Chapter-1: INTRODUCTION

Plants and microorganisms are the assets of bioactive metabolites including useful chemical ligands. A wide array of plant derived active principles representing numerous chemical compounds has demonstrated activity consistent with their possible use in the treatment of Diabetes mellitus (DM). Chemical ligands that induce insulin secretion and β-cell regeneration may be useful as new therapeutic agents for both type 1 and type 2 diabetes (Takatsuna & Umezawa, 2004). The use of plants as therapeutic tools, especially those used to relieve chronic pathologies, have had a remarkable role in the popular medicine of different countries. Many indigenous drugs have been used by practitioners for the treatment of DM throughout the world (Bailey & Day, 1989). However, only a few have received scientific or medical scrutiny and the World Health Organization has recommended accordingly that those traditional plant treatments for diabetes warrant further evaluation (WHO, 1980).

A botanical substitute for insulin seems unlikely, but traditional treatments may provide valuable clues for the development of new oral hypoglycemic agents and simple dietary adjuncts. Several hundred plants are known to have antidiabetic properties and a large number of compounds from plant extracts have been reported to have beneficial effects for treatment of diabetes (Anhauser, 2003). But, the use of medicinal plants in modern medicine suffers from the fact that though hundreds of plants are used in the world to prevent or to cure diseases, scientific evidence in terms of modern medicine is lacking in most cases. Thus, identification of potential antidiabetic agents using mechanism-based studies holds great promise for elucidating mechanisms and devising more specific and effective treatments for diabetes-related diseases (Izzo & Ernst, 2001).

1.1 . DEFINITION AND DESCRIPTION OF DIABETES MELLITUS

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 (ADA, 2008).
Numerous pathogenic processes are involved in the intensification of DM. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The reasons for the abnormalities in carbohydrate, fat and protein metabolism in diabetes is deficient action of insulin on target tissues. 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. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycemia (WHO, 2001).

1.2. SYMPTOMS OF DM

- The symptoms of hyperglycemia include polyuria, polydipsia, weight loss, sometimes with polyphagia and blurred vision.
- The life-threatening consequences of uncontrolled diabetes (acute) are hyperglycemia with ketoacidosis or non-ketotic hyperosmolar syndrome.

1.3. CLASSIFICATION OF DIABETES MELLITUS AND DIFFERENT CATEGORIES OF GLUCOSE REGULATION

World Health Organization (1980) documented two major forms of diabetes which they termed as type 1 diabetes, or juvenile onset diabetes or Insulin dependent diabetes mellitus (IDDM) and type 2 diabetes or Non-Insulin dependent diabetes mellitus (NIDDM).

1.3.1. Insulin dependent diabetes mellitus

Juvenile-onset diabetes or type 1 diabetes is an autoimmune disease that is eminence by the destruction of insulin-producing β-cells. Type 1 diabetes can occur at any age usually begins in childhood or at young adult years. People with type 1 diabetes depend on insulin, daily by injection or insulin pump (IDF 2006).

The autoimmune obliteration of β-cells has multiple genetic predispositions and is also allied to environmental factors that are still poorly defined. The destruction of β-cells rate is quite variable, being rapid in infants and children and slow in adults. Immune destruction markers 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. In addition, 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 (ADS, 2010).

1.3.2. Non-Insulin dependent diabetes mellitus

Non-Insulin dependent diabetes mellitus or Type 2 diabetes is a major health problem affecting more than 170 million people worldwide. In the next 20 years, Asia will be hit hardest, with the diabetic populations in India and China more than doubling (Wild et al., 2004). NIDDM is characterized by the presence of insulin resistance and pancreatic β-cell dysfunction, resulting from the interaction of genetic and environmental factors. The risk of developing this form of diabetes increases with age, obesity, and lack of physical activity (CDCP, 2008). 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 macro vascular and micro vascular complications (NIH 2006).

1.3.3. Gestational diabetes mellites (GDM)

Gestational diabetes (GDM) is defined as a carbohydrate intolerance that normally develops during the 24th through the 32nd week of pregnancy. This condition affects 2 to 5% of pregnant women and is the most common disease affecting pregnancy (Harris, 1995). Women who have had gestational diabetes have a 40% to 60% chance of developing diabetes in the next 5-10 years. Gestational diabetes often can be controlled by diet, but insulin is sometimes necessary to maintain glycemic control. An elevated blood glucose level during pregnancy is associated with an increase in complications for both mother and infant. Following pregnancy, normal blood glucose tolerance usually returns (CDCP, 2008).

1.3.4. Other Specific Types of Diabetes

1.3.4.1. Genetic defects of the β-cell

Several forms of diabetes are associated with monogenetic defects in β-cell function. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age.
(generally before age 25 years). 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. The most common form is associated with mutations on chromosome in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)-1α. A second form is associated with mutations in the glucokinase gene on chromosome 7p and results in a defective glucokinase molecule. Glucokinase converts glucose to glucose-6-phosphate, the metabolism of which, in turn, stimulates insulin secretion by the β-cell (Musso et al., 2004).

