INTRODUCTION
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Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or insulin receptor or post receptor events affecting metabolism involving carbohydrates, proteins and fat metabolism in addition to pancreatic β-cell damage. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.

Several pathogenic processes are involved in the development of diabetes. This ranges from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action.

Distribution and prevalence

Diabetes is a major health problem, affecting approximately 150 million people worldwide and its incidence rate is expected to double during the next 20 years (Cohen and Goedert, 2004). The global prevalence of DM for all age groups was estimated to be 4.2 % in 2000 and is projected to rise to 5.4% in 2025. The prevalence rates for type 2 diabetes in India are still increasing sharply with the number of sufferers predicted to rise from 19.4 million in 1995 to 57.2 million in 2025 (Wild et al., 2004) (Table 1).
Table 1: Top ten countries for estimated number of adults with diabetes, 1995 and 2025

<table>
<thead>
<tr>
<th>Rank</th>
<th>Country</th>
<th>1995 (Millions)</th>
<th>Rank</th>
<th>Country</th>
<th>2025 (Millions)</th>
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<td>135.3</td>
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Classification of diabetes mellitus

National Diabetic Data Group (1979) and World Health Organization (1985) recognized two major forms of diabetes which they termed as type I diabetes or juvenile onset diabetes, Insulin dependent diabetes mellitus (lDDM) and type 2 diabetes or Non-Insulin dependent diabetes mellitus (NIDDM).

Insulin dependent diabetes mellitus

Insulin dependent diabetes, type I diabetes or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β-cells of the pancreas (Atkinson and Maclaren, 1994). Immune-mediated diabetes commonly occurs in childhood and adolescence, but it can occur at any age, even in the 8th and 9th decades of life. The rate of β-cell destruction is quite variable, being rapid in infants and children and slow in adults (Huang et al., 1996). Markers of the immune destruction of the β-cell include islet cell autoantibodies (ICAs), autoantibodies to insulin (IAAs), autoantibodies to glutamic acid decarboxylase (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2B (Lan et al., 1996). 85-90% of patients have one and more of these autoantibodies. Also, the disease has strong HLA associations, with linkage to the DQA and B genes, and it is influenced by the DRB genes. At this stage of the disease, there is little or no insulin secretion, as manifested by low or undetectable levels of plasma C-peptide (Huang et al., 1996).
Non-insulin dependent diabetes mellitus

Noninsulin dependent diabetes or type 2 diabetes or adult onset diabetes, is a term used for individuals who have insulin resistance and usually have relative insulin deficiency. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity (Kolterman et al., 1985). Most patients with this form of diabetes are obese, and obesity itself causes some degree of insulin resistance. This form of diabetes frequently goes undiagnosed for many years because the hyperglycemia develops gradually and at earlier stages is often not severe enough for the patient to notice any of the classic symptoms of diabetes. Nevertheless, such patients are at increased risk of developing macrovascular and microvascular complications (Kuusisto et al., 1994).

Gestational diabetes mellitus (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. The definition applies regardless of whether insulin or only diet modification is used for treatment or whether the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with the pregnancy. The prevalence may range from 1 to 14% of pregnancies (Engelgau et al., 1988) and it represents nearly 90% of all pregnancies complicated by diabetes (Coustan 1995). Clinical recognition of GDM is important because therapy, including
medical nutrition therapy, insulin when necessary, and antepartum fetal surveillance, can reduce the well described GDM-associated perinatal morbidity and mortality (Langer et al., 1994).

**Other specific types of diabetes**

**Genetic defects of the β-cell:**

Several forms of diabetes are associated with monogenetic defects in β-cell function. They are referred to as maturity onset diabetes of the young (MODY) and are characterized by impaired insulin secretion with minimal or no defects in insulin action. Genetic abnormalities that result in the inability to convert pro insulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern (Gruppuso et al., 1984). The resultant glucose intolerance is mild. Similarly, the production of mutant insulin molecules with resultant impaired receptor binding has also been identified in a few families and is associated with an autosomal inheritance and only mildly impaired or even normal glucose metabolism (Tager et al., 1979).

**Virus induced diabetes:**

Certain viruses have been associated with β-cell destruction. Diabetes occurs in patients with congenital cytomegalovirus and rubella which may induce autoimmunity, leading to type 1 diabetes (Forrest et al., 1971). In addition, cox sackievirus B, cytomegalovirus, adenovirus,
and mumps have been implicated in inducing certain cases of the disease (Karjalainen et al., 1988).

**Drug or chemical-induced diabetes:**

Many drugs can impair insulin secretion. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. Certain toxins such as Vacor (a rat poison), nicotinic acid and glucocorticoids can impair insulin action (Pandit et al., 1993). Body builders who take enormous doses of anabolic androgens can develop impaired glucose tolerance. Several drugs including theophyline, aspirin, isoniazid and nalidixic acid can cause transient hyperglycemia in overdoses (Ferner, 1992).

**Environmental Toxins:**

Environmental genotoxins are known to be potential risk factors for some form of diabetes mellitus. Cycasin, a toxin obtained from the cycad plant is of special interest since this agent may be implicated in diabetes mellitus in the western pacific area (Eizirik et al., 1996).

**Diseases of the exocrine pancreas:**

Any process that diffusely injures the pancreas can cause diabetes. Acquired processes include pancreatitis, trauma, infection, pancreatectomy, and pancreatic carcinoma (Cersosimo et al., 1991). Cystic fibrosis and hemochromatosis will also damage β -cells and impair insulin secretion (Handwerger et al., 1969).
Endocrinopathies:

Several hormones antagonizing insulin action (e.g., growth hormone, cortisol, glucagon, epinephrine) can cause diabetes. Somatostatinoma- and aldosteronoma- induced hypokalemia can cause diabetes by inhibiting insulin secretion (Berelowitz and Eugene, 1996).

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (The Expert Committee, 2003)

The Expert Committee recognized an intermediate group of subjects whose glucose levels, although not meeting criteria for diabetes, are nevertheless too high to be considered normal. This group is defined as having fasting plasma glucose (FPG) levels ≥100 mg/dL (5.6 mmol/L) but <126 mg/dL (7.0 mmol/L) or 2-hr values in the oral glucose tolerance test (OGTT) of ≥140 mg/dL (7.8 mmol/L) but <200 mg/dL (11.1 mmol/L). Thus, the categories of FPG values are as follows:

- FPG <100 mg/dL (5.6 mmol/L) = normal fasting glucose;
- FPG 100-125 mg/dL (5.6-6.9 mmol/L) = IFG (impaired fasting glucose);
- FPG >126 mg/dL (7.0 mmol/L) = provisional diagnosis of diabetes (the diagnosis must be confirmed).

The corresponding categories when the OGTT is used are the following:
2-hr post load glucose <140 mg/dL (7.8 mmol/L) = normal glucose tolerance;

2-hr post load glucose 140-199 mg/dL (7.8 -11.1 mmol/L) = IGT (impaired glucose tolerance);

2-hr post load glucose >200 mg/dL (11.1 mmol/L) = provisional diagnosis of diabetes (the diagnosis must be confirmed).

Diagnostic criteria for diabetes mellitus:

Three ways to diagnose diabetes are possible, and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by anyone of the three methods given below. The use of the glycated hemoglobin for the diagnosis of diabetes is not recommended at this time.

1. Based on symptoms of diabetes and a casual plasma glucose concentration ≥200 mg/dL (11.1 mmol/L). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss. (or)

2. FPG ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hr (or)

3. 2-hr post load glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75-g anhydrous glucose dissolved in water.
Symptoms of diabetes mellitus

➢ The symptoms of marked hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia and blurred vision.

