1.0 INTRODUCTION

1.1 General:

Traditional medicine is the sum total of knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures that are used to maintain health, as well as to prevent, diagnose, improve or treat physical and mental illnesses. Nature provides the modern medical world with a number of highly potential drugs. Each individual is unique. This uniqueness encompasses voluntary activities, such as decision-making, personality development, and emotional response, and involuntary activities like metabolism of nutrients, cellular processing of information and communications among the body’s organ systems. The concept of biochemical individuality is central to every aspect of the practice of functional medicine from clinical assessment and diagnosis to the broad spectrum of treatment modalities (Pizzorno and Murray, 1999).

Natural products have been considered the primary source of commercial medicines and drug leads. A recent survey revealed that 61% of the 877 drugs introduced worldwide can be traced by natural products. The roughly 350,000 species of plants believed to exist, one-third of those have yet to be discovered. Only a fraction of the quarter million reported have been chemically investigated (Cseke et al., 2006).

Inventorisation of herbal drugs used in traditional and modern medicines for a country like India, appears to be a stupendous task, where a number of well established indigenous or traditional systems, including Ayurveda, Unani, Siddha, Homoeopathy, Tibetan, Amchi, Yoga and Naturopathy are practised along with modern medicine for the management of total health care system. Traditional systems of medicine continue to be widely practised on many accounts. Population rise, inadequate supply of drugs, prohibitive cost of treatments, side effects of several allopathic drugs and development of resistance to currently used drugs for infectious diseases have led to increased emphasis on the use of plant materials as a source of medicines for a wide variety of human ailments. Global estimates indicate that 80% of about 4 billion population can not afford the products of the Western Pharmaceutical Industry and have to rely upon the use of
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traditional medicines which are mainly derived from plant material. This fact is well documented in the inventory of medicinal plants, listing over 20,000 species. In spite of the overwhelming influences and our dependence on modern medicine and tremendous advances in synthetic drugs, large segments of the world population still like drugs from plants. In many of the developing countries the use of plant drugs is increasing because modern life saving drugs are beyond the reach of three quarters of the third world’s population although many such countries spend 40-50% of their total wealth on drugs and health care (Rsnakk et al., 2011).

As a part of the strategy to reduce the financial burden on developing countries, it is obvious that an increased use of plant drugs will be followed in the future. Among ancient civilizations, India has been known to be rich repository of medicinal plants. The forest in India is the principal repository of large number of medicinal and aromatic plants, which are largely collected as raw materials for manufacture of drugs and perfumery products. About 8,000 herbal remedies have been codified in Ayurveda. Plants, especially used in Ayurveda can provide biologically active molecules and lead structures for the development of modified derivatives with enhanced activity and /or reduced toxicity. The small fraction of flowering plants that have so far been investigated have yielded about 120 therapeutic agents of known structure from about 90 species of plants. Some of the useful plant drugs include vinblastine, vincristine, taxol, podophyllotoxin, camptothecin, digitoxigenin, gitoxigenin, digoxigenin, tubocurarine, morphine, codeine, aspirin, atropine, pilocarpine, capscicine, allicin, curcumin, artemesinin and ephedrine among others (Doble et al., 2011).

In some cases, the crude extract of medicinal plants may be used as medicaments. On the other hand, the isolation and identification of the active principles and elucidation of the mechanism of action of a drug is of paramount importance. Hence, works in both mixture of traditional medicine and single active compounds are very important. Where the active molecule cannot be synthesized economically, the product must be obtained from the cultivation of plant material. About 121 (45 tropical and 76 subtropical) major plant drugs have been identified for which no synthetic one is currently available. The scientific study of traditional medicines, derivation of drugs through bioprospecting and
systematic conservation of the concerned medicinal plants are thus of great importance (Mouli et al., 2009).

A major lacuna in Ayurveda is the lack of drug standardization, information and quality control. Most of the Ayurvedic medicines are in the form of crude extracts which are a mixture of several ingredients and the active principles when isolated individually fail to give desired activity. This implies that the activity of the extract is the synergistic effect of its various components (Joy et al., 1998).

1.2 Overview of Diabetes Mellitus:

Diabetes mellitus is a heterogeneous group of metabolic disorders characterized by chronic hyperglycemia. Some forms of diabetes mellitus are characterized in terms of their specific etiology or pathogenesis, but the underlying etiology of the most common forms remains unclear. Regardless of the etiology, diabetes progresses through several clinical stages during its natural history. Persons developing the disease can be categorized according to clinical stages and other characteristics even in the absence of knowledge of the etiology (WHO, 1999).

Diabetes mellitus, (DM) hereafter referred to as diabetes, is a disorder characterized by the presence of an excess of glucose in the blood and tissues of the body. The word diabetes is Greek for a siphon, referring to the discharge of an excess quantity of urine; and mellitus is Latin for honey. Thus diabetes mellitus means the passage of large amounts of sweet urine. This is derived from the fact that excess glucose in the blood spills over into the urine, absorbing fluids with it. DM is a clinically and genetically heterogeneous group of disorders characterized by abnormally high levels of glucose in the blood. The hyperglycemia is due to deficiency of insulin secretion or to resistance of the body's cells to the action of insulin, or to a combination of these. Often there are also disturbances of carbohydrate, fat, and protein metabolism. Glucose metabolism involves small intestine, pancreas, liver and muscle cell. If there are, any problem with any of this diabetes organ leads to defect in glucose metabolism and can develop diabetes (The expert committee on the diagnosis and classification of diabetes mellitus, 2002).
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1.2.1 The Pancreas (General anatomy):

The vertebrate pancreas is an essential organ, responsible for both digestion and glucose homeostasis. The pancreas is also the sole source of insulin production in vertebrates, and impairment leads to a major health problem, diabetes mellitus. The pancreas is a solid organ that lies transversely in the retroperitoneum deep within the epigastrium. The human pancreas is a racemose, lobulated gland that weighs 60 to 170 g, 13 to 25 cm long, and is located just caudal to the stomach and opposite the liver along the gastrointestinal tract (Gray, 1994).