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. 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 (ADA 2008).

1.3.4.2. Virus induced diabetes

From the time when turn of the century, several case reports showing a temporal relationship between the onset of certain viral infections and the subsequent development of diabetes (Forrest et al., 1971).

1.3.4.3. Uncommon forms of immune-mediated diabetes

In this type, the stiff-man syndrome is an autoimmune disorder of the CNS characterized by stiffness of the axial muscles with painful spasm. Patients usually have high titters of the GAD autoantibodies, and approximately one-third will develop diabetes.

1.3.4.4. 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. With the exception of that caused by cancer, damage to the pancreas must be extensive for diabetes to occur; adenocarcinomas that involve only a small portion of the pancreas have been associated with diabetes. This implies a mechanism other than simple reduction in β-cell mass (Sander et al., 1997).

1.3.4.5. Endocrinopathies

Several hormones (e.g., growth hormone, cortisol, glucagon, and epinephrine) antagonize insulin action. Excess amounts of these hormones (e.g., acromegaly, Cushing's syndrome, gluca-
gonoma, pheochromocytoma, respectively) can cause diabetes. This generally occurs in individuals with pre-existing defects in insulin secretion, and hyperglycemia typically resolves when the hormone excess is resolved (Berelowitz & Eugene, 1996).

1.3.4.6. **Drug or chemical-induced diabetes**

There are many drugs and hormones that can impair insulin action. These drugs may not cause diabetes by themselves, but they may precipitate diabetes in individuals with insulin resistance. In such cases, the classification is unclear because the sequence or relative importance of β-cell dysfunction and insulin resistance is unknown. Certain toxins such as Vacor and pentamidine can permanently destroy pancreatic β-cells. Such drug reactions fortunately are rare. Patients receiving α-interferon have been reported to develop diabetes associated with islet cell antibodies and, in certain instances, severe insulin deficiency (ADA, 2008).

1.3.5. **Etiologic classification of diabetes mellitus**

1. Type 1 diabetes
2. Type 2 diabetes
3. Immune mediated
4. Idiopathic

**Other specific types**

5. Genetic defects of β-cell function
   1. Chromosome 12, HNF-1α (MODY3)
   2. Chromosome 7, glucokinase (MODY2)
   3. Chromosome 20, HNF-4α (MODY1)
   4. Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)
   5. Chromosome 17, HNF-1β (MODY5)
   7. Mitochondrial DNA
   8. Others

6. Genetic defects in insulin action
   1. Type A insulin resistance
   2. Leprechaunism
   3. Rabson-Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

7. Diseases of the exocrine pancreas
   1. Pancreatitis
   2. Trauma/pancreatectomy
   3. Neoplasia
   4. Cystic fibrosis
   5. Hemochromatosis
   6. Fibrocalculous pancreatopathy
   7. Others

8. Endocrinopathies
   1. Acromegaly
   2. Cushing's syndrome
   3. Glucagonoma
   4. Pheochromocytoma
   5. Hyperthyroidism
   6. Somatostatinoma
   7. Aldosteronoma
   8. Others

9. Drug- or chemical-induced
   1. Vacor
   2. Pentamidine
   3. Nicotinic acid
   4. Glucocorticoids
   5. Thyroid hormone
   6. Diazoxide
   7. β-adrenergic agonists
   8. Thiazides
   9. Dilantin
   10. α-Interferon
   11. Others
10. Infections
   1. Congenital rubella
   2. Cytomegalovirus
   3. Others
11. Uncommon forms of immune-mediated diabetes
   1. “Stiff-man” syndrome
   2. Anti–insulin receptor antibodies
   3. Others
12. Other genetic syndromes sometimes associated with diabetes
   1. Down's syndrome
   2. Klinefelter's syndrome
   3. Turner's syndrome
   4. Wolfram's syndrome
   5. Friedreich's ataxia
   6. Huntington's chorea
   7. Laurence-Moon-Biedl syndrome
   8. Myotonic dystrophy
   9. Porphyria
   10. Prader-Willi syndrome
   11. Others
13. Gestational diabetes mellitus (GDM)

1.4. 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-h 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:
1.5. CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS AND IMPAIRED GLUCOSE HOMEOSTASIS (ADA, 2008)

DM--positive findings from any two of the following tests on different days:
Symptoms of DM* plus casual† plasma glucose concentration >=200 mg per dL (11.1 mmol per L)
OR
FPG >=126 mg per dL (7.0 mmol per L)
OR
2hrPPG >=200 mg per dL (11.1 mmol per L) after a 75-g glucose load

Impaired glucose homeostasis
Impaired fasting glucose: FPG from 110 to <126 (6.1 to 7.0 mmol per L)
Impaired glucose tolerance: 2hr PPG from 140 to <200 (7.75 to <11.1 mmol per L)