➢ Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.

➢ Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the nonketotic hyperosmolar syndrome.

Pathogenesis of diabetes mellitus

Pathogenesis refers to the sequence of events in the response of the cells or tissues to the etiologic agent, from the initial stimulus to the ultimate expression of the diseases. The study of pathogenesis remains one of the main domains of pathology. In diabetes mellitus, the pathogenesis of two types is discussed separately (Robbin's Pathological Basis of Disease, 1999).

Pathogenesis of Type-I diabetes mellitus

Type-I diabetes mellitus usually occurs or develops in childhood, becoming, manifest and severe in puberty. This form of diabetes results from a severe and absolute lack of insulin caused by a reduction in β-cell mass. Patients depend on insulin for survival. Acute ketoacidosis and coma may be caused by without insulin.
Genetic susceptibility, autoimmunity and an environmental pollution are the three interlocking mechanisms responsible for islet cell destruction. Genetic susceptibility linked to specific allele of the class II MHC predisposes certain persons to the development of autoimmunity against \( \beta \)-cells of the islets. The autoimmune reaction either develops spontaneously or, more likely is triggered by environmental events that alter \( \beta \)-cells, rendering them immunogenic. Diabetes appears after most of the \( \beta \)-cells have been destroyed (Robbin's Pathological Basis of Disease, 1999).

**Genetic susceptibility**

Type-1 diabetes mellitus occurs frequently in persons of Northern European descent compared to Native Americans, Asians and among other radical groups including blacks (Kyvik et al., 1995). At least one of the genetic susceptibility genes for type-1 diabetes resides in the region that encodes the class II antigens of the MHC on chromosome 6P21 (HLAD) (Bain, 1997). The genetic variation in the HLA class II molecule may alter recognition by the T-cell receptor or modify the presentation of antigen causing variation in antigen binding cleft. Thus, class II HLA genes may affect the degree of immune responsiveness to a pancreatic \( \beta \)-cell autoantigen, or a \( \beta \)-cell auto antigen may be present in a manner that promotes an abnormal immunological reaction (Reed et al., 1997).
Autoimmunity

This disease, in fact, results from a chronic autoimmune attack of β-cells that is associated with increased expression of class 1 MHC molecule and aberrant expression of class II MHC molecules on the β-cells (Laufer et al., 1993). The aberrant expression is mediated in part by locally produced cytokines (IFN-γ) derived from activated T cells (Robinovitch, 1994). It produces the development of diabetes in mouse model (Rothe et al., 1997).

Environmental factors

Epidemiological studies suggest that the action of viruses may cause type-1 diabetes. Seasonal trends that often correspond to the prevalence of common viral infections have long been noted in the diagnosis of new causes, Coxsackie’s virus of group B cause diabetes and pancreatic diseases (Verge, 1997). The viruses cause mild β-cell injury which is followed by an autoimmune reaction by virally altered β-cells with HLA linked susceptibility.

Pathogenesis of Type-II diabetes mellitus

Epidemiological studies indicate that type-2 diabetes appears to result from a collection of multiple genetic defects or problem of polymorphisms, each contributing its own predisposing risk and modified by environmental factors. A deranged β-cell secretion of insulin and a decreased response of peripheral tissues responding to
insulin (insulin resistance) are the two major metabolic defects that characterize type-2 diabetes.

**Deranged β-cell secretion of insulin**

Risk for developing type-2 diabetes, a modest hyperinsulinemia, may be attributed to β-cell hyper responsiveness to physiological elevations in blood glucose. Observations suggest that derangements in β-cells responses to hyperglycemia and a mild to moderate deficiency of insulin develops in type-2 diabetes. According to one view, all the somatic cells are genetically vulnerable to injury, leading to accelerated cell turnover and premature aging, and ultimately to a modest reduction in β-cell mass. Glucose toxicity caused by chronic hyperglycemia may exhaust the ability of β-cells to function (Ronard Kahn, 1997) (Fig. 1).
Fig. 1: Mechanism of blood glucose elevation in type 2 diabetes mellitus.
**Insulin resistance**

In type-2 diabetes, there may be a decrease in the number of insulin receptors, and post receptor signaling by insulin is impaired. In this condition that reduces synthesis and translocation of GLUTs in muscle and fat cells underlies the insulin resistance noted in obesity. The mobility of circulating insulin properly directs the disposition of glucose and a more persistent hyperglycemia. Therefore, more prolonged stimulation of pancreatic β-cell (Ronard Kahn, 1997).

**Obesity**

Life style plays a clear role as is evident from the study of obesity. Abdominal obesity and insulin resistance could be coincidental expression of third unknown factor; the possibility whether they are causally related must be considered (Groop, 1997).

**COMPLICATIONS OF DIABETES MELLITUS**

The complications of diabetes mellitus are heterogeneous group of clinical disorders which can affect the vascular system, kidney, eye, nervous system and other tissues.

**Microvascular complications:**

Micro vascular abnormalities and dysfunction are systemic disease in diabetes. Clinically micro angiopathy leads to retinopathy, nephropathy, neuropathy and embryopathy.
**Macro vascular complications:**

Cardiovascular disease is the primary cause of early mortality in patients with type 2 diabetes. Coronary heart disease, hypertension, stroke and peripheral vascular disease occur with high frequency in diabetics due to altered lipid profile.

**Retinopathy**

Diabetic retinopathy (DR) occurs in about 95% of patients with type 1 diabetes mellitus (DM) and in 60% of type 2 DM patients. DR is the most common cause of blindness and characterized by increased proliferation of blood vessels, vascular occlusion, angiogenesis, microaneurysms, hemorrhages and infarction affecting the retina of the eye and hard exudates are described as 'background retinopathy' or preferably nonproliferative retinopathy. The nonproliferative retinopathy occurs near the maculae and causes macular edema. Macular edema occurs when leakage of fluid from abnormal vessels near the macular disrupts the light path to the macule and results in the loss of visual acuity (Nathan et al., 1986). These changes are accompanied by thickening of the capillary basement membrane, increased permeability of capillaries, loss of pericytes and increased endothelial cell turnover and death (Krolewski et al., 1986). Other visual damage caused or facilitated by diabetes includes cataract, keratitis, and optic nerve damage.
Nephropathy

Diabetic nephropathy is characterized by a thickening of the basement membrane, expansion of the mesangium, reduced filtration, albuminuria and ultimately renal failure (Mauer et al., 2001). The renal lesions underlying renal dysfunction differ in type 1 and type 2 diabetes, although the clinical manifestations of diabetic nephropathy, proteinuria, decreased glomerular filtration rate and increasing blood pressure are similar. Indeed, in type 1 diabetes, although also tubular, interstitial and arteriolar lesions are present, the most important structural changes involve the glomerulus, while several type 2 diabetic patients, despite the presence of microalbuminuria or proteinuria (30 to 300 mg of albumin per 24 hours), have normal glomerular structure with or without tubulo-interstitial and arteriolar abnormalities, which may occur as early as five years after the onset of diabetes (Viberti and Keen, 1984). This stage of incipient nephropathy may be more likely in patients with glomerular hyperfiltration. Overt diabetic nephropathy is clinically characterized by proteinuria, nephritic syndrome development and the falling of glomerular filtration rate resulting in end stage renal disease (Mogensen, 1986).