- Head (proximal portion) lies in the duodenum,
- Tail (distal portion) contacts the spleen.

It is also in juxtaposition to a number of large blood vessels, including the aorta, the inferior vena cava, and the superior mesenteric vein and artery and is in direct contact with the portal and splenic veins. The organ is covered by a thin capsule of connective tissue that sends septa into it, separating it into lobules.

The pancreas is made up of two types of glands:

- Exocrine: The exocrine gland secretes digestive enzymes. These enzymes are secreted into a network of ducts that join the main pancreatic duct, which runs the length of the pancreas.
- Endocrine: The endocrine gland, which consists of the islets of Langerhans, secretes hormones into the bloodstream (Sturmhofel and Bartke, 1998).

The pancreas has digestive and hormonal functions. The enzymes secreted by the exocrine gland in the pancreas help break down carbohydrates, fats, proteins, and acids in the duodenum. These enzymes travel down the pancreatic duct into the bile duct in an inactive form. When they enter the duodenum, they are activated. The exocrine tissue also secretes bicarbonate to neutralize stomach acid in the duodenum. The hormones secreted by the endocrine gland in the pancreas are insulin and glucagon (which regulate the level of glucose in the blood), and somatostatin (which prevents the release of the other two hormones) (Constanti et al., 1998).
Figure 1.1: Anatomy of the human adult pancreas
1.2.2 Insulin:
Insulin, the major hormonal regulator of glucose metabolism, was first isolated from pancreatic tissue (Banting and Best, 1922).

Insulin biosynthesis occurs in rough endoplasmic reticulum from a single-chain precursor, preproinsulin, with a molecular weight of 11,500 and containing 109 amino acids. This molecule consists of proinsulin plus a hydrophobic extension of 23 amino acids (preregion) on the N terminus of proinsulin. Proinsulin is cleaved to form equimolar amounts of C-peptide and insulin. Insulin is a protein composed of 51 amino acids in two chains (A and B chains), connected by two disulfide bonds. Insulin is synthesized and stored in the β-cells of the islets of langerhans, which are located in the pancreas. The normal pancreas contains approximately 200 U insulin, and a basal amount of insulin is secreted continuously at a rate of approximately 0.5 to 1.0 U/h.

The important metabolic sites that are sensitive to insulin include the liver, where glycogen is synthesized, stored and broken down; skeletal muscle, where glucose oxidation produces energy; and adipose tissue, where glucose can be converted to fatty acids, glyceryl phosphate and triglycerides. Insulin affects carbohydrate, protein and lipid metabolism (Kitabchi, 1982). Additional insulin is also released in response to blood glucose levels of 100 mg/dL or more. The average daily insulin secretory rate in the adult is 25 to 50 U/day. Insulin is cleared metabolically by the liver, peripheral tissues, and kidneys. Insulin follows first-order elimination kinetics, and the serum half-life is approximately 4 to 5 minutes (Helms and Quen, 2006).

Each pancreatic islet includes four types of hormones, secreting cells

1. Insulin is produced by pancreatic β (or B) cells, which constitute 70% of pancreatic endocrine cells. It acts on all cells in the body to increase the uptake of glucose from the blood into the cells.

2. Glucagon is produced by pancreatic α (or A) cells (20%) and it acts mainly on the liver. It increases glycogenolysis and gluconeogenesis to raise the blood glucose concentration.
3. Somatostatin is secreted from δ (or D) cells (5–10%). It acts locally as a paracrine agent, inhibiting the production of insulin and glucagon. It also inhibits the gut peptides secretin, cholecystokinin (CCK), gastrin and motilin.

4. Pancreatic polypeptide is produced by PP or F cells (1–2%).

Other cell types include vasoactive intestinal polypeptide (VIP)-secreting cells and enterochromaffin cells, which secrete serotonin, motilin and substance P (Unger and Orci, 1976).

**Figure 1.2:** Pancreatic islet and its secreting cells

### 1.2.2.1 Normal insulin production and its effects:

The primary function of the pancreatic β-cell is the production, storage, and regulated secretion of insulin. Under normal circumstances, the β-cell maintains a condition such that there is always a readily available pool of insulin that can be rapidly secreted in response to a stimulus, such as an increase in blood glucose level. Any increase in insulin release is compensated by a increase in insulin biosynthesis, so that β-cell insulin stores are constantly maintained. Thus, the biosynthesis and processing of the insulin molecule along the secretory pathway of the β-cell is a highly regulated and dynamic process. The pancreas secretes about 1.5 L of fluid a day (over ten times its own weight). This fluid
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contains cations, anions, albumin, globulin and digestive enzymes. The bulk of the fluid is the sodium- and bicarbonate-rich juice secreted by cells of the small ducts, which neutralizes acid entering the duodenum from the stomach. The acinar cells secrete a small volume of fluid rich in digestive enzymes, which break down carbohydrates, fats, proteins and nucleic acids. Most of these enzymes are secreted in an inactive form to protect the pancreas from autodigestion and are activated in the duodenum (Johnson, 2000).

Figure No. 1.3: Insulin synthesis and secretion process
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After preproinsulin mRNA transcription, preproinsulin is synthesized in the ER and converted into proinsulin, proinsulin is transported through the Golgi apparatus and packaged into immature clathrin-coated granules, where proinsulin is processed into insulin and c-peptide. The immature granules can then become mature granules containing crystallized insulin. After glucose stimulation insulin granules exhibit two characteristic phases that consist of a rapidly initiated but transient first phase and a sustained second phase, because the granules are divided into two different pools. (1) A limited pool of granules (< 5%) ready for immediate release and is referred to as the "readily releasable pool" (RRP), which account for the first release phase. (2) Most of the granules (> 95%) belong to a reserve pool responsible for the second-phase of insulin secretion, granules in this pool must undergo mobilization before they can gain release competence (Ren et al., 2007).