Normal
FPG <110 mg per dL (6.1 mmol per L)
2hrPPG <140 mg per dL (7.75 mmol per L)

*Symptoms include polyuria, polydipsia or unexplained weight loss.
†Casual is defined as any time of day without regard to time since last meal.
FPG=fasting plasma glucose; 2hr PPG=two-hour postprandial glucose

Impaired fasting glycaemia or impaired fasting glucose (IFG) refers to a condition in which the fasting blood glucose is elevated above what is considered normal levels but is not high enough to be classified as diabetes mellitus. It is considered a pre-diabetic state, associated with insulin resistance and increased risk of cardiovascular pathology, although of lesser risk than impaired glucose tolerance (IGT). IFG sometimes progresses to type 2 diabetes mellitus. There is a 50% risk over 10 years of progressing to overt diabetes. A recent study cited the average time for progression as less than three years (Nichols et al., 2007). IFG is also a risk factor for mortality (Barr et al., 2007).

1.6. COMPLICATIONS OF DIABETES MELLITUS

The complications of DM can be classified as microvascular or macrovascular disease (Figure 1). Microvascular complications consist of neuropathy (nerve damage); nephropathy (kidney disease) and retinopathy (e.g. vision disorders, glaucoma, cataract and corneal disease). Macrovascular complications consist of heart disease, stroke and peripheral vascular disease.
(which can lead to ulcers, gangrene and amputation). Other complications of diabetes are infections, metabolic difficulties, impotence, autonomic neuropathy and pregnancy problems.

Figure 1: Complications of diabetes mellitus

1.6.1. Retinopathy

Diabetic retinopathy (DR) is an eye problem caused by DM. It occurs when diabetes damages the blood vessels in the retina, which is the light sensitive tissue in the back of the eye. This disease occurs in about 95% of patients with type 1 diabetes mellitus and in 60% of type 2 DM patients. Diabetic retinopathy (Figure 2) is the most common cause of blindness and diagnosed by increased proliferation of blood vessels, vascular occlusion, microaneurysms, angiogenesis, haemorrhages and infarction affecting the retina of the eye (Nathan et al., 1986). These changes are occurred by thickening of the capillary basement membrane, increased permeability of capillaries, loss of pericytes and death (Krolewski et al., 1986).
1.6.2. 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 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 micro albuminuria 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 & Keen, 1984). This stage of incipient nephropathy may be more likely in patients with glomerular hyper-filtration. 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).

1.6.3. 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 (Figure 3). Diabetic neuropathy may be present clinically as pain or numb-
ness 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 hyperlipidaemia.

![Figure 3: Diabetes kidney](image)

### 1.6.4. Embryopathy

Diabetic mothers with poor glycaemic 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. 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. 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 im-
plicated in its pathogenesis (Eriksson et al., 1998).

1.6.5. Diabetic foot

Diabetic foot ulcer is one of the major complications of Diabetes mellitus. It occurs in 15% of all patients with diabetes and precedes 84% of all lower leg amputations. Major increase in mortality among diabetic patients, observed over the past 20 years is considered to be due to the development of macro and micro vascular complications, including failure of the wound healing process. Wound healing is a ‘make-up’ phenomenon for the portion of tissue that gets destroyed in any open or closed injury to the skin. 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 (Figure 4) (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 anaemia and leucocytosis (Ogbera et al., 2008). Therefore controlled and accurate rebuilding becomes essential to avoid under or over healing that may lead to various abnormalities. But in some cases, certain disorders or physiological insult disturbs wound healing process that otherwise goes very smoothly in an orderly manner. Diabetes mellitus is one such metabolic disorder that impedes normal steps of wound healing process. Many histopathological studies show prolonged inflammatory phase in diabetic wounds, which causes delay in the formation of mature granulation tissue and a parallel reduction in wound tensile strength (McLennan, 1988).
Figure 4 Diabetic foot ulcers usually occur on the bottom of the foot. They can also appear along the top and bottom of each toe.

1.6.6. Cardiovascular diseases

Cardiovascular diseases are 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 dyslipidaemia (increased serum triglyceride and decreased HDL-cholesterol levels). However, independently of these variables, diabetes remains a major risk factor for coronary artery disease. The levels of subacute glycaemia, as determined by measurements of glycosylated haemoglobin, may also be an independent risk factor for coronary artery disease (Singer et al., 1992).

1.6.7. Hypertension and stroke

The diagnosis of type 2 DM often is 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, 1998). Despite this, 20% to 25% of patients with DM do not develop macrovascular complications (Koda-Kimble, 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 (Alberti et al., 1982). An increased prevalence of hypertension and concur-
rent 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 hyperglycaemic episodes through aggressive control of blood glucose can lower the risk of macrovascular complications, although this has not been confirmed Study (UKPDS, 1998).

1.6.8. 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. 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 and it’s complications are as follows.

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

1.6.9. Non-Ketotic Hyperglycemia

Non-Ketotic hyperglycemia (NKH) is a clinical syndrome seen in patients with Sub-Acute 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 losses of Na and also mild elevations in serum ketone body levels and ketonuria. In general, the syndromes (NKH & 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).