Neuropathy

Diabetic neuropathy is characterized by segmental demyelination and axonal degeneration of peripheral neurons, together with functional
abnormalities such as reduced nerve conduction and blood flow. Diabetic neuropathy may be present clinically as pain or numbness of limbs or as impotence in men. There is increased glycation of myelin in diabetes. The progression of neuropathy is dependent on the degree of glycemic control in both Type 1 and Type 2 diabetes. A peripheral symmetric sensorimotor neuropathy is the most common form of diabetic neuropathy, whose other forms include cranial and peripheral motor neuropathies and autonomic neuropathy. Although neuropathy is more common with a longer duration of diabetes (Said et al., 1992), the principal risk posed by peripheral neuropathy is of foot trauma and diabetic ulcer. A minority of patients have painful peripheral neuropathy with lancinating or burning dysesthesia, severe enough for some to be associated with depression and anorexia (Ellenberg, 1974). Risk factors for diabetic neuropathy are duration of diabetes, age, cigarette smoking, hypertension, height and hyperlipidemia.

**Embryopathy**

Diabetic mothers with poor glycemic control are prone to embryopathy, where the newborn has an increased frequency of congenital malformations. The precise mechanism underlying embryopathy in diabetes is unknown, but a reduction in congenital malformations is seen in pregnancies where the hyperglycemia is well controlled (Mills et al., 1988). Embryopathy may arise because of
glycation of DNA and histones by reactive intracellular sugars and indeed increased AGEs have been detected on histones isolated from diabetic rats (Gugliucci and Bendayan 1995). Glycation and AGE formation on DNA and histones could cause errors in replication and transcription thereby promoting mutations responsible for embryopathy. However, the cause of diabetic embryopathy is likely to be multifactorial as elevated concentrations of ketone bodies and branched chain amino acids have also been implicated in its pathogenesis (Eriksson et al., 1998).

**Diabetic foot**

Foot ulceration is a prominent cause of diabetes mellitus morbidity and mortality in developing countries. A problem in diabetic patient is the development of ulcers in the feet and lower extremities and is attributed primarily to abnormal pressure distribution, secondary to diabetic neuropathy. Diabetic motor neuropathy is expressed as the loss of function and the contracture of the intrinsic muscles of the foot, leading to the classic claw toe deformity. This deformity predisposes the foot to ulcerations on the dorsum or tip of the toes (Kim et al., 2008). The risk factors/precipitants of foot ulceration include neuropathy, vasculopathy, spontaneous blisters, walking unshod, and wearing inadequate shoes. Prominent hematologic abnormalities include anemia and leucocytosis (Ogbera et al., 2008).
**Cardiovascular diseases**

Cardiovascular disease is generally similar in patients with type 1 or type 2 diabetes and patients without diabetes. Mortality from first or subsequent myocardial infarctions is higher in diabetic than non-diabetic patients (Singer et al., 1989). Patients with NIDDM and impaired glucose tolerance are commonly obese and have hypertension and dyslipidemia (increased serum triglyceride and decreased HDL cholesterol levels). However, independently of these variables, diabetes remains a major risk factor for coronary artery disease (Singer et al., 1992). The levels of chronic glycemia, as determined by measurements of glycosylated hemoglobin, may also be an independent risk factor for coronary artery disease (Singer et al., 1992).

**Hypertension and stroke**

The diagnosis of type 2 DM often made 4 to 7 years after the disease process has begun, when most patients already have an increased risk of macrovascular processes (UK Prospective Diabetes Study (UKPDS) Group, 1998). Despite this, 20% to 25% of patients with DM do not develop macrovascular complications (KodaKimble and Carlisle 1995). However, people with diabetes have 2-8-fold risk for cardiovascular mortality than people without diabetes. Diabetic patients have about twice the prevalence of hypertension and about twice the incidence of stroke compared to non-diabetic patients (Zimmet and
Alberti, 1997). An increased prevalence of hypertension and concurrent lipid abnormalities (i.e., abnormally decreased high density lipoprotein, elevated low density lipoproteins, and elevated triglycerides) may be responsible for macrovascular complications in patients with DM. Hyperglycemia and hyperinsulinemia also have been implicated as contributors to macrovascular complications, although it is difficult to determine the extent of their contribution (Savage, 1996). Reduction of the degree and duration of hyperglycemic episodes through aggressive control of blood glucose can lower the risk of macrovascular complications, although this has not been confirmed (UK Prospective Diabetes Study (UKPDS) Group, 1998).

**Diabetic Ketoacidosis**

Diabetic Ketoacidosis (DKA) develops due to either an absolute or a relative absence of insulin. An absolute insulin deficiency is the major precipitant for those patients presenting in DKA who have new onset type I diabetes. It is estimated that 10% to 20% of patients with new onset of diabetes will present in DKA as their initial presentation. Another major cause of absolute insulin deficiency is omission of normal insulin in a patient with known type I diabetes (Balasubramanyam et al., 1999). Myocardial infarction should always be considered in the list of precipitating factors of DKA, particularly in older patients, as the condition associated with elevations of
epinephrine, which may stimulate a pathologic process that results in DKA. Diabetic Ketoacidosis is secondary to increased serum levels of Ketoacids in an individual with type I diabetes mellitus.

- Serum glucose > 300
- Serum pH < 7.20
- Plasma Ketone bodies > 2 nM/L
- Diagnosed before 25 years of age (Matthew Kane, 2002).

**Non-Ketotic Hyperglycemia**

Non-Ketotic hyperglycemia (NKH) is a clinical syndrome seen in patients with chronic diabetes mellitus. NKH and DKA are not entirely separated and many patients will present features of both. It is characterized by marked hyperglycemia, hyperosmolarity and increased urinary losses of free water, excessive loss of Na and also mild elevations in serum ketone body levels and ketonuria. In general, the syndromes (NKH and DKA) are distinguished on the relative severity of hyperosmolarity and acidosis (Balasubramanyam et al., 1999).

- Serum glucose >600
- Serum osmoles >320 m osm/kg
- Serum pH > 7.3
- Serum bicarbonate > 15 (Matthew Kane, 2002).
DIABETES AND METABOLIC ABNORMALITIES

Diabetes mellitus is not only associated with carbohydrate metabolism, but also with lipid and protein metabolisms.

Diabetes and carbohydrate metabolism

Alterations in glucose metabolism in diabetes are accompanied by changes in the activities of the enzymes that control glycolysis and gluconeogenesis in liver and muscle, such that the latter process becomes favored (Gerich, 1993). Insulin suppresses hepatic glucose output by stimulating glycogen synthesis and inhibiting glycogenolysis and gluconeogenesis. Increased rate of hepatic glucose production results in the development of overt hyperglycemia, especially fasting hyperglycemia, in patients with type 2 diabetes (DeFronzo et al., 1992). Insulin exerts direct effect on the liver (Michael et al., 2000) as well as influences the substrate availability and fluxes of free fatty acids (FFA) (Bergman and Ader, 2000). There are several important enzymatic checkpoints that act to control hepatic glycolysis and glycogen synthesis (glucokinase, glycogen synthase kinase-3), glycogenolysis (phosphorylase), gluconeogenesis (phosphoenolpyruvate carboxykinase, fructose 1,6-bisphosphatase), or steps that are common to the pathways (glucose 6-phosphatase). Some of them are directly controlled by insulin via phosphorylation and dephosphorylation (Zhang, 2002).
Diabetes and lipid metabolism

