto the market (Newman et al., 2003). In addition, 24% of these NCEs were synthetic or natural mimic compounds, based on the study of pharmacophores related to natural products (Newman et al., 2000). This combined percentage (52% of all NCEs) suggests that natural products are important sources for new drugs and are also good lead compounds suitable for further modification during drug development. The large proportion of natural products in drug discovery has stemmed from the diverse structures and the intricate carbon skeletons of natural products. Since secondary metabolites from natural sources have been elaborated within
living systems, they are often perceived as showing more “drug-likeness and biological friendliness than totally synthetic molecules” (Koehn and Garter, 2005), making them good candidates for further drug development (Balunas and Kinghorn, 2005; Drahl et al., 2005).

Inspite of so much potential and scope of future development of plant drugs, a mere 2% of the total flora provided by nature is being used beneficially. Apart from lack of coordination, the major pitfalls in plant drug research include lack of true identity, standardization, quality control of the plant drugs, confusion in nomenclature, controversial botanical identification, danger of extinction of some plants due to extensive exploitation, lack of proper dosage formulation and bitter experiences of searching for a single active principle.

In addition to this, another major problem concerning the medicinal plants is their adulteration and substitution. The most important factor that stands in the way of wider acceptance of traditional herbal drugs is the non-availability or inadequacy of standards for their identity and quality. Standardisation of plant drug has been stressed by the World Health Organization.

Besides all this, the demand by traditional systems, for medicinal plants, as their raw material and by the modern pharmaceutical industries has also increased manifold. Also, medicinal plants constitute a group of industrially important crops which bring appreciable income to the country by way of export.

1.2 **DIABETES MELLITUS**

Diabetes mellitus (DM) is a metabolic disorder resulting from a defect in insulin secretion, insulin action, or both (ECDCDM, 1997). Insulin deficiency in turn leads to chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. As the disease progresses, tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular
complications and ulceration. Thus, diabetes covers a wide range of heterogeneous
diseases (Bastaki, 2005). At present it has been estimated to be affecting nearly 10% of
the population all over the world (Burke et al., 2003) and by the year 2010, it is estimated
that more than 200 million people worldwide will have DM (Amos et al., 1997) and 300
million will subsequently have the disease by 2025. By 2025, diabetes prevalence in
India, China, and the USA will increase by 195%, 134%, and 58% respectively from
1995. This means 57.2, 37.6, and 21.9 million people in each country (King et al., 1998).

Diabetes mellitus may be categorized into several types but the two major types are type
1 and type 2 (WHO, 1985). On the basis of etiology, the term type 1 and type 2 were
widely used to describe Insulin Dependent Diabetes Mellitus (IDDM) and Non Insulin
Dependent Diabetes Mellitus (NIDDM), respectively. The term juvenile-onset diabetes
has sometimes been used for IDDM and maturity-onset for NIDDM.

On the basis of etiology, type 1 is present in patients who have little or no endogenous
insulin secretory capacity and who therefore require insulin therapy for survival. The two
main forms of clinical type 1 diabetes are type 1a (about 90% of type 1 cases in Europe)
which is thought to be due to immunological destruction of pancreatic β cells resulting in
insulin deficiency; and type 1b (idiopathic, about 10% of type 1 diabetes), in which there
is no evidence of autoimmunity. Type 1a is characterized by the presence of islet cell
antibody (ICA), anti-glutamic acid decarboxylate (anti-GAD), IA-2 or insulin antibodies
that identify the autoimmune process with β-cell destruction (Zimmet et al., 2004).
Autoimmune diseases such as Grave’s disease, Hashimoto’s thyroiditis and Addison’s
disease may be associated with type 1 diabetes mellitus (Atkinson and Maclaren, 1994;
Betterle, 1983). There is no known etiological basis for type 1b diabetes mellitus. This
form is more prevalent among individuals of African and Asian Origin (Ahrén and
Corrigan, 1984).