1.7. PATHOGENESIS OF DIABETES MELLITUS

1.7.1. Pathophysiology and the Pathogenesis of Type 1 Diabetes

Type 1 DM is a Sub-Acute autoimmune disease associated with selective destruction of insulin-producing pancreatic β-cells. The onset of clinical disease represents the end stage of β-cell destruction leading to type 1 DM. Several features characterize type 1 DM as an autoimmune disease:

- Presence of immuno-competent and accessory cells in infiltrated pancreatic islets;
- Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA);
- Presence of islet cell specific autoantibodies;
- Alterations of T-cell mediated immuno-regulation, in particular in CD4 + T cell compartment;
- The involvement of monokines and TH1 cells producing interleukins in the disease process.

Genetic susceptibility, autoimmunity and an environmental insult 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 β-cells of the islets. The autoimmune reaction either develops spontaneously or, more likely is triggered by environmental events that alter β-cells, rendering them immunogenic. Diabetes appears after most of the β-cells have been destroyed (Robbin’s Pathological Basis of Disease, 1999).

1.7.2. Pathophysiology and the Pathogenesis of Type 2 Diabetes

Type 2 diabetes mellitus is a heterogeneous disorder with varying prevalence among different ethnic groups. The pathophysiology of type 2 diabetes mellitus is characterized by peripheral in-
insulin resistance, impaired regulation of hepatic glucose production, and declining β-cells function, eventually leading to β-cells failure (Stumvoll et al., 2005).

1.7.2.1. β-cells Dysfunction
β-cells dysfunction is initially characterized by impairment in the first phase of insulin secretion during glucose stimulation and may antedate the onset of glucose intolerance in type 2 diabetes (Robertson, 1995). Initiation of the insulin response depends upon the trans membranous transport of glucose and coupling of glucose to the glucose sensor. The glucose/glucose-sensor complex then induces an increase in glucokinase by stabilizing the protein and impairing its degradation. The induction of glucokinase serves as the first step in linking intermediary metabolism with the insulin secretory apparatus (Hull et al., 2004). Other defects in β-cells function in type 2 diabetes mellitus include defective glucose potentiation in response to non-glucose insulin secretagogues, asynchronous insulin release, and a decreased conversion of pro-insulin to insulin. Autoimmune destruction of pancreatic β-cells may be a factor in a small subset of type 2 diabetic patients and has been termed the syndrome of latent autoimmune diabetes in adults. Glucokinase is absent within the β-cells in some families with maturity-onset diabetes of young. However, deficiencies of glucokinase have not been found in other forms of type 2 diabetes (Hoppener et al., 2002).

1.7.2.2. Insulin secretion
Insulin secretion by beta cells requires glucose transport into the cell, which is at least in part mediated by the glucose transporter 2 (GLUT-2). A mouse model with a genetic alteration affecting GLUT-2 expression produced mice with glucose intolerance; similar changes in GLUT-2 could be induced in normal mice fed a high-fat diet and suggests a possible mechanism for the link between high-fat diet and the development of diabetes (Ohtsubo et al., 2005; Thorens, 2006).

1.7.2.3. Insulin Resistance
Insulin resistance has been considered to play an integral role in the pathogenesis of type 2 diabetes. 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 (Ronard Kahn, 1997).
Moreover, in the majority of type 2 diabetic patients who are insulin resistant, obesity is almost invariably present. As obesity or an increase in intra-abdominal adipose tissue is associated with insulin resistance in the absence of diabetes, it is believed by some that insulin resistance in type 2 diabetes is entirely due to the coexistence of increased adiposity. Additionally, insulin resistance is found in hypertension, hyperlipidemia, and ischemic heart disease, entities commonly found in association with diabetes, again raising the question as to whether insulin resistance results from different pathogenic disease processes or is unique to the presence of type 2 diabetes (Hull et al., 2004).

1.8. DIABETES AND METABOLIC ABNORMALITIES

1.8.1. Diabetes and lipid metabolism

The lipid metabolism process is linked to the breakdown of carbohydrates and fat, both of which are fundamental elements of diabetes mellitus. Lipid metabolism occurs in the pancreas and many of the lipid metabolism steps are regulated by insulin. Insulin issues relating to both type 1 and type 2 diabetes can have a profound impact on the lipid metabolism process. 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 low 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 1 diabetes, Lp (a) levels are frequently elevated and improvements in glycemic control result in decreases 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).
1.8.2. Diabetes and carbohydrate metabolism

Variations 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 favoured (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. Insulin exerts direct effect on the liver as well as influences the substrate availability and fluxes of free fatty acids (Bergman & 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).