In patients with type 1 diabetes in good glycemic control, the lipid profile is very similar to lipid profiles in the general population. In contrast, in patients with type 2 diabetes, even when in good glycemic control, there are abnormalities in lipid levels. Specifically, patients with type 2 diabetes often have an increase in serum triglyceride (TG) levels, increased VLDL and an intermediate density lipoprotein (IDL), decreased HDL, and an increase in small dense LDL, a lipoprotein particle that may be particularly atherogenic. In both type 1 and type 2 diabetes, poor glycemic control increases serum TG levels, VLDL and IDL, and decreases HDL. Poor glycemic control can also result in a modest increase in LDL cholesterol, which because of the elevation in TG is often in the small dense sub fraction. It is therefore important to optimize glycemic control in patients with diabetes because this will have secondary beneficial effects on lipid levels. Lipoprotein (Lp) (a) levels are usually within the normal range in patients with type 2 diabetes and do not appear to be greatly affected by glycemic control. In patients with type I diabetes, Lp (a) levels are frequently elevated and improvements in glycemic control result in decreased in Lp (a) levels. The development of micro albuminuria and the onset of renal disease are associated with an increase in Lp (a) levels (Feingold, 2004).
Diabetes and protein metabolism

In the presence of absolute insulin deficiency (type 1 diabetes), increased protein breakdown and body protein loss occur (Nair and Copeland, 1992). Lean body mass and protein turnover are normal in individuals with type 2 diabetes (Bier, 1992), where insulin deficiency is only relative because of insulin resistance. An association between diabetes mellitus and protein catabolism has been well documented. Many of the chronic complications of diabetes involve changes in structural proteins. It is thus possible that changes in protein metabolism are responsible for many of the chronic complications of diabetes mellitus, because even a minor imbalance between protein synthesis and degradation can potentially have a profound effect over the long term on cell viability and metabolism. Alterations in protein synthesis and degradation can also adversely affect the repair of tissue after injury or infection.

Free radicals and oxidative stress in diabetes

A free radical is simply defined as any species capable of independent existence containing one or more unpaired electrons. They are unstable and highly reactive molecules that have unpaired electrons in their outermost orbit (Halliwell, 1994). Reactive oxygen species (ROS) and reactive intermediates are produced under physiological and pathophysiological conditions (Halliwell and Gutteridge, 1986). ROS
are chemical entities that include oxygen free radicals, such as superoxide anion radicals $O_2^-$, hydroxyl radicals (OH$^-$), nitric oxide (NO), peroxinitrite and also non-radical species, such as $H_2O_2$ and singlet oxygen ($^1O_2$) (McDermott, 2000). The generation of free radicals involves the principle of iron dependent Fenton reaction and superoxide derived Haber-weiss reaction: 

\[
Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + OH^-
\]

Fenton Reaction; 

\[
O_2^- + H_2O_2 \rightarrow OH^- + OH^+ + O_2
\]

Haber-weiss reaction (Chatterje and Shinde, 2000).

Oxidative stress may be defined as a measure of the steady state level of reactive oxygen species or oxygen radicals in a biological system (Baynes, 1991). Increased oxidative stress may result from overproduction of precursor of reactive oxygen radicals and decreased efficiency of inhibition of scavenger system (Wolf, 1987). The stress then may be amplified and propagated by autocatalytic cycle of metabolic stress, tissue damage and cell death leading to simultaneous increase in free-radical production and comprised inhibition of scavenger mechanism which further exacerbates the oxidative stress. Chronic oxidative stress due to hyperglycemia may, therefore, play an important role in progression of $\beta$-cell dysfunction. Antioxidants, molecules that inhibit or prevent oxidation of a substrate have evolved to protect biological systems against damage induced by RONS.
Lipid peroxidation and antioxidants

Lipid peroxidation can be defined as the oxidative deterioration of lipids containing a number of carbon-carbon double bonds. Lipid hydroperoxides are nonradical intermediates derived from unsaturated fatty acids, phospholipids, glycolipids, cholesterol esters and cholesterol itself. Their formation occurs in enzymic or nonenzymic reactions involving activated chemical species known as "reactive oxygen species" (ROS) (Fridorich, 1988), which are responsible for toxic effects in the body via various tissue damages. These chemical forms are defined as, any species capable of independent existence that contain one or more unpaired electrons (Halliwell and Gutteridge, 1990). Lipid peroxidation has been associated with several types of diseases including atherosclerosis, cancer and diabetes (Kurimura et al., 1988). Increased oxidative stress may contribute to the development of complications of diabetes mellitus.

Antioxidants are a group of substances which, when present at low concentration, in relation to oxidizable substances, significantly inhibit or delay oxidative process, while often being oxidized themselves. Antioxidants can retard lipid oxidation through competitive binding of oxygen, retardation of the initiation step, blocking the propagation step by destroying or binding free radicals, inhibition of catalysts or stabilization of hydro peroxides (Diplock, 1991). Antioxidants can scavenge the active forms of oxygen involved in the
initiation step of oxidation or can break the oxidative chain reaction by reacting with the fatty acid peroxy radicals to form stable antioxidant radicals, which are either too unreactive for further reactions or form nonradical products (Machin and Bendich, 1987). The antioxidants found in biological systems include enzymes, vitamins, metal ion chelators and a variety of small molecules. The important enzymic antioxidants include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). The non-enzymic antioxidants and other small molecules with antioxidant property include reduced glutathione (GSH), ascorbic acid (vitamin C), α-tocopherol (vitamin E), β-carotene, uric acid and bilirubin (Halliwell, 1990).

**Superoxide dismutase (SOD)** catalyzes the one-electron dismutation of superoxide into hydrogen peroxide and oxygen. In animal cells, CulZn-SOD is present in the cytosol and mitochondria, while Mn-SOD is present only in the mitochondrial matrix.

\[
O_2^- + 2 H^+ \rightarrow H_2O_2 + O_2
\]

**Catalase (CAT)** is a porphyrin-containing enzyme which catalyzes two electron dismutation into oxygen and water. It is located in the cytoplasm of red blood cells but compartmentalized in the peroxisomes of the other cells.

\[
2H_2O_2 \rightarrow 2 H_2O + O_2
\]
**Glutathione peroxidase (GPx)**, containing active selenium, is involved not only in hydrogen peroxide removal but also in converting lipid hydroperoxides (LOOH) to their corresponding alcohols (LOH) and oxidizing GSH to glutathione disulphide (GSSG).

\[
\text{LOOH} + 2\text{GSH} \rightarrow \text{LOH} + \text{GSSG} + \text{H}_2\text{O}.
\]

GSSG is reduced back to GSH by the NADPH-dependent glutathione reductase.

\[
\text{GSSG} + \text{NADPH} + \text{H}_2\text{O} \rightarrow \text{NADP}^+ + 2\text{GSH}.
\]

**α-Tocopherol** is widely present within membranes representing the most abundant lipid soluble antioxidants. α-Tocopherol can be regenerated from its oxidized form by reduction with vitamin C, but whether this mechanism is actively operative *in vivo* is still uncertain.

**β-Carotene** is lipid-soluble and in addition to acting as a vitamin A precursor, is an efficient quencher of singlet oxygen.

**Vitamin C (Ascorbic acid)** is water-soluble and has a broad spectrum of antioxidant activities due to its ability to react with different ions.
GSH is synthesized from glutamate, cysteine, and glycine and occurs in millimolar concentration in cells but only in trace amounts in plasma. GSH in the diet can be partly absorbed from the small intestine and it can be synthesized de novo. It is, therefore, an exogenous and endogenous antioxidant.

Bilirubin, the end product of heme catabolism, has also been shown to act as an efficient antioxidant.