Type 2 diabetes is the most common form of diabetes and is characterized by disorders of
insulin secretion and insulin resistance. In Western countries the disease affects up to 7% of
the population (WHO, 1994). Globally, it affects 5-7% of the world’s population
(Harris et al., 1998). This prevalence is underestimated because many cases, perhaps 50% in some population, remain undiagnosed. The prevalence of type 2 diabetes varies considerably throughout the world, ranging from <1% in certain population of the developing countries (Zimmet, 1982) Its incidence is associated with population whose lifestyle has changed from traditional patterns to a modern “Westernized” model (Bloomgarden, 1996). Traditionally, type 2 diabetes is common in individuals over the age of 40. It is often associated with obesity, decreased physical activity and heredity. Recent data from several countries show that type 2 diabetes is increasingly becoming a problem among adolescents and even children (Scott, 1997). In some countries, childhood diabetes type 2 is more common than type 1. The disease is usually controlled through dietary therapy, exercise and hypoglycemic agents (Miller, 2001).

1.2.1 Challenges Due to Diabetes

Diabetes mellitus is possibly the world’s largest growing metabolic disease, and as the knowledge on the heterogeneity of this disorder is advanced, the need for more appropriate therapy increases (Baily and Flatt, 1986). Taking into account the prospects and challenges for diabetes, better ways of influencing patterns of behaviour and compliance and of motivating lifestyle changes are the only hope for fulfilling the promise of diabetes demise in the 21st century (Ferguson, 1993).

During the last 10 years our understanding of the etiology, natural history and management of diabetes (in particular type 2 diabetes) has taken an exponential leap forward. This is largely due to those professionals who have dedicated themselves to research activities. There is, still incomplete, but a much better understanding of the etiology of diabetes mellitus. The relative contributions of genetic predisposition, developmental influences and environmental triggers leading to the disturbed metabolic homeostasis that characterizes diabetes are more clearly understood (Björntorp and Rosmond, 2000). The role of insulin resistance in the aetiology of type 2 diabetes has been clarified (Hunter and Garvey, 1998; Haffner, 1999). The contribution of β-cell
dysfunction has been elucidated and the complex inter-relationship of insulin and leptin resistance to hypertension, obesity and diabetes is gradually being unraveled.

Not only is diabetes rapidly becoming a global burden but also there are still many unanswered questions about prevention and management. As one third of all diabetic patients will reside in this part of the world by 2025, health professionals must continue to be informed about new developments.

1.2.2 Role of Herbal Medicines in Diabetes

Mankind has a long history in the use of herbal medicines. Several medicinal plants have been used as dietary adjunct and in the treatment of numerous diseases without proper knowledge of their function. Rigveda and Ayurveda (4500-1600 BC) reveal that ancient Indians had a rich knowledge of the use of medicinal plants. India unquestionably occupies the topmost position in the use of herbal drugs since ancient times, utilizing nearly 600 plant species in different formulations. Great majorities of people in India have been depending on crude drugs for the treatment of various diseases as evidenced from well-documented indigenous system of medicines, Ayurveda and Unani. The Materia Medica of these systems contain a rich heritage of indigenous herbal drugs (Nadkarni, 1954). Although phytotherapy continues to be used in several countries, few plants have received scientific or medical scrutiny.

The role of traditional medicines in the solution of health problems is invaluable on a global level. This is all the more striking when we consider the fact that approximately 80% of the people living in less developed countries rely exclusively on traditional medicine for their health care needs (Farnsworth, 1994). Global traditional medicine also has great promise of a number of plants and plant products with anti-diabetic activity (Bailey and Day 1989; Balasubramanyam and Mohan 1999). Since time immemorial, patients with non-insulin dependent diabetes mellitus have been treated orally by folklore with a variety of plant extracts. In the indigenous Indian system of medicine, a mention was made on good number of plants for the cure of diabetes and some of them have been
experimentally evaluated and the active principles were isolated (Ivorra et al., 1989; Grover et al., 2002). There are several literature reviews by different authors about antidiabetic herbal agents, but the most informative is the review by Atta-ar-Rahman who has documented more than 300 plant species accepted for their hypoglycaemic properties (Atta-ar-Rahman and Zaman, 1989). In fact a survey of 166 Ayurvedic plants showed that 13% of them were used for diabetes treatment (Khan and Balick, 2001).

Table 1.1 presents a sampling from a wide array of plants that have been traditionally used or are now in focus for their use in diabetes therapy. It is not a comprehensive survey but still shows how vast the arena is for exploring the natural resources for treatment or prevention of diabetes. An attempt has been made to present summarily in a tabulated form the plants which find mention in the literature, both classical and modern, as well as those that have been studied according to the modern methods of scientific validation, or are part of a traditional antidiabetic herbal formulation.