1.8.3. Diabetes and protein metabolism

An association between diabetes mellitus and protein catabolism has been known to man for millennia. Protein deposition occurring after meal ingestion is the net result of a complex interplay among the effects of substrates and several hormones on the rates of protein synthesis, breakdown and amino acid oxidation. In the presence of absolute insulin deficiency (type 1 diabetes), increased protein breakdown and body protein loss occur (Nair & Copeland, 1992). Lean body mass and protein turnover are normal in individuals with type 2 diabetes where insulin deficiency is only relative because of insulin resistance (Bier, 1992). An association between diabetes mellitus and protein catabolism has been well documented. Many of the Sub-Acute complications of diabetes involve changes in structural proteins. It is thus possible that changes in protein metabolism are responsible for many of the Sub-Acute 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 (Charlton & Nair, 1998).
1.9. FREE RADICALS AND OXIDATIVE STRESS IN DIABETES

Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications. Diabetes is usually accompanied by increased production of free radicals or impaired antioxidant defences (Ceriello, 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.

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. Reactive oxygen species (ROS) and reactive intermediates are produced under physiological and pathophysiological conditions (Halliwell & 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$_2$O$_2$ and singlet oxygen (O$_2^+$) (McDermott, 2000). The generation of free radicals involves the principle of iron dependent Fenton reaction and superoxide derived Haber-Weiss reaction- Fe$^{2+}$ + H$_2$O$_2$ → Fe$^{3+}$ + OH$^-$ + OH$^-$ + OH$^-$ Fenton Reaction; O$_2^+$ + H$_2$O$_2$ → OH$^+$ + OH$^+$ + O$_2$ Haber-Weiss reaction (Chatterje & Shinde, 2000).

1.9.1. Lipid Peroxidation and Antioxidants

Lipid peroxidation is a well-established mechanism of cellular injury in both plants and animals, and is used as an indicator of oxidative stress in cells and tissues. It is a process whereby free radicals "steal" electrons from the lipids in cell membranes, resulting in cell damage. This process proceeds by a free radical chain reaction mechanism. It most often affects polyunsaturated fatty acids, because they contain multiple double bonds in between which lies methylene -CH2- groups that possess especially reactive hydrogen. The general process of lipid peroxidation consists of three stages: initiation, propagation, and termination (Catala, 2006).
Lipid per oxidation has been associated with several types of diseases including atherosclerosis, cancer and diabetes (Catala, 2007).

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 non-radical products (Machin & Bendich, 1987). The antioxidants found in biological systems include enzymes, vitamins, metal ion chelators and a variety of small molecules. The important enzymatic antioxidants include superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx). The non-enzymatic 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)** are a class of enzymes that catalyze the dismutation of superoxide into oxygen and hydrogen peroxide. In animal cells, Cu/Zn-SOD is present in the cytosol and mitochondria, while Mn-SOD is present only in the mitochondrial matrix. 

\[
\text{O}_2^- + 2 \text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2
\]

**Catalase (CAT)** has one of the highest turnover numbers of all enzymes; one molecule of catalase can convert millions of molecules of hydrogen peroxide to water and oxygen per. It is located in the cytoplasm of red blood cells but compartmentalized in the peroxisomes of the other cells. 

\[
2\text{H}_2\text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2
\]

**Glutathione peroxidase (GPx)** is the general name of an enzyme family with peroxidase activity whose main biological role is to protect the organism from oxidative damage. GPx containing active selenium is involved not only in hydrogen peroxide removal but also in converting lipid hydro peroxides (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.
GSSG + NADPH + H⁺ → NADP⁺ + 2GSH.

**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 an organic compound and classified as a terpenoid. It is a strongly-coloured red-orange pigment abundant in plants and fruits. β-Carotene is also the substance in carrots that colours them orange. 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 an essential nutrient for humans and certain other animal species, in which it functions as a vitamin. In living organisms, ascorbate is an anti-oxidant, since it protects the body against oxidative stress is water-soluble and has a broad spectrum of antioxidant activities due to its ability to react with different ROS.

**Glutathione (GSH)**, an antioxidant, helps protect cells from reactive oxygen species such as free radicals and peroxides. 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**, is an oxidative end product of heam catabolism, has also been shown to act as an efficient antioxidant.

**1.10. INSULIN SENSITIVITY AND GLUCOSE TRANSDUCTION**

**1.10.1. Insulin receptor**

Insulin resistance (IR) is a physiological condition where the natural hormone, insulin, becomes less effective at lowering blood sugars (Thibaud *et al*., 1982). The resulting increase in blood glucose may raise levels outside the normal range and cause adverse health effects. People with insulin resistance, on the other hand, need a lot of insulin to process glucose, and this leads to health problems. Several diagnostic tests can be used to determine how sensitive someone is to insulin, and these tests may be ordered if a doctor suspects that a patient is having difficulty with glucose metabolism. The pancreas is responsible for secreting insulin. Insulin triggers tissues in the body to absorb glucose from the blood, lowering blood sugar levels so that they will remain relatively stable. These tissues can store glucose in the form of glycogen. In someone with insulin sensitivity, the insulin works as it should; when insulin-sensitive tissues like the liver and the
muscles are exposed to the hormone, they respond by absorbing glucose (Flores & Riveros, 1993).