Mechanisms of hyperglycemia-induced cell damage:

Polyol pathway

An increase in the concentration of glucose contributes to the elevated intracellular sorbitol and fructose content due to enhanced activities of aldose reductase and sorbitol dehydrogenase activity. Aldose reductase is the first rate limiting enzyme of the polyol pathway (Bhatnagar and Srivastava, 1992). Under euglycemic conditions, aldose reductase plays a minor role in glucose metabolism. However, during diabetes, its contribution is significantly enhanced (Kinoshita and Nishimura, 1988). The increase in aldose reductase activity by hyperglycemia has been proposed to be the underlying metabolic cause of secondary diabetes complications such as cataractogenesis, retinopathy, neuropathy, and nephropathy (Bhatnagar and Srivastava, 1992; Kinoshita and Nishimura, 1988; Yabe-Nishimura, 1998). It has
been suggested that the activation of aldose reductase enzyme depletes the reducing equivalents NADPH that may be otherwise required for the detoxification of oxidants (Yabe-Nishimura, 1998). An increase in aldose reductase activity also results in sorbitol accumulation. This could potentially disrupt cellular integrity and function by imposing osmotic stress.

**Increased hexosamine pathway flux**

Shunting of excess intracellular glucose into the hexosamine pathway might also cause several manifestations of diabetic complications (Kolm-Litty et al., 1998). In this pathway, fructose 6-phosphate is diverted from glycolysis to provide substrates for reactions that require UDP-N-acetylglucosamine, such as proteoglycan synthesis and the formation of O-linked glycoproteins. Inhibition of the rate-limiting enzyme in the conversion of glucose to glucosamine-glutamine:fructose 6-phosphate amidotransferase blocks hyperglycemia-induced increases in the transcription of TGF-α, TGF-β1 (Kolm-Litty et al., 1998) and plasminogen activator inhibitor (PAI-I) (Du et al., 2000). The activation of the hexosamine pathway by hyperglycemia may result in many changes in both gene expression and protein function, which together contribute to the pathogenesis of diabetic complications (Brownlee, 2001).
Activation of protein kinase C (PKC)

The PKC family comprises at least eleven isoforms, nine of which are activated by the lipid second messenger diacylglycerol (DAG). This is achieved primarily by increasing de novo DAG synthesis from the glycolytic intermediate dihydroxyacetone phosphate, through reduction of the latter to glycerol-3-phosphate and stepwise acylation (Koya and King, 1998). Increased de novo synthesis of DAG activates PKC. Hyperglycemia may also activate PKC isoforms indirectly through both ligation of AGE receptors (Portilla et al., 2000) and increased activity of the polyol pathway (Keogh et al., 1997) presumably by increasing reactive oxygen species.

Abnormal activation of PKC has been implicated in the decreased glomerular production of nitric oxide induced by experimental diabetes (Craven et al., 1994) and in the decreased production of nitric oxide in smooth muscle cells that is induced by hyperglycemia (Ganz and Seftel, 2000). Activation of PKC contributes to increased microvascular matrix protein accumulation by inducing expression of tumor growth factor (TGF)-β 1, fibronectin and type IV collagen both in cultured mesangial cells (Studer et al., 1997) and in glomeruli of diabetic rats (Koya et al., 1997).
Increased advanced glycation end-product formation

Advanced glycation end products (AGEs) are closely related to hyperglycemia. AGEs are produced when glucose and other reducing sugars react with amino groups in proteins, lipids and nucleic acids. This is a nonenzymatic series of reactions (Maillard reactions) forming Schiff bases and Amadori products. These are then converted to AGEs. Enzymatic activity can be altered by glycosylation and this can produce acute or chronic effects, depending on the turnover of the enzymes. Glycosylation can also alter the properties of structural proteins with long-term effects (Duckworth, 2001).

Accumulation of AGEs has several toxic effects. AGEs can modify proteins (especially, long-lived proteins such as collagens, lens crystallines and nerve proteins), directly damage the structure and metabolism of extracellular matrix or act via their specific receptors (Bierhaus et al., 1998). In addition to circulation in the blood, AGEs accumulate in tissues and thus take part in the development of diabetic complications. They cause damage to biological membranes and endothelium. Moreover, they modify LDL particles and together with vascular damage, they are involved in the acceleration of atherosclerosis (Vlassara, 1997) (Fig. 2).
Management of diabetes mellitus

Type 2 diabetes is usually treated by a combination of diet, exercise and lifestyle changes, or pharmacological agents (e.g., oral antidiabetic agents and insulin).

Diet and lifestyle changes

Medical nutrition therapy is an essential component of diabetes management; unfortunately, patient adherence to nutrition principles is one of the most challenging aspects of diabetes care. A goal of medical nutrition therapy is to achieve and maintain blood glucose concentrations as close to normal as possible by balancing food intake with antidiabetic drug therapy and physical activity levels. No more than 30% of the total daily caloric intake should come from fats; 10% to 20% from protein, and the balance of daily calories from carbohydrates. Exercise improves insulin sensitivity and glycemic control, especially in patients with mild diabetes or a high degree of insulin resistance (ADA, 2007).
Fig. 2: Over view of mechanisms of hyperglycemia-induced damage (Brownlee, 2001). AGEs- advanced glycation end products; GFAT- glutamine: fructose-6-phosphate amidotransferase; DAG- 1,2-diaocylglycerol; GlcNAc - N-acetyl glucosamine; PKC protein kinase C; GAPDH - glyceraldehydes 3-phosphate dehydrogenase; DHAP- dihydroxy acetone phosphate.
**Sulphonyl ureas:**

Sulphonyl ureas are a class of compounds containing sulphonamide drug. These sulphonyl ureas lower the blood glucose *in vivo* and *in vitro* by increasing the plasma insulin levels. These chemicals stimulate the secretion of insulin from β-cells. The receptors of sulphonyl urea are present in cardiac muscle cells, smooth muscle cells, liver and adipose tissue. There are several side effects mediated by the use of sulphonyl ureas. They are chronic renal failure, hepatic and cardio vascular diseases. Patients who are using the sulphonyl urea therapy tend to gain weight from 1-5 kg (Zimmerman, 1997).

**Biguanides:**

Biguanides are derivatives of guanide especially phenformin, metformin and buformin. Recently metformin gained popularity in diabetic patients because of its variations in the chemical structure. These biguanides enhances the utilization of glucose in peripheral tissues and increases the gluconeogenesis in liver. Metformin treatment does not stimulate insulin secretion, but it improves insulin mediated glucose uptake. Lipid peroxidation and lipolysis are reduced by metformin. The side effect of the usage of metformin is: anorexia, nausea, diarrhea and unpleasant metabolic taste. The other problem
associated with metformin is lactic acid acidosis which is associated with heart failure. The side effect is vomiting non specific abdominal discomfort and rashes on the skin.

**α-glycosidase inhibitors**

α-glycosidase inhibitors are a group of compounds which inhibit the rate of breakdown of oligosaccharides and polysaccharides. This delays the absorption of glucose. A high dose of acarbose causes abnormalities in the liver and also impairs the iron absorption in the intestine. These drugs can be used in combination with others to decrease the blood glucose levels.