Table 1.1: Effect of Insulin on target tissues

<table>
<thead>
<tr>
<th>Immediate</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membrane transport of glucose</td>
<td>Muscle, adipose, liver</td>
</tr>
<tr>
<td>Membrane transport of amino acids</td>
<td>Muscle, adipose, liver</td>
</tr>
<tr>
<td>Membrane transport of certain ions</td>
<td>Red blood cell</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intermediate</th>
<th>Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbohydrate Metabolism</strong></td>
<td></td>
</tr>
<tr>
<td>Increase Glycogen synthesis</td>
<td>Muscle, liver</td>
</tr>
<tr>
<td>Decrease Glycogenolysis</td>
<td>Muscle, liver</td>
</tr>
<tr>
<td>Decrease Gluconeogenesis</td>
<td>Liver</td>
</tr>
</tbody>
</table>

| **Protein Metabolism**            |                              |
| Increase Protein synthesis        | Liver, muscle, adipose       |
| Decrease Proteolysis              | Liver, muscle                |

| **Fat Metabolism**                |                              |
| Increase Lipogenesis              | Liver, adipose               |
| Increase Esterification           | Liver, adipose               |
| Decrease Lipolysis                | Adipose                      |

(Foucherau and Freychept, 1976)
1.2.3 Diagnosis of Diabetes Mellitus:
The National Diabetes Data Group and World Health Organization have issued diagnostic criteria for DM:
1. The spectrum of fasting plasma glucose (FPG) and the response to an oral glucose load varies among normal individuals,
2. DM is defined as the level of glycemia at which diabetes-specific complications occur rather than on deviations from a population-based mean (The expert committee on the diagnosis and classification of diabetes mellitus, 2002).

Table 1.2: Glucose tolerance is classified into 3 categories based on the FPG levels.

<table>
<thead>
<tr>
<th>Categorization</th>
<th>FPG levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&gt; 5.6 mmol/L (≥100 mg/dL)</td>
</tr>
<tr>
<td>Prediabetic / high normal</td>
<td>&lt; 5.6 mmol/L (≤100 mg/dL) but 7.0 mmol/L (≥126 mg/dL)</td>
</tr>
<tr>
<td>Diabetic</td>
<td>&gt; 7.0 mmol/L (≥126 mg/dL)</td>
</tr>
</tbody>
</table>
1.2.4 Classification of Diabetes Mellitus:

Diabetes mellitus appears in two varieties, each with its own cause: diabetes mellitus type I (formerly known as juvenile onset diabetes), caused by deficiency of the pancreatic hormone insulin (whose chief function is to promote the entry of glucose into cells); and diabetes mellitus type II (formerly known as maturity onset diabetes), in which insulin is available but cannot be properly utilized (The expert committee on the diagnosis and classification of diabetes mellitus, 2002).

1.2.4.1 Type 1 Diabetes Mellitus:

Type 1 diabetes is the form of the disease due primarily to β-cell destruction. This usually leads to a type of diabetes in which insulin is required for survival. Individuals with type 1 diabetes are metabolically normal before the disease is clinically manifest, but the process of β-cell destruction can be detected earlier by the presence of certain autoantibodies. Type 1 diabetes usually is characterized by the presence of anti-GAD, anti-islet cell, or anti-insulin antibodies, which reflect the autoimmune processes that have led to β-cell destruction. Individuals who have one of more of these antibodies can be subclassified as having type 1A, immune-mediated type 1 diabetes. Particularly in nonwhites, type 1 diabetes can occur in the absence of autoimmune antibodies and without evidence of any autoimmune disorder. In this form of type 1 diabetes, the natural history also is one of progressive disease with marked hyperglycemia resulting in an insulin requirement for prevention of ketosis and survival. Such individuals are classified as having type 1B, or idiopathic, diabetes. Type 1A diabetes shows strong associations with specific haplotypes or alleles at the DQ-A and DQ-B loci of the human leukocyte antigen (HLA) complex. The rate of β-cell destruction is quite variable, being rapid in some individuals, especially in infants and children, and slower in adults. Some have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia or ketoacidosis, and others, particularly adults, may retain some residual β-cell function for many years and have sometimes been termed as having “latent autoimmune diabetes”. Such individuals may become dependent on insulin for survival only many years after the detection of diabetes. Individuals with type 1 diabetes have low or undetectable levels of
insulin and plasma C-peptide. Patients with type 1A diabetes are also more likely to have other concomitant autoimmune disorders, such as Graves disease, Hashimoto thyroiditis, Addison disease, vitiligo, or pernicious anemia. Type 1B, or idiopathic, diabetes is characterized by low insulin and C-peptide levels similar to those in type 1A. Such patients are prone to ketoacidosis, although they have no clinical evidence of autoimmune antibodies. Many of these patients are of African or Asian origin. They may suffer from episodic ketoacidosis, but the pathogenetic basis for their insulinopenia remains obscure (Alberti and Zimmet, 1998).