Obesity, the most common cause of insulin resistance, is associated with a decreased number of receptors and with post receptor failure to activate tyrosine kinase. While adiposity and insulin resistance are related, they are not necessarily synonymous, and each may make independent and different contributions to increasing the risk of cardiovascular disease. Insulin resistance plays a major pathogenic role in the development of the metabolic syndrome, which may include any or all of the following:
The mechanisms responsible for insulin resistance syndromes include genetic or primary target cell defects, autoantibodies to insulin, and accelerated insulin degradation

- Hyperinsulinemia
- Type 2 diabetes or glucose intolerance
- Central obesity
- Hypertension
- Dyslipidemia that includes high triglyceride levels
- Low HDL-C level and low-density lipoprotein (LDL) particles
- Hypercoagulability characterized by an increased plasminogen activator inhibitor–1 (PAI-1) level

Insulin promotes a number of metabolic and mitogenic responses through a highly coordinated signalling network (Figure 5). Insulin binds to a specific cell-surface receptor composed of two α-subunits and two β-subunits. Insulin binding to the α-subunits activates the receptor tyrosine kinase, leading to autophosphorylation of (Figure 6) (Cushman & Wardzala, 1980). The original hypothesis was later confirmed in skeletal muscle using subcellular fractionation techniques to show that insulin stimulated glucose transport involves the recruitment of GLUT₄ to the cell surface in rat (Hirshman et al., 1990; Marette et al., 1992), as well as in human skeletal muscle (Guma et al., 1995).
The best known of the many actions of insulin is control of glucose transport over the plasma membrane of skeletal muscle and fat cells (Figure 7). Glucose transport protein 4 (GLUT4) carries out insulin-stimulated glucose transport. The general consensus in the field is that GLUT4 is the primary transporter responsible for insulin- and contraction-stimulated glucose transport in insulin-sensitive tissue such as skeletal muscle. Insulin stimulation of human skeletal
muscle leads to an increase in cell-surface GLUT$_4$ content that is accompanied by a corresponding increase in glucose transport activity (Ryder et al., 2000). The major effect of insulin on GLUT$_4$ traffic to the cell surface is to stimulate exocytosis, rather than to inhibit endocytosis (Holman & Kasuga, 1997). Insulin-stimulated glucose transport activity is correlated with cell-surface GLUT$_4$ content in skeletal muscle (Lund et al., 1997). Thus, strategies which increase the amount of GLUT$_4$ at the cell surface should increase the rate of glucose disposal.

Insulin has many actions in addition to regulation of glucose uptake by muscle and fat. Insulin is strongly involved in regulation of cyclic AMP levels through its effects on phosphodiesterase. Thus, insulin counters actions of the many hormones that modify metabolism through activation of adenyl cyclase. Perhaps the most important of these in regulation of homeostasis is glucagon. Insulin reduces the rate of lipolysis and is a major element in regulation of hepatic gluconeogenesis. Insulin activates amino acid uptake in most cells and is necessary for activation of protein synthesis at the nuclear level.

![Functional GLUT4](image)

**Muscle activity alone can activate this mechanism!**

Figure 7: Insulin-activated GLUT4 transport

### 1.11. NEW ADDITIONS IN ANTIDIABETIC AGENTS

#### 1.11.1. Benzoic acid derivatives (repaglinide)

Repaglinide is a sulfonylurea derivative stimulates insulin secretion in a different way. It is rapidly absorbed and quickly metabolized in the body; Repaglinide seems to have little effect
on lipids and can, like the sulfonylureas, cause weight gain and hypoglycaemia (Huang et al., 1996).

### 1.11.2. Thiazolidinediones

The Thiazolidinediones (TZDs) enhance insulin action in muscle, fat and other tissues and are known as insulin sensitizers. The major side effect, seen with troglitazone, the first TZD to be approved by the FDA, is liver damage. Other side effects of TZD are mild elevations of LDL cholesterol and fluid retention (Martens et al., 2002).

### 1.11.3. Glucosidase inhibitors

Glucosidase inhibitors act in the intestine to block the action of enzymes that are responsible for breaking down complex carbohydrates into simple sugars. Gastrointestinal side effects are common, affecting up to 30% of patients. Bloating, flatulence, diarrhoea and abdominal discomfort and pain are the major complaints.

### 1.11.4. New drug formulations for type 2 diabetes mellitus

The sulphonylureas and biguanides have well-established experimental, clinical documentation proving their safety, better tolerability and superior pharmacodynamic effects.

The advantages of controlled release products are well known and documented in the pharmaceutical art. Advantages include the ability to maintain a desirable blood level of a medicament over an extended period, such as twenty-four hours, by minimizing the peak-to-trough variations in plasma concentrations. Reducing the number of administrations necessary to achieve a desired therapeutic effect increases patient compliance.