**Thiazolidinediones**

These are oral hypo glycemic agents like cigilitazone, troglitazone and rosiglitazone are antidiabetic drugs which are currently available for clinical use in the treatment of diabetes. The mechanism of the action of these drugs is not completely understood. They reduce the gluconeogenesis by inhibiting at the level of fructose 1, 6-bis phosphatase. They protect the regranulation of β-cells and increase the production of pancreatic insulin. The usage of these drugs leads to the alteration of the enzyme activities in liver mainly affecting the transaminases.
Oral hypoglycemic agents

The present treatment of diabetes is focused on controlling and lowering blood glucose. The mechanisms to decrease blood glucose in western medicines are i) to stimulate β-cells of pancreatic islet to release insulin; ii) to resist the hormones which rise blood glucose; iii) to increase the number or rise the appetency and sensitivity of insulin receptor site to insulin; iv) to The beta cell stimulators act at the level of the pancreatic beta cells to stimulate insulin release. They require the presence of functioning beta cells, and used only in the treatment of type 2 diabetes, and have the potential for producing hypoglycemia. The sulfonylureas reduce blood glucose by stimulating the release of insulin from beta cells in the pancreas and increasing the sensitivity of peripheral tissues to insulin decrease the leading out of glycogen; v) to enhance the use of glucose in tissue and organ; vi) to clear away free radicals, resist lipid peroxidation and correct the metabolic disorder of lipid and protein; and vii) to improve microcirculation in the body (Li et al., 2004).

Metformin, the only currently available biguanide, inhibits hepatic glucose production and increases the sensitivity of peripheral tissues to the actions of insulin. Secondary benefits of metformin therapy include weight loss and improved lipid profiles. Unlike the sulfonylureas, whose primary action is to increase insulin secretion, metformin exerts its beneficial effects on glycemic control through
decreased hepatic glucose production (main effect) and increased peripheral use of glucose. This medication does not stimulate insulin secretion; therefore, it does not produce hypoglycemia. Because of the risk for lactic acidosis, metformin is contraindicated in people with elevated serum creatinine levels, clinical and laboratory evidence of liver disease, or conditions associated with hypoxemia or dehydration.

The α-glucosidase inhibitors block the action of the brush border enzymes in the small intestine that break down complex carbohydrates. By delaying the breakdown of complex carbohydrates, the α-glucosidase inhibitors delay the absorption of carbohydrates from the gut and blunt the postprandial increase in plasma glucose and insulin levels. The postprandial hyperglycemia probably accounts for sustained increases in HbA\textsubscript{1c} levels.

The thiazolidinediones (TZDs), or glitazones, are the only class of drugs that directly target insulin resistance, a fundamental defect in the pathophysiology of type 2 diabetes. The TZDs improve glycemic control by increasing insulin sensitivity in the insulin-responsive tissues, liver, skeletal muscle, and fat allowing the tissues to respond to endogenous insulin more efficiently without increased output from already dysfunctional beta cells. A secondary effect is the suppression of hepatic glucose production. The mechanism of action of the TZDs is complex and not fully understood but is believed to be associated with
binding of the drug to a nuclear receptor that plays a role in the regulation of genes involved in lipid and glucose metabolism. Because of a potential problem with liver toxicity, liver enzymes should be measured when using these drugs.

**Insulin therapy**

Insulin is an important hormone needed by the human body to utilize carbohydrates, protein, and fats. However, in type 1 diabetes the pancreas does not produce insulin, and replacement therapy is required with exogenous insulin. Type 2 diabetics, on the other hand, have a problem with either the secretion of insulin or have become insulin-resistant; thus, the common name for the condition is non insulin dependent diabetes mellitus. Insulin injections are a necessary daily component of therapy for type 1 diabetics. Insulin injections however, are not always necessary for treatment and control of diabetes in type 2 diabetics (Buse, 1999).

**Disadvantages of insulin therapy:**

The major disadvantage associated with insulin therapy is incidence of insulin allergy and insulin resistance. Insulin injection causes a localized loss of subcutaneous fat in the area of injection. Insulin therapy is also associated with weight gain. The maintenance of blood glucose requires the addition of OHA’s along with the insulin. With the progress of the disease exogenous intake of insulin, suppresses
the secretion of insulin and leads to the loss of β-cells. Keeping the
above points in view WHO declared that the diabetes is one of the
priority areas of research and gave slogan “Prevent and Cure Diabetes”.
Due to the existence of various side effects with the use of OHA’s and
insulin, there is a challenge before us regarding the management of
diabetes without any side effects to the human beings (Table 2).

**Indigenous treatment for diabetes mellitus**

Practice of healing is known as medicine which is an important
branch of science. From the time immemorable, human beings (animals
and birds also) self medicate themselves with natural sources of animal
and plant origin to get rid of their illness. Use of herbs has been
practiced for centuries in all parts of the world in various systems of
medicine like Ayurveda, Siddha, Unani and Naturopathy etc. A reference
to a number of herbal remedies has been made in Vedas (Rigveda and
Atharvanaveda).

Plants have played a major role in the introduction of new
therapeutic agents. Every ancient ethnic culture has its own treasure
house of herbal medicines. At least 130 drugs from higher plants are
being used throughout the world. Japanese pharmacopoeia (1986)
contains 123 plant drugs of which 29 are used in the Western medicine.
During 1959-1980, in USA, 25% of all prescriptions contained plant
extracts or active principles, from higher plants.
Table 2: The composition, onset, peak value and duration of the action of different insulins

<table>
<thead>
<tr>
<th>Type of preparations</th>
<th>Composition</th>
<th>Action profile (in hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Onset</td>
</tr>
<tr>
<td><strong>1. SHORT ACTING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular Insulin</td>
<td>Unbuffered insulin</td>
<td>0.5</td>
</tr>
<tr>
<td>Buffered regular</td>
<td>insulin solution, phosphate buffer</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>2. INTERMEDIATE ACTING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>Protamine zinc suspension, Phosphate buffer.</td>
<td>1-2</td>
</tr>
<tr>
<td>Lente</td>
<td>Amorphous and crystalline Suspension, acetate buffer.</td>
<td>1-3</td>
</tr>
<tr>
<td>Isophene/U-500</td>
<td>NPH 70%, regular 30%. Concentrated, unmodified Insulin.</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-3</td>
</tr>
<tr>
<td><strong>3. LONG ACTING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td>Crystalline suspension and acetate buffer</td>
<td>4-6</td>
</tr>
</tbody>
</table>
Plant derived drugs constitute important monographs in the German and Russian pharmacopoeias: Even now, almost 75-80% of world population depends on crude plant drug preparations to tackle their health problems. In China, Japan & other far eastern countries Chinese medicine (Zhong Yao in China and Kampo in Japan) has been practiced, and its crude drugs are mostly plant based. Chinese pharmacopoeia (1990) lists 784 traditional Chinese drugs of which 630 are of plant origin. Results from modern investigations on Chinese medicinal plants strengthen the idea that folklore or classical medicinal reports generate a higher score in our search for molecular therapeutic agents from higher plants. There are so many outstanding contributions to therapeutics of plant origin.

Ayurveda literally means science of life which originated from prehistoric antiquity, but its concepts matured between 2500 BC and 500 BC in India. It has a vast literature in sanskrit and various indian languages, covering all aspects of diseases, therapeutics and pharmacy. Plants form a dominant part of Ayurvedic pharmacopoeia along with animal products, mineral and metals. Vegetable products dominated Indian Materia Medica which made extensive use of bark, leaves, flowers, fruits, roots, tubers and juices. Rauwolfia and guggul (Commiphora wightii) are indicative of the untapped wealth of the medicinal plants of Ayurveda. Sukh Dev (1997) listed 15 crude Ayurvedic drugs which have received support for their therapeutic claims.
Ethnotherapeutics and traditional modern drugs

The starting point in the development of so many drugs is some reference to the use of plants as an indigenous cure in the traditional system of medicine or in folk medicine (Ethnotherapeutics). The tribals in India have been using the plant materials for treatment of various diseases for ages. Though some of the plants are reputed in the indigenous system for their activities it remains to be scientifically established.