1.2.4.2 Type 2 Diabetes Mellitus:
Type 2 diabetes is the most common form of diabetes. It is characterized by disorders of insulin action and insulin secretion, either of which may be the predominant feature. Usually, both are present at the time diabetes becomes clinically manifest. Although the specific etiology of this form of diabetes is not known, autoimmune destruction of the β-cells does not occur. Patients with type 2 diabetes usually have insulin resistance and relative, rather than absolute, insulin deficiency. At the time of diagnosis of diabetes, and often throughout their lifetimes, these patients do not need insulin treatment to survive, although ultimately many require it for glycemic control. This form of diabetes is associated with progressive β-cell failure with increasing duration of diabetes. Ketoacidosis seldom occurs spontaneously but can arise with stress associated with another illness such as infection (Abate and Chandalia, 2003).
Most patients with type 2 diabetes are obese when they develop diabetes, and obesity aggravates the insulin resistance. Type 2 diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and in the earlier stages is not severe enough to produce the classic symptoms of diabetes; however, such patients are at increased risk of developing macrovascular and microvascular complications. Their circulating insulin levels may be normal or elevated yet insufficient to control blood glucose levels within the normal range because of their insulin resistance. Thus, they have relative, rather than absolute, insulinopenia. Insulin resistance may improve with weight reduction or pharmacologic treatment and results in normalization of their
glycemia. Type 2 diabetes is seen frequently in women who have a previous history of gestational diabetes and in individuals with other characteristics of the insulin resistance syndrome, such as hypertension or dyslipidemia. Patients who are not obese and who have relatives with type 1 diabetes, especially those of European origin, may present with a clinical picture consistent with type 2 diabetes but may have autoantibodies similar to those found in type 1 diabetes. Such patients have type 1A diabetes yet may appear to have type 2 diabetes unless antibody determinations are made. The risk of developing type 2 diabetes increases with age, obesity, and physical inactivity. Type 2 diabetes shows strong familial aggregation, so that persons with a parent or sibling with the disease are at increased risk, as are individuals with obesity, hypertension, or dyslipidemia and women with a history of gestational diabetes. The disease can occur at any age and is now seen in children and adolescents (Ward et al., 1986).

1.2.4.3 Gestational Diabetes Mellitus:
Gestational diabetes mellitus (GDM) is carbohydrate intolerance associated with hyperglycemia of variable severity with the onset or first recognition during pregnancy. Gestational diabetes can have deleterious consequences for both the fetus and mother. Diabetes occurring before or recognized during pregnancy with elevated fasting glucose concentrations is associated with an increased risk of intrauterine fetal death during the last 4 to 8 weeks of gestation and other complications, including congenital abnormalities. GDM without severe fasting hyperglycemia has not been associated with increased perinatal mortality, but GDM of any severity increases the risk of fetal macrosomia. Neonatal hypoglycemia, jaundice, polycythemia, and hypocalcemia are other fetal complications of GDM. Offspring of women with GDM or with type 2 diabetes preceding pregnancy are at increased risk of obesity, glucose intolerance, and diabetes in adolescence or as young adults. The recent classification system for diabetes and related states of hyperglycemia has focused on etiopathogenesis whenever possible. Although the underlying causes of the more common forms of diabetes are still unknown, their characteristics are sufficiently distinct for classification to be made with reasonable
certainty in most instances. This, along with defined clinical stages, provides a clinically useful framework that can be modified as more precise information on the specific etiology of certain forms of diabetes becomes known. The classification and staging also provide a framework for further research into the etiology, treatment, and prevention of the many forms of diabetes (ADA, 2008).

1.2.4.4 Other specific types of Diabetes:
Other specific types of diabetes are those in which the underlying defect or disease process can be identified in a relatively specific way or those that have other distinctive, distinguishing features. This category encompasses a variety of types of diabetes secondary to other specific conditions or associated with particular diseases or syndromes with a distinct etiology. These include genetic defects of β-cell function, which encompass several types of diabetes that are associated with specific monogenic defects. Most of these are characterized by a dominant pattern of inheritance and the onset of hyperglycemia at an early age. They are often referred to as maturity-onset diabetes of the young (MODY). They are characterized by impaired insulin secretion with minimal or no defects in insulin action. They are inherited in an autosomal dominant pattern but are heterogeneous. A number of specific genetic defects have been identified, including variations in hepatic nuclear factor 4α (HNF4α) (MODY1), glucokinase (MODY2), HNF1α (MODY3), insulin-promoting factor 1 (IPF1) (MODY4), and HNF3β genes (MODY5).

There are also some forms of MODY for which the genetic defect remains to be identified. Another form of autosomal dominant diabetes is due to a mutation in the K\text{ATP} channel subunit (SUR1) of the sulfonylurea receptor that gives rise to congenital hyperinsulinemia and loss of insulin secretory capacity in young adults, leading to impairment of glucose tolerance and diabetes in middle age. Another genetic defect of β-cell function is due to a mutation in mitochondrial DNA. The mitochondrial DNA variant, Leu-Ala at position 3243, leads to diabetes mellitus associated with deafness. Because this form of diabetes is due to a mitochondrial defect, it may be suspected when there is evidence of maternal inheritance, particularly when associated with deafness. The
same mitochondrial variant also is found in the MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome), although diabetes is not part of this syndrome (Maassen et al, 2004).

Some forms of diabetes are associated with rare autosomal dominantly inherited genetic defects of insulin or insulin action. In one form affected individuals are unable to convert proinsulin to insulin. In general the glucose intolerance is mild. Structurally abnormal insulins, from specific mutations in the insulin gene, with resultant impaired receptor binding, have been identified in a few families. Affected individuals may have either mildly impaired or even normal glucose metabolism but have high circulating levels of insulin or C-peptide. A number of specific mutations of the insulin receptor gene have been identified that also result in impaired insulin action (Kahn et al., 1996).

Although these are rare causes of diabetes, they should be considered if circulating insulin levels are exceptionally high and if there are other clinical characteristics of insulin resistance syndromes such as acanthosis nigricans, ovarian dysfunction, hyperandrogenism, lipodystrophy, or extreme hypertriglyceridemia. The possibility of diabetes due to antibodies in the insulin receptor should be entertained if other autoimmune diseases such as systemic lupus erythematosus, Sjögren syndrome, or ataxia-telangiectasia are present. Defects of insulin action with a genetic basis are present in leprechaunism, the Rabson-Mendenhall syndrome, and lipoatrophic diabetes (Kakehi et al., 1998).