### 1.12. DIABETOGENIC AGENTS

#### 1.12.1. Streptozotocin

Streptozotocin (STZ) is a naturally occurring chemical that is particularly toxic to the insulin-producing beta cells of the pancreas in mammals. Streptozotocin is a glucosamine-nitrosourea compound that shows selective cytotoxicity to pancreatic β-cells. The chemical name is 2-deoxy-2-(3-methyl-3-nitrosourido)-O-glucopyranose. Molecular formula is $C_{8}H_{13}N_{3}O_{7}$ (Figure
8). The structure is composed of a nitrosourea moiety with a methyl group attached at one end and a glucose molecule at the other end (Wang et al., 1999).

Streptozotocin is approved by the U.S. Food and Drug Administration (FDA) for treating metastatic cancer of the pancreatic islet cells. Since it carries a substantial risk of toxicity and rarely cures the cancer, its use is generally limited to patients whose cancer cannot be removed by surgery. In these patients, Streptozotocin can reduce the tumour size and reduce symptoms (Brentjens and Saltz, 2001).

![Figure 8: Structure of Streptozotocin](image)

Diabetes is induced by single intraperitonial injection of freshly prepared Streptozotocin (55 mg kg\(^{-1}\) b.wt) in 0.1M citrate buffer (PH-4.5) in a volume of 1 ml Kg\(^{-1}\) rats (Siddique et al., 1987). In case of mice the dose 175-200 mg kg\(^{-1}\) and Dog 15 mg kg\(^{-1}\) for 3 days). Streptozotocin also induces diabetes in Hamster, monkey and Guinea pig (Chattopadhyay et al., 1997).

1.12.1.1. Mechanism of action

STZ is diabetogenic because it selectively destroys the insulin-producing beta cells by inducing necrosis. It is postulated that the selective beta-cell toxicity of STZ is related to the glucose moiety in its chemical structure, which enables STZ to enter the cell via the low affinity glucose transporter GLUT2 in the plasma membrane (Elsner, 2000). It is generally accepted that the cytotoxicity produced by STZ depends on DNA alkylation and subsequent activation of poly ADP-ribose synthetase causes rapid and lethal depletion of NAD in pancreatic β-islets, thereby causing cell death (Figure 9).
Several lines of evidences indicate that free radicals, highly reactive carbonium radicals originating from the decay of STZ molecules might increase the production of oxygen free radicals including hydroxyl radicals and nitric oxide, may play an essential role in the mechanism of β-cell damage and diabetogenic effect of STZ.

1.13. MANAGEMENT OF DIABETES MELLITUS

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

1.13.1. Diet and life style 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. Not 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.

1.13.2. 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 necessary daily component of type-1 diabetes therapy. Insulin injections however, are not always necessary for treatment and control of diabetes in type 2 diabetics (Buse, 1999).

1.13.3. Oral hypoglycemic agents

Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, and pramlintide, all are administered orally and are thus called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the diabetes, age and situation of the person, as well as other factors.

Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in type I diabetes mellitus, which must be injected or inhaled.

Type 2 Diabetes mellitus is a disease of insulin resistance by cells. Treatments include

1) Increases the amount of insulin secreted by the pancreas,
2) Increases the sensitivity of target organs to insulin, and
3) Decreases the rate at which glucose is absorbed from the gastrointestinal tract.

Several groups of drugs, mostly given by mouth, are effective in Type II, often in combination. The therapeutic combination in Type II may include insulin, when oral agents have failed completely. The great advantage of injected insulin in Type II is that a well-educated patient can adjust the dose, or even take additional doses, when blood glucose levels measured by the patient, usually with a simple meter, as needed by the measured amount of sugar will be in the blood.
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 β-cells of pancreatic islet.

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 HbA1c 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. TZAs allowing the tissues to respond to endogenous insulin more efficiently without increased output from already dysfunctional β-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 (ADA, 2007).
1.13.4. Current treatment for diabetes mellitus

Treatments for diabetes can include many elements. Conventional treatments in addition to complementary and alternative treatments are available. Many oral hypoglycaemic agents, such as biguanides and sulfonylureas are available along with insulin for the treatment of diabetes mellitus, but these synthetic agents can produce serious side effects, and in addition, they are not suitable for use during pregnancy. Even though several therapies are in use for treatment, there are certain limitations due to high cost and side effects such as development of hypoglycemia, weight gain, gastrointestinal disturbances, liver toxicity etc (Dey et al., 2002).

A health treatment that is not classified as standard Western medical practice is referred to as complementary and alternative medicine. Complementary and alternative therapy encompasses a variety of disciplines that include everything from diet and exercise to mental conditioning and lifestyle changes. Examples include acupuncture, guided imagery, chiropractic treatments, yoga, hypnosis, biofeedback, aromatherapy, relaxation, herbal remedies, massage, and many others.

1.13.5. Supplements

Chromium has been widely publicized as therapy to improve diabetes control. Although there are several studies that support a role for chromium as beneficial in diabetes, currently there are no recommendations for its use in diabetes management.