During the last few years there has been increased interest in the study of plants used by various aboriginal tribes in different parts of India. These studies have brought to light numerous medicinal and other useful plants. This knowledge on medicinal plants among the tribals developed through their age-old trial and error methods and was transmitted orally from generation to generation. Various tribal people used more than 3000 plants as food, beverages, narcotics and medicines. Due to advancement of civilization, ignorance, misconception, wrong identification of plants, dishonest practice and extinction of valuable herbs, the knowledge on tribal medicine is steadily dwindling. Based on the information obtained from the ancient literature as well as from the knowledge from folklore medicine, considerable trials of plant materials have been made in various maladies in India. Per and Laurent Rivier insisted for ethnopharmacological research than development of
synthetic drugs because the amount spent on both fields is almost the same.

From 1959, National Cancer Institute (USA), screened around 180,000 plants extracts for their pharmacological activities. In India, Central Drug Research Institute, Lucknow screened approximately 2500 plants for a wide range of pharmacological activities. Recently more than 50,000 compounds for antidiabetic activity and found a molecule from a fungal extract with antidiabetic activity. This shows the importance for the search of plant materials for pharmacological activity, but there are a few problems associated with this. They are, plant collection (which leads to ecological problem), standardization and supply, and secondly random screening of plant extracts has not proved economically effective. Mukherjee (1981) reviewed that conventional chemical procedures to obtain an active principle may result in decreased or loss of activity or at times becomes toxic in the process of concentration. Despite all this, the interest in screening plant extracts grows because higher plants constitute a large untapped source of structurally novel compounds that might serve as leads for developing new drugs. However, instead of random search of plants, a selective search based on traditional knowledge would be more focussed and productive, and certainly more economic.
The production of drugs and other preparations based on indigenous systems of medicine in India has increased many folds during the past few decades. The number of plant based crude drugs finding regular use is put around four hundred and its number is increasing. Yet we know relatively little about the active ingredients in many of these plants. The fact that plant derived compounds are showing promise in the treatment of cancer, HIV and diabetes has the interest in plants. In the present scenario, herbal medicines are gaining popularity because they are cheap, easily available and have rare or no side effects. The herbal drugs often contain similar stable chemical components as the food we eat daily. According to some workers plant drugs are frequently considered to be less toxic and more free from side effects than synthetic ones. Through India has a rich tradition in the use of medicinal plants, there are no scientific studies on some of the medicinal plants which are used in the treatment of various diseases. Because of their effectiveness, minimal side effects in clinical experience and relatively low costs, herbal drugs are prescribed widely even when their biologically active compounds are unknown.

Long before the use of Insulin, since the time of Charaka and Sushruta (6th century BC. and 400 B.C.), indigenous remedies have been in use for the treatment of diabetes. Management of diabetes without any side effects is still a challenge to the medical system. There is an increasing demand by patients for the natural products with
antidiabetic activity, because insulin and OHAs are having so many side effects as described earlier. The available literature shows that there are more than 400 plant species showing hypoglycemic activity. Presently several laboratories are involved in isolating new herbal oral hypoglycemic agents. The renowned OHA, metformin which gained popularity in recent years is derived from its ancestor, Galegine or isoamylene guanidine which is an active ingredient of *Galega officinalis*. Medicinal plants are used in ayurveda as complex mixtures. In contrast, the herbal preparations which are increasingly used in the west are standardized single plant extracts. Their safety and efficacy are proved, even though the nature of biologically active component(s) may not be known.

Many scholars had earlier made valuable contributions to the field of indigenous drug trials in diabetes. In Central Drug Research Institute, Lucknow, India, more than 2000, plants have been evaluated for their blood sugar lowering activity. Mukherjee (1981) reviewed about 24 plant species with hypoglycemic activity. Rai (1995) listed the contributions of many scientists in the field of herbal medicine in relation to diabetes and listed around 56 plant species with hypoglycemic activity. A number of plants have constituents which have antidiabetic properties when taken orally. There is great diversity in the nature and action of these constituents, but a number of them do seem to
belong to certain chemical classes, such as sitosterol glycosides (β sitostero 3-β-D-glucose from the bark of Ficus religiosa O., Moraceae and the Charantin, equal parts of β sitosterol β -D-glucoside and Δ5,25 stigmastadien 3 β -ol from the fruits of Momordica charantia L, Cucurbitaceae etc), Alkaloids (Berberine from the aerial parts of Coptis chinensis Fanch. Ranunculaceae, and Galegin from the seeds of Galega officinalis L. Leguminosae etc.), Sulphur compounds (S-methyl cysteine sulfoxide from Allium cepa Liliaceae and S-allyl cysteine sulphoxide from the bulbs of A.sativum etc.), Flavanoids ((-) epicatechin from the bark of Pterocarpus marsupium Roxb., Leguminosae and Quercetin from the leaves of Bauhinia purpurea L., Leguminosae etc.) and glycans or glycoproteins (Ephedrans A,B,C,D and E from the aerial parts of Ephedra distachya L. Ephedraceae, and Olyzbans A,B,C and D from external seed coats of Oryza sativa L. Graminae. etc.) (Subramoniam et al., 1996).

The glycosides isolated from the species belonging to the families Caesalpinaceae, Compositae, Convolvulaceae, Ericaceae, Moraceae, Myrtaceae, Papavaraceae, Zygophyllaceae were particularly effective in diabetes. Saponins from Araliaceae, glycoproteins from Malvaceae,peptides, amino acids and proteins from Papillionaceae and Rubiaceae families also showed beneficial effects in reducing the blood sugar. A hypoglycemic principle Charantin, a mixture of equal parts of β
sitosterol p-D-glucoside and $\Delta^5, 25$ stigmastadien 3 $\beta$-ol, was isolated from the fruits of *Momordica charantia*. A polypeptide p-insulin, was also isolated from this plant with potent hypoglycemic activity. Foetidin is a hypoglycemic compound isolated from *M. foetida*. Phytosterin a glycoside is a hypoglycemic principle of *Syzygium cumini*. Three alkaloids leurosine, vindoline and vindolinine which were isolated from *Catharanthus roseus* showed good hypoglycemic activity. Trigonellin, a hypoglycemic active principle isolated from *Trigonellafoenumgraecum* (fenugreek) seeds. S-methyl cysteine sulphoxide and S-ally cysteine sulphoxide are antihyperglycemic agents isolated from the bulbs *Allium cepa* and *Allium sativum* respectively. (-)-Epicatechin from the bark of *Pterocarpus marsupium* showed insulin mimetic activity. 180-182 Hexane fraction of *Swertia chirata* (Swervirin, dihydroxy-3,5-dimethoxy xanthone) is potent to reduce blood glucose levels. Dimethyl ether of leucopelargonodin-3-$\alpha$-rhamnoside decreases blood glucose levels, which was isolated from *Ficus bengalensis*. Aqueous extracts of tender leaves of neem (*Azadirachta indica* Juss.), neem oil, nimbidin and acetyl nimbin and nimbolid from the leaves also shown antidiabetic activity. Gymnnimic acids isolated from the leaves of *Gymnema sylvestre*, which are chewed in India reduce glycosuria and normalize the blood sugar in diabetic subjects in about 3-4 weeks (Singh *et al.*, 1985; Panlasigui *et al.*, 1995; Chattopadhyay *et al.*, 1997).
In accordance with the recommendations of the WHO expert committee on diabetes mellitus, an investigation of hypoglycemic agents of plant origin used in traditional medicine seems important. Many herbs and plant products have been shown to have hypoglycemic action. This shows the importance for the search of compounds of plant origin with potent antidiabetic activity (Table 3).