It is high time that we fully exploit our medicinal biodiversity to look for new chemical entities using high throughput biological screening assays. It is possible that many insulin mimetic properties may lie hidden in plants of Indian systems of medicine. Traditional plant medicines are used throughout the world for a range of diabetic complications. The study of such medicines might offer a natural key to unlock a diabetologist’s pharmacy for the future. Some plants like Syzygium cumini, Gymnema sylvestre and Pterocarpus marsupium are now well established as potent herbal antidiabetic drugs. Many modern scientific studies have established the credentials of these plants time and again but it has to be borne in mind that the search for a drug that could effectively cure or act as a palliative for diabetes does not come to an end with these few plants. Newer plants and drugs need to be constantly explored and tested for their potential towards controlling the menace of diabetes which is growing at an alarming rate worldwide generally and the third world particularly.
<table>
<thead>
<tr>
<th>S. No.</th>
<th>Botanical Name</th>
<th>Common Name</th>
<th>Part Used</th>
<th>Active Principle</th>
<th>Research Studies</th>
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<tbody>
<tr>
<td>1.</td>
<td>Acacia arabica</td>
<td>Babool, Indian gum,</td>
<td>Seeds</td>
<td>Flavonols</td>
<td>Wadood et al., 1989; Singh et al., 1975; Singhal and Joshi, 1984</td>
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<td>2.</td>
<td>Aegle marmelos</td>
<td>Bael fruit, Bilva</td>
<td>Leaf</td>
<td>Aegelin, Marmelos</td>
<td>Krishnan, 1968; Gholap and Kar, 2004; Ponnachan et al., 1993</td>
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<td>/mussabar</td>
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<td>4.</td>
<td>Asparagus racemosus</td>
<td>Shatavari, Root</td>
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<td>Shatavarin I-IV</td>
<td>Rana et al., 1994; Govindarajan et al., 2004</td>
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<td>5.</td>
<td>Azadirachta indica</td>
<td>Neem, Indian lilac,</td>
<td>Leaf, seed oil</td>
<td>Bitter principles</td>
<td>Murthy et al., 1978; Pari et al., 2001</td>
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<td>Nimbin, Nimbinin</td>
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<td>Nimbidin</td>
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<td>6.</td>
<td>Butea monosperma</td>
<td>Palash</td>
<td>Seed</td>
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<td>Budhe et al., 1996</td>
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<td>7.</td>
<td>Cassia auriculata</td>
<td>Tea tree, Flowers</td>
<td>Flowers</td>
<td>Seeds</td>
<td>Shiva, 1998; Shroti et al., 1963; Pari et al., 2001; Pari and Lata, 2002</td>
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<td>Tannins</td>
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<td>8.</td>
<td>Cinnamomum tamala</td>
<td>Dalchini Tamal</td>
<td>Leaf</td>
<td></td>
<td>Swanson-Flatt et al., 1989; Kar et al., 2003</td>
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<td>9.</td>
<td>Clitoria ternatea</td>
<td>Butterfly pea, Gokurna</td>
<td>Roots</td>
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<td>Sharma and Majumdar, 1990</td>
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<td>mula</td>
<td>Leaves</td>
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<td>10.</td>
<td>Citrullus colocynthis</td>
<td>Indian wild gourd</td>
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<td>Colocynthin</td>
<td>Nadkarni, 1954; Abdel et al., 2000</td>
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<td>11.</td>
<td>Emblica officinalis</td>
<td>Amla</td>
<td>Fruit</td>
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<td>Sadasiv, 1998; Rao et al., 2005</td>
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<td>12.</td>
<td>Eugenia jambolana</td>
<td>Jamun, Black plum/berry</td>
<td>Seed</td>
<td>Jamboline</td>
<td>Sepha and Bose, 1956; Shroti et al., 1963; Lal and Chaudhary, 1968; Teixeira, 1997; Prince et al., 1998; Pepato et al., 2005</td>
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<td>syn. Syzygium cumini</td>
<td>Jambul</td>
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<td>14.</td>
<td>Ficus carica</td>
<td>Fig tree, Leaves</td>
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<td>Perez et al., 1998; Serraclara et al., 1998</td>
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<td>15.</td>