Diabetes mellitus may be secondary to a variety of diseases of the exocrine pancreas. Fibrocalculous pancreatopathy, which was considered one of the subtypes of “malnutrition-related” diabetes in the 1985 WHO classification, is now placed in that category. Diabetes may also result from pancreatitis, pancreatectomy, neoplastic disease of the pancreas, cystic fibrosis, and hemochromatosis. One specific form of exocrine pancreatic deficiency associated with a genetic abnormality of the PEK gene is the rare Wolcott-Rallison syndrome, which is associated with early-onset diabetes and multiple epiphyseal dysplasia.

Diabetes mellitus may result from several endocrinopathies. It may occur in association with Cushing syndrome, acromegaly, pheochromocytoma, glucagonoma,
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hyperthyroidism, and soma-tostatinoma. A variety of drugs or chemicals have been associated with the development of diabetes. These include glucocorticoids, nicotinic acid, diazoxide, phenytoin, and pentamidine. When diabetes is associated with such agents, it is often uncertain whether or not the drug has been the direct cause of the diabetes or the diabetes has appeared coincidentally in association with administration of the drug. A few specific infections may result in diabetes mellitus, including congenital rubella and cytomegalovirus infections. There are also a number of other relatively rare genetic syndromes sometimes associated with diabetes (Kakehi et al., 1998).

1.3 Treatment and Management of Diabetes Mellitus:
The goals of treatment for diabetes are to reduce and control blood glucose levels, relieve the symptoms of the disease, and prevent complications. Intensive treatment and careful control of blood glucose levels can reduce the risk of complications from diabetes.
The American Diabetes Association recommends the formulation of an individualized diabetes management plan in collaboration with the patient. A high degree of patient involvement in self-management should be part of this plan, including frequent self-monitoring of blood glucose (ADA, 2003 a).

1.3.1 Lifestyle management:
   a) Structured education programmes based upon adult learning theories.
   b) Avoid Smoking
   c) Individualized interventions to encourage weight loss in order to improve metabolic control.

1.3.2 Psychosocial factors:
Regular assessment of a broad range of psychological and behavioral problems like
   a) Eating disorders, behavioral, emotional and family functioning problems (Children).
   b) Anxiety, depression and eating disorders (Adults).

1.3.3 Psychological interventions like motivational interviewing, goal setting skills:

1.3.4 Management of type 1 diabetes:
   a) Regular human or rapid-acting insulin analogues.
b) Basal insulin analogues are recommended in adults with type 1 diabetes who are experiencing severe or nocturnal hypoglycemia.

1.3.5 Pharmacological management of glycemic control in people with type 2 diabetes:

a) DPP-4 inhibitors may be used to improve blood glucose control
b) GLP-1 agonists (exenatide or liraglutide) may be used to improve glycaemic control in obese adults.
c) Oral metformin and sulphonylurea therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control.
d) Once daily bedtime NPH insulin should be used when adding insulin to metformin and/or sulphonylurea therapy.
e) Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycemic control.

1.3.5.1 Management of diabetes in pregnancy:

a) A suitable programme to detect and treat gestational diabetes should be offered to all women in pregnancy.
b) Dietary advice and blood glucose monitoring.
c) Metformin or glibenclamide may be considered as initial pharmacological, glucose lowering treatment in women with gestational diabetes.

1.3.5.2 Management of diabetic cardiovascular disease:

a) Lifestyle modification and drug therapy.
b) Lipid-lowering drug therapy with simvastatin 40 mg or atorvastatin
c) Intensive lipid-lowering therapy with atorvastatin 80 mg should be considered for patients with diabetes and acute coronary syndromes.

1.3.5.3 Management of kidney disease in diabetes:

a) ACE inhibitors and/or ARBs should be used as agents of choice in patients with chronic kidney disease and proteinuria (Alwan, 1994).
1.4 Herbal medicine and their potential to treat Diabetes Mellitus:
Diabetes mellitus (DM) is described in Ayurveda as *madhumeha kshaudrameha*, which literally means “excessive urine with sweet taste like honey,” or *dhatupak janya vikriti*, which means a disease caused by a defective metabolism leading to derangement in body tissue (seven *dhatus*) transformation process.

Historically, Ayurvedic texts have described 20 types of urinary disorders (*pramehas*) based on the predominant dosas (10 *kaphaja*, 6 *pittaja* and 4 *vataja* urinary disorders) and physical characteristics of the urine (e.g., volume, color, odor, taste, sediments, solid particles, presence of seminal fluid, and mucus). The urine is discharged in excessive quantities and is generally turbid. DM is one of these *pramehas* that may occur in any of the three (*vata, kapha*, or *pitta*) body constitutions (Rao et al., 2010). DM may result in premature disability, mortality, blindness, end-stage renal disease (ESRD), and nontraumatic limb amputations. DM is also known to increase the risk of heart, cerebral, and vascular diseases by two- to sevenfold (Lee et al., 2007).

Many of the complications of DM are preventable or can be delayed by appropriate treatment of hyperglycemia and other cardiovascular risk factors. Synthetic drugs like sulphonyl ureas and biguanides may be effective in controlling the blood sugar level for some time, but they may cause side effects like hypoglycemia, nausea, vomiting, cholestatic jaundice, and other health problems. Most type 2 DM patients initially respond to lowering of blood glucose levels (BGLs), but after some time about 20% become resistant and do not benefit from these agents (Woolf et al., 1999).

Patients may also not respond fully to these agents due to the loss of interest in regular diet and exercise, the progression of beta cell failure, drug resistance, and other medical problems. Many patients eventually require insulin treatment. Plant materials which are being used as traditional medicine for the treatment of diabetes are considered one of the good sources for a new drug or a lead to make a new drug. Plant extract or different folk plant preparations are being prescribed by the traditional practioners and also accepted by the users for diabetes like for any other diseases in many countries especially in third world countries (Wadkar et al., 2008). Regardless of the type of diabetes, patients are required to control their blood glucose with medications and/or by adhering to an
exercise program and a dietary plan. Insulin therapy by injection is given to those with type 1 DM and also to some patients with type 2 DM when oral hypoglycaemic drugs fail to lower blood glucose (Mudaliar and Edelman, 2001).