Table 3: Important antidiabetic plants, their parts used and their reported effect on experimental models (Li et al., 2004; Mukherjee et al., 2006).

<table>
<thead>
<tr>
<th>Botanical Name and Family</th>
<th>Parts used</th>
<th>Antidiabetic effects reported in experimental study</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Abelmoschus moschatus</em> (Linn) Fabaceae</td>
<td>Aerial part</td>
<td>Antidiabetic effect.</td>
</tr>
<tr>
<td><em>Aegle marmelos</em> (Lam.) Muhl. Ex. Willd. Rutaceae</td>
<td>Fruit, Leaf</td>
<td>Hypoglycemic, Antidiabetic effect, Anti-lipid peroxidative and antioxidant activity</td>
</tr>
<tr>
<td><em>Allium sativum</em> L. Liliaceae</td>
<td>Bulb</td>
<td>Hypoglycemic, Antihyperglycemic and Antihyperlipidemic effect.</td>
</tr>
<tr>
<td><em>Aloe vera</em> L. Liliaceae</td>
<td>Leaf gel</td>
<td>Anti-hyperlipidaemic, Hypoglycemic and antioxidant effects</td>
</tr>
<tr>
<td><em>Annona squamosa</em> L. Annonaceae</td>
<td>Leaf, Fruit pulp</td>
<td>Hypoglycemic and Antidiabetic effects.</td>
</tr>
<tr>
<td><em>Azadirachta indica</em> A. Juss. Meliaceae</td>
<td>Leaf, Kernel</td>
<td>Hypoglycemic and Antihyperglycemic effect.</td>
</tr>
<tr>
<td><strong>Caesaeria esculenta</strong></td>
<td>Root</td>
<td>Antihyperglycaemic, Hypolipidaemic and Antiperoxidative effect.</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Cassia auriculata L.</strong></td>
<td>Flower</td>
<td>Hypoglycemic, Antihyperglycemic, Antihyperlipidemidic and Antiperoxidative effect.</td>
</tr>
<tr>
<td><strong>Caesalpinia pulcherrima</strong></td>
<td>Flower</td>
<td>Hypoglycemic, Antihyperglycemic, Antihyperlipidemidic and Antiperoxidative effect.</td>
</tr>
<tr>
<td><strong>Catharanthus roseus (L.) G. Don</strong>, <strong>Apocynaceae</strong></td>
<td>Flowers and whole plant</td>
<td>Antidiabetic activity and antiperoxidative effect.</td>
</tr>
<tr>
<td><strong>Coccinia indica, W and A.</strong></td>
<td>Leaf, Leaves and roots</td>
<td>Hypoglycemic, hypolipidemic effects, Increase antioxidant level and Anti peroxidative effect.</td>
</tr>
<tr>
<td><strong>Cucurbitaceae</strong></td>
<td><strong>Curcuma longa L.</strong>, <strong>Zingiberaceae</strong></td>
<td>Rhizome</td>
</tr>
<tr>
<td><strong>Enicostemma littorale Blume. Gentianaceae</strong></td>
<td>Whole plant</td>
<td>Hypoglycemic, Antidiabetic, Antihyperlipidemidic and Antiperoxidative effect.</td>
</tr>
<tr>
<td><strong>Eugenia jambolana Lam.</strong></td>
<td><strong>Syzygium cumini (L.) Skeels</strong>, <strong>Myrtaceae</strong></td>
<td>Seed, Fruit pulp</td>
</tr>
<tr>
<td><strong>Ficus benghalensis L. Moraceae</strong></td>
<td>Bark</td>
<td>Hypoglycemic, hypolipidemic and serum insulin raising effects.</td>
</tr>
<tr>
<td><strong>Gymnema montanum Asclepiadaceae</strong></td>
<td>Leaf</td>
<td>Hypoglycemic, Antidiabetic, Antiperoxidative and antioxidant effects.</td>
</tr>
<tr>
<td><strong>Plant</strong></td>
<td><strong>Part Used</strong></td>
<td><strong>Pharmacological Effect</strong></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td><em>Gymnema sylvestre</em> R. Br.</td>
<td>Leaf</td>
<td>Hypoglycemic, Antihyperglycemic, Antiperoxidative effect, Regeneration of endocrine pancreas Antidiabetic and decrease glycoprotein levels and decreased insulin resistance.</td>
</tr>
<tr>
<td><em>Helicteres isora</em> L. S terculiaceae</td>
<td>Stem, bark, Root</td>
<td>Hypoglycemic, Hypolipidemic effects and hepatoprotective activity.</td>
</tr>
<tr>
<td><em>Momordica charantia</em> L. Cucurbitaceae</td>
<td>Fruit pulp, seed &amp; whole plant</td>
<td>Hypoglycemic, hyperinsulinemic, Hypolipidemic, Hypotriglyceridermic and hypocholesterolemic effects.</td>
</tr>
<tr>
<td><em>Nigella sativa</em> L</td>
<td>Seeds</td>
<td>Hypoglycemic, antihyperlipidemic, Antioxidant effect.</td>
</tr>
<tr>
<td><em>Ocimum sanctum</em> L. Lamiaceae</td>
<td>Seed oil, Leaf, Seeds and leaves</td>
<td>Anti - hyperglycemic, hypoglycemic, Antidiabetic, Antiperoxidative, antihypercholesterolaemic and antioxidant effect.</td>
</tr>
<tr>
<td><em>Panax ginseng</em> C.A. Mey Araliaceae</td>
<td>Roots, stems, leaf and fruits</td>
<td>Hypoglycemic, Anti-hyperglycemic, Antidiabetic Hypolipidemic effects.</td>
</tr>
<tr>
<td><em>Phyllanthus emblica</em> L. Euphorbiaceae</td>
<td>Fruits</td>
<td>Hypoglycemic, Antihyperlipidemic and Antioxidant effect.</td>
</tr>
<tr>
<td><strong>Punica granatum</strong> L. Punicaceae</td>
<td>Seeds Flower</td>
<td>Antidiabetic, Hypoglycemic, effect.</td>
</tr>
<tr>
<td><strong>Scoparia dulcis</strong> L. Scrophulariaceae</td>
<td>Whole plant</td>
<td>Antihyperlipidemic, Hyperglycemic, Antidiabetic effect, Insulin-secretagogue and cytoprotective activity.</td>
</tr>
<tr>
<td><strong>Tinospora cordifolia</strong> Miers. Menispermaceae</td>
<td>Root</td>
<td>Hypoglycemic, hypolipidemic, Anti hyperglycemic and Restoration of antioxidants effects.</td>
</tr>
<tr>
<td><strong>Trigonella foenum-graecum</strong> L. Fabaceae</td>
<td>Seeds Leaf</td>
<td>Hypoglycemic, Anti-hyperglycemic, antiperoxidative, antioxidant, antidiabetic, Hypocholesterolemic effects.</td>
</tr>
</tbody>
</table>

**Aims and objectives of present study:**

The aims and objectives of the present study are given below:

1) To prepare the aqueous extract from the leaves of *Coccinia grandis* by using distilled water as solvent.

2) To investigate the changes in enzyme activities related to the carbohydrate metabolism in diabetic albino rats on long term treatment with plant extracts.

3) To investigate the effect of plant extract on the lipid peroxidation and its role in the antioxidant defense mechanism.

4) To characterize the histopathological changes in the tissues of liver and kidney.