<td>Gymnema sylvestre</td>
<td>Gurmar</td>
<td>Leaves</td>
<td>Gymnema saponins I-II, Gymnemic acids I-IX</td>
<td>Baskaran and Kizar, 1990; Murakami et al., 1996; Gholap and Kar, 2004; Gholap and Kar, 2005</td>
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<td>16. Lactuca sativa</td>
<td>Kaahu</td>
<td>Seeds</td>
<td>NFUM, 1981; Roman-Ramos et al., 1995</td>
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<td>17. Momordica charantia</td>
<td>Bitter gourd</td>
<td>Fruits</td>
<td>Momordicine</td>
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<td>Seeds</td>
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<td>Charantin</td>
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<td>Momordin</td>
<td>Akhtar, 1982; Lolikar and Rao, 1966; Ahmed et al., 1998; Matsuda, 1998; Miura et al., 2004</td>
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<td>18. Murraya/Bergaria koenigi</td>
<td>Curry leaves</td>
<td>Leaf</td>
<td>Shiva, 1998; Khan et al., 1995; Kesari et al., 2005</td>
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<td>20. Nigella sativa</td>
<td>Kalonji</td>
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<td>El-Dakhakhny, 2002</td>
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<td>21. Ocimum sanctum</td>
<td>Tulsi</td>
<td>Seeds</td>
<td>Leaves</td>
<td>Kar et al., 2003; Gholap and Kar, 2004; Chattopadhyay, 1993</td>
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<td>23. Pterocarpus marsupium</td>
<td>Vijaysar</td>
<td>Heartwood</td>
<td>Pterostilbene</td>
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<td></td>
<td></td>
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<td>isoliquiritigenin</td>
<td>Shah, 1967; Saifi et al., 1971; Vats et al., 2004; Anandharajan et al., 2005</td>
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<td>24. Panica granatum</td>
<td>Anaar,</td>
<td>Seeds</td>
<td>Flowers</td>
<td>Jafri et al., 2000; Das et al., 2001</td>
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<td>25. Salacia macrosperma</td>
<td>Roots</td>
<td>Salaicinol</td>
<td>kotalanol</td>
<td>Venkateshwarlu et al., 1990; Augusti et al., 1995; Yoshikawa et al., 1998</td>
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<td>S. reticulata</td>
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<td>S. oblonga</td>
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<td>26. Svertia chiraita</td>
<td>Chiraita</td>
<td>Swerchirin</td>
<td>Chandrahekhar et al., 1990; Saxena et al., 1991; Saxena et al., 1993; Bajpai et al., 1991</td>
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<td>27. Syzygium cumini</td>
<td>Jammun</td>
<td>Seeds</td>
<td>Teixeira et al., 1997; Prince et al., 1998; Teixeira et al., 2004</td>
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<td>28. Tinospora cordifolia</td>
<td>Giloe</td>
<td>Root</td>
<td>Stanley et al., 2003; Wadood et al., 1992</td>
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</table>
1.3 AIMS AND OBJECTIVES

On the basis of a study of literature and reports mentioned in this chapter a few plants were selected for a study of their efficacy as an anti-diabetic. To make the study more relevant towards the purpose of standardisation, which was the original aim of this work, the plants were sourced from four different geographical regions, viz., Delhi, Amritsar, Chennai and Lucknow. This provided for the recording of any differences in the activity of plants due to the differences in geographical source and thus arrive at a list of plants with potent antidiabetic activity belonging to any specific geographical location. The selection of the plants was done keeping in mind that new, previously untested or not much studied plants be compared with a few well established anti-diabetic plants.

The present work has been undertaken to fulfill the following objectives:

1. Collection and authentication of herbal antidiabetic Unani drugs *viz.*, *Lactuca sativa*, *Rumex vesicarius*, *Gymnema sylvestre*, *Portulaca oleracea* and *Syzygium cuminii* from different regions.

2. Preparation of extracts of herbal drugs in different solvents.

3. Screening of their anti-diabetic activity using the aqueous extracts of the drugs.

4. Standardisation and development of HPTLC fingerprints of aqueous extracts of drugs from different regions.

5. Isolation and development of chemical markers by chromatographic techniques and their structural elucidation by spectral data and chemical reactions.
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