Due to modernization of lifestyle, non-insulin dependent diabetes mellitus is becoming a major health problem in developing countries (Zimmet, 1998). Patients with type 2 DM are usually placed on a restricted diet and are instructed to exercise, the purpose of which primarily is weight control. If diet and exercise fail to control blood glucose at the desired level, oral antidiabetic medication is prescribed. Oral antidiabetic agents exert their effects by various mechanisms: (1) stimulation of beta cells in the pancreas to produce more insulin (sulfonylureas and meglitinides), (2) increasing the sensitivity of muscles and other tissues to insulin (thiazolidinediones), (3) decreasing gluconeogenesis by the liver (biguanides), and (4) delaying the absorption of carbohydrates from the gastrointestinal tract (alpha-glucosidase inhibitors) (Jayasri et al, 2009). These treatments have their own drawbacks, ranging from the developing of resistance and adverse effects to lack of responsiveness in large segment of patients population. Sulfonylureas lose effectiveness for 44% of patients within six years. Also, these treatments are associated with side effects or even toxic effects (e.g., thiazolidinediones may cause liver toxicity; sulphonylureas might worsen heart disease, lower the glucose below the normal range and increase the body weight gain; bloating, flatulence, diarrhea and abdominal discomfort and pain are the major complaints with glucosidase inhibitors) (Alice et al., 2005).

According to literature, two-thirds of medications prescribed for use in children have not been proven safe or effective for this patient population. Moreover, none of these glucose-lowering agents adequately controls the hyperlipidemia that frequently met with the disease. The limitations of currently-available oral antidiabetic agents either in terms of efficacy/safety coupled with the emergence of the disease into a global epidemy have encouraged a concerted effort to discover drugs that can manage type 2 diabetes more efficiently. Also, with increasing incidence of diabetes mellitus in rural population throughout the world and due to adverse effects of synthetic medicine, there is a clear need for development of indigenous, inexpensive botanical sources for anti-diabetic
crude or purified drugs (Jarald et al., 2008). As per ancient literature, more than 800 plants are reported to have antidiabetic properties. Ethnopharmacological surveys indicate that more than 1200 plants are used in traditional medicine for their alleged hypoglycemic activity. Medicinal plants, since times immemorial, have been used in virtually all cultures as a source of medicine. A study of ancient literature indicates that diabetes was fairly well known and well conceived as an entity in ancient India. The knowledge of the system of diabetes mellitus, as the history reveals, existed with the Indians since prehistoric age (Raju et al., 2012).

Its earliest reference (1000 BC in the Ayurvedic literature) is found in mythological form where it is said to have originated by eating Havisha, a special food, which used to be offered at the times of yagna organized by Dakshaprajapati. Ayurvedic antidiabetic herbs improve digestive power, increase one of the Rasas (gastric secretions); being Laghu, get easily digested in the body; and being Ruksha, decrease output of overall body fluids e.g. urine, sweat etc. Food items, which are ‘madhumehaghna’ (antidote), are an important underlying principle of therapy for the prameha (diabetes) patient. Food items which correct the metabolic imbalance by their action e.g. foods exhibiting ‘rasa’, ‘katu’, ‘laghu’, ‘medaghna’, properties are old cereals, roasted cereals, barley, jawar, ragi, mung dal, horsegram, tur dal, drumstick leaves, bittergourd, jamun, amla, fig, raw papaya, milk, meat of animals that live in dry region, etc. The indigenous diet may not be useful in lowering the blood sugar to the same extent as insulin and other hypoglycaemic agent (Alexiou and Demopoulos, 2010). Indian materia medica has mentioned numerous dravyas, which have been reported effective in Madhumeha (Pandey et al., 2011).

Plants-based products have been popular all over the world for the centuries. In diabetes, some herbal alternatives are proven to provide symptomatic relief and assist in the prevention of the secondary complications of the disease. Some herbs have also been proven to help in the regeneration of β-cells and in overcoming resistance. In addition to maintaining normal blood sugar level, some herbs are also reported to possess antioxidant activity and cholesterol-lowering action. In modern system of medicine, there is no drug, which is reported to posses both of these properties. However, the hypoglycemic effect of some herbal extracts have been confirmed in human and animal models of type 2 diabetes.
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and conventional drugs have been derived from the active molecules of these medicinal plants. Metformin, a less toxic biguanides and potent oral glucose-lowering agent, was developed from *Galega officinalis* and used to treat diabetes. Out of dozens of oral medications for diabetes, only one medication (metformin) is approved for use in children and it has been originated from herbs (Michael et al., 2005).

1.4.1 Scientifically validated antidiabetic plants

Among the traditional plants used for diabetes, only a small number of these have received scientific and medical evaluation as follows:

<table>
<thead>
<tr>
<th>S.No</th>
<th>Biological Sources</th>
<th>Family</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>Acacia arabica</em> (Lam.) Muhl. Ex Willd</td>
<td>Mimosaceae</td>
</tr>
<tr>
<td>2.</td>
<td><em>Aegle marmelos</em> (L.) Correa Ex Roxb</td>
<td>Rutaceae</td>
</tr>
<tr>
<td>3.</td>
<td><em>Allium cepa</em> L.</td>
<td>Liliaceae</td>
</tr>
<tr>
<td>4.</td>
<td><em>Allium sativum</em> L.</td>
<td>Alliaceae</td>
</tr>
<tr>
<td>5.</td>
<td><em>Aloe vera</em> (L.) Burm</td>
<td>Aloaceae</td>
</tr>
<tr>
<td>6.</td>
<td><em>Anthemis mobilis</em> Linn.</td>
<td>Compositae</td>
</tr>
<tr>
<td>7.</td>
<td><em>Areca catechu</em> L.</td>
<td>Arecaceae</td>
</tr>
<tr>
<td>8.</td>
<td><em>Artemisia pallens</em> Wall. Ex DC.</td>
<td>Compositae</td>
</tr>
<tr>
<td>9.</td>
<td><em>Annona squamosa</em> L.</td>
<td>Annonaceae</td>
</tr>
<tr>
<td>10.</td>
<td><em>Andrographis paniculata</em> Nees</td>
<td>Acanthaceae</td>
</tr>
<tr>
<td>11.</td>
<td><em>Aerva lanata</em> (L.) Juss. ex Schult</td>
<td>Amaranthaceae</td>
</tr>
<tr>
<td>12.</td>
<td><em>Asteracantha longifolia</em> Nees</td>
<td>Acanthaceae</td>
</tr>
<tr>
<td>13.</td>
<td><em>Azadirachta indica</em> A. Juss</td>
<td>Meliaceae</td>
</tr>
<tr>
<td>14.</td>
<td><em>Biophytum sensitivum</em> (L.) DC.</td>
<td>Oxalidaceae</td>
</tr>
<tr>
<td>15.</td>
<td><em>Bombax ceiba</em> L.</td>
<td>Bombacaceae</td>
</tr>
<tr>
<td>16.</td>
<td><em>Beta vulgaris</em> L.</td>
<td>Chenopodiaceae</td>
</tr>
<tr>
<td>17.</td>
<td><em>Brassica juncea</em> (L.) Czern</td>
<td>Brassicaceae</td>
</tr>
</tbody>
</table>
18. *Barleria lupulina* Lindl | Acanthaceae  
19. *Boerhavia diffusa* L | Nyctaginaceae  
20. *Brickellia veronicaefolia* A. Gray | Asteraceae  
21. *Cassia auriculata* L. | Leguminosae  
22. *Caesalpinia bonducella* (L.) Roxb. | Cesalpinaceae  
23. *Capparis decidua* (Forsk.) Edgew. | Capparidaceae  
24. *Cajan s cajan* (L.) Millsp. | Fabaceae  
25. *Citrus colocynthis* (L.) Schrad. | Cucurbitaceae  
26. *Coccinia indica* Wight & Arn | Cucurbitaceae  
27. *Casearia esculenta* Roxb. | Flacourtiaceae  
28. *Catharanthus roseus* (L.) G. Don | Apocynaceae  
29. *Camellia sinensis* Kuntze | Theaceae  
30. *Coriandrum sativum* L | Apiaceae  
31. *Cuminum cyminum* L. | Apiaceae  
32. *Daucus carota* L. | Apiaceae  
33. *Eugenia uniflora* L | Myrtaceae  
34. *Eugenia jambolana* L. | Myrtaceae  
35. *Eucalyptus globulus* Labill. | Myrtaceae  
36. *Enicostemma littorale* Blume | Gentianaceae  
37. *Ficus bengalensis* L. | Moraceae  
38. *Gymnema montanum* Hook.f. | Asclepiadaceae  
40. *Glycyrrhiza glabra* L. | Fabaceae  
41. *Hibiscus rosa sinensis* L. | Malvaceae  
42. *Helicteres isora* L. | Sterculiaceae  
43. *Ipomoea batatas* (L.) Lam. | Convolvulaceae  
44. *Lantana camara* L | Verbenaceae
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<table>
<thead>
<tr>
<th></th>
<th>Scientific Name</th>
<th>Family</th>
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</thead>
<tbody>
<tr>
<td>45.</td>
<td><em>Mangifera indica</em> L.</td>
<td>Anacardiaceae</td>
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<td>46.</td>
<td><em>Memecylon umbellatum</em> Burm. F.</td>
<td>Melastomataceae</td>
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<td>47.</td>
<td><em>Momordica cymbalaria</em> Fenzl Ex</td>
<td>Cucurbitaceae</td>
</tr>
<tr>
<td>48.</td>
<td><em>Mucuna pruriens</em> (L.) DC.</td>
<td>Leguminosae</td>
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<td>49.</td>
<td><em>Musa sapientum</em> L.</td>
<td>Musaceae</td>
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<tr>
<td>50.</td>
<td><em>Momordica charantia</em> L.</td>
<td>Cucurbitaceae</td>
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<tr>
<td>51.</td>
<td><em>Morus alba</em> L</td>
<td>Moraceae</td>
</tr>
<tr>
<td>52.</td>
<td><em>Murraya koenigii</em> (L.) Spreng.</td>
<td>Rutaceae</td>
</tr>
<tr>
<td>53.</td>
<td><em>Nelumbo nucifera</em> Gaertn.</td>
<td>Nymphaeaceae</td>
</tr>
<tr>
<td>54.</td>
<td><em>Ocimum sanctum</em> L.</td>
<td>Lamiaceae</td>
</tr>
<tr>
<td>55.</td>
<td><em>Panax ginseng</em> Mey.</td>
<td>Araliaceae</td>
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<tr>
<td>56.</td>
<td><em>Picrorrhiza kurroa</em> Royle ex Benth.</td>
<td>Scrophulariaceae</td>
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<td>57.</td>
<td><em>Phyllanthus amarus</em> Schumach. &amp; Thonn</td>
<td>Euphorbiaceae</td>
</tr>
<tr>
<td>58.</td>
<td><em>Pterocarpus marsupium</em> Roxb</td>
<td>Fabaceae</td>
</tr>
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<td>59.</td>
<td><em>Punica granatum</em> L.</td>
<td>Punicaceae</td>
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<td>60.</td>
<td><em>Psacalium peltatum</em> Cass.</td>
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<td>61.</td>
<td><em>Pterocarpus santalinus</em> L. F.</td>
<td>Leguminosae</td>
</tr>
<tr>
<td>64.</td>
<td><em>Scoparia dulcis</em> L.</td>
<td>Scrophulariaceae</td>
</tr>
<tr>
<td>65.</td>
<td><em>Syzygium alternifolium</em> Walp.</td>
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</tr>
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<td>66.</td>
<td><em>Sida cordifolia</em> L.</td>
<td>Malvaceae</td>
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<tr>
<td>67.</td>
<td><em>Trigonella foenum graecum</em> L.</td>
<td>Fabaceae</td>
</tr>
<tr>
<td>68.</td>
<td><em>Terminalia catappa</em> L.</td>
<td>Combretaceae</td>
</tr>
<tr>
<td>69.</td>
<td><em>Tinospora cordifolia</em> (Willd.)</td>
<td>Menispermaceae</td>
</tr>
<tr>
<td>70.</td>
<td><em>Zingiber officinale</em> Roscoe</td>
<td>Zingiberaceae</td>
</tr>
<tr>
<td>71.</td>
<td><em>Zizyphus sativa</em> Gaertn</td>
<td>Rhamnaceae</td>
</tr>
</tbody>
</table>
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1.4.2 Antidiabetic plants in clinical trials:

Allium ceca L., Clerodendron phlomoides Linn., Cinnamomum tamala (Buch.-Ham.) T. Nees & Eberm., Coccinia indica Wight & Arn., Enicostemma littorale Blume, Ficus bengalensis L., Momordica charantia L., Pterocarpus marsupium Roxb., Cyamopsis tetragonolobus (L.) Taub., Cephalandra indica Naud., Casearia esculenta Roxb., Cannabis indica (Lam.) E. Small & Cronq., and Syzygium cumini L. when subjected to clinical trials, showed promising hypoglycaemic effects. Cecropia obtusifolia Bertol. And Marrubium vulgare L. produced beneficial effects on carbohydrate and lipid metabolisms when it was administered as an adjunct on patients with type 2 diabetes and reduced the blood glucose levels (Herrera et al., 2004).

Asteracantha longifolia Nees was reported to improve glucose tolerance in healthy human subjects and diabetic patients. Significant reduction in glycaemia was observed when Panax quinquefolius L was taken 40 min before glucose load in non-diabetic subjects and the same result was seen in diabetic subjects. Gymnema Sylvestre R. Br. treated patients showed a significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins. Intake of Opuntia streptacantha L. by the type II group was followed by a significant reduction in serum glucose and insulin concentration reaching 40.8 mg/dL and 7.8 μU/mL less than basal values at 180 min. Acute hypoglycaemic effect of nopal was observed in patients with type II diabetes but not in healthy subjects. In 10 human subjects, when treated with a preparation of the whole plant, Phyllanthus amarus Shum. & Thon. for ten days, the blood glucose level was reduced. The treatment with Withania somnifera produced a decrease in blood glucose levels that was comparable with effects of an oral hypoglycemic drug (Ali et al., 2006).

1.4.3 Mechanism of action of herbal antidiabetic:

The antidiabetic activity of herbs depends upon variety of mechanisms. The mechanism of action of herbal anti-diabetic could be grouped as-

- Adrenomimeticism, pancreatic beta cell potassium channels blocking, cAMP (2nd messenger) stimulation (Marles and Farnsworth, 1996).
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- Inhibition in renal glucose reabsorption (Eddouks and Maghrani, 2004).
- Stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes (Pulok et al, 2006).
- Reduction in insulin resistance (Pulok et al, 2006).
- Providing certain necessary elements like calcium, zinc, magnesium, manganese and copper for the beta-cells (Mohamed et al, 2006).
- Regenerating and/or repairing pancreatic beta cells (Mohamed et al, 2006).
- Increasing the size and number of cells in the islets of Langerhans (Mohamed et al, 2006).
- Stimulation of insulin secretion (Esmaeili and Yazdan 2004).
- Stimulation of glycogenesis and hepatic Glycolysis (Miura et al., 2001).
- Protective effect on the destruction of the beta cells (Kim et al., 2003).
- Improvement in digestion along with reduction in blood sugar and urea (Krishnan, 1968).
- Prevention of pathological conversion of starch to glucose (Sepha and Bose, 1956).
- Inhibition of β -galactocidase and α– glucocidase (Sharma and Mujumdar, 1990).
- Cortisol lowering activities (Gholap and Kar, 2004).
- Inhibition of alpha-amylase (Heidari et al., 2005).
- Preventing oxidative stress that is possibly involved in pancreatic β-cell dysfunction found in diabetes (Kaneto et al., 2005).

Hence, the wide range of plant constituents could have different sites of action within the body, herbs exerts different mechanism of actions including the mechanism of actions of synthetic oral hypoglycemic drugs. Herbal therapy for diabetes has been followed all over the World successfully. Herbs are used to manage Type 1 and Type II diabetes and their complications. The above-mentioned plants have been considered for their possible hypoglycaemic actions and the researchers have carried out some preliminary investigations. Scientific validation of several Indian plant species has proved the efficacy of the botanicals in reducing the sugar level. However, there are numerous other
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plants still await scientific inquiry, which have mentioned in the indigenous systems of health care all over the world (Donga et al., 2011). A large number of plants, screened for their antidiabetic effect, have yielded certain interesting leads as mentioned above, but till to date no plant-based drug has reached such an advanced stage of investigation or development as to substitute or reduce the need for the currently-available oral synthetic drugs. However, the interest in herbal drug research continues with an expectation that some day or the other, we would be able to bring a safer and more effective compound with all the desired parameters of a drug that could replace the synthetic medicines. The potency of herbal drugs is significant and they have negligible side effects than the synthetic antidiabetic drugs. There is increasing demand by patients to use the natural products with antidiabetic activity. In recent times there has been renewed interest in the plant remedies. Plants hold definite promises in the management of Diabetes mellitus.