Magnesium has been studied for years as a form of therapy to improve blood sugar control in people with diabetes. A lack of magnesium has been associated with insulin secretion abnormalities and has been associated with diabetes complications.

Vanadion is derived from plant sources and has been shown in a few studies to increase a person's sensitivity to insulin. Thus far, no recommendations exist for supplementation to be given to people with diabetes.

1.13.6. Plant Foods

The following plant foods have been found to help people with type 2 diabetes.

- Brewer’s yeast
- Buckwheat
- Broccoli and other related greens
- Okra
- Peas
- Fenugreek seeds
- Sage

1.13.7. Indigenous treatment for diabetes mellitus

Plant based drugs have been in use against various diseases since time immemorial. The nature has provided abundant plant wealth for all living creatures, which possess medicinal virtues. In traditional medicine, diabetes mellitus is treated with diet, physical exercise and medicinal plants, even though, more than 1200 plants are used around the world in the empirical control of diabetes mellitus and approximately 30% of the traditionally used antidiabetic plants were pharmacologically and chemically investigated. World ethnobotanical information about medicinal plants reports almost 800 plants used in the control of diabetes mellitus. Recent surveys of literature have shown that most of the works on hypoglycemic property of medicinal plants are carried out at extract level (Table 1). Therefore there is an urgent need for further studies to identify the active natural principle which is responsible for the hypoglycemic property. Major hindrance in incorporation of herbal medicine in modern medical practices is lack of scientific and clinical data proving their efficacy and safety.

There are many hypoglycemic plants known through the folklore but their introduction into the modern therapy awaits the discovery of animal test system that closely parallel to the pathological course of diabetes in human. Hypoglycemic activity has been reported in many plants during the last twenty years.

There is a need for conducting clinical research in medicinal plants, developing simple bioassays for biological standardization, pharmacological and toxicological evaluation, and developing various animal models for toxicity and safety evaluation. It is also important to establish the active component/s from these plant extracts.
Table 1: Important antidiabetic plants and their parts used 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, Antilipidperoxidative 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><em>Caesaeria esculenta</em></td>
<td>Root</td>
<td>Antihyperglycaemic, Hypolipidemic and Antiperoxidative effect.</td>
</tr>
<tr>
<td><em>Cassia auriculata</em> L. Caesalpiniaceae</td>
<td>Flower</td>
<td>Hypoglycemic, Antihyperglycemic, Antihyperlipidemic and Antiperoxidative effect.</td>
</tr>
<tr>
<td><em>Catharanthus roseus</em> (L.) G. Don, Apocynaceae</td>
<td>Flowers and whole plant</td>
<td>Antidiabetic activity and antiperoxidative effect.</td>
</tr>
<tr>
<td><em>Coccinia indica</em>, W &amp; A. Cucurbitaceae</td>
<td>Leaf, Leaves and roots</td>
<td>Hypoglycemic, hypolipidemic effects, Increase antioxidant level and Antiperoxidative effect.</td>
</tr>
<tr>
<td><em>Curcuma longa</em> L. Zingiberaceae</td>
<td>Rhizome</td>
<td>Hypoglycemic and Antidiabetic effect.</td>
</tr>
<tr>
<td><em>Eugenia jambolana</em> Lam. = <em>Syzygium cumini</em> (L.) Skeels, Myrtaceae</td>
<td>Seed, Fruit pulp</td>
<td>Hypoglycemic, Anti-hyperglycemic, Antidiabetic and hypolipidemic effects.</td>
</tr>
<tr>
<td><em>Ficus benghalensis</em> L. Moraceae</td>
<td>Bark</td>
<td>Hypoglycemic, hypolipidemic and serum insulin raising effects.</td>
</tr>
<tr>
<td><em>Gymnema montanum</em> Asclepiadaceae</td>
<td>Leaf</td>
<td>Hypoglycemic, Antidiabetic, Antiperoxidative and antioxidant effects.</td>
</tr>
<tr>
<td><em>Gymnema sylvestre</em> R. Br. Asclepiadaceae</td>
<td>Leaf</td>
<td>Hypoglycemic, Antihyperglycemic, Antiperoxidative effect, Regeneration of endo-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------</td>
<td>-----------------------------------------------------------------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Crine pancreas</strong></td>
<td>Antidiabetic and decrease glycoprotein levels and decreased insulin resistance.</td>
<td></td>
</tr>
<tr>
<td><strong>Helicteres isora</strong> L. Sterculiaceae</td>
<td>Stem bark Root</td>
<td>Hypoglycemic, Hypolipidemic effects and hepatoprotective activity.</td>
</tr>
<tr>
<td><strong>Momordica charantia</strong> L. Cucurbitaceae</td>
<td>Fruit pulp, seed &amp; whole plant</td>
<td>Hypoglycemic, hyperinsulinemic, Hypolipidemic, Hypotriglyceridemic and hypocholesterolemic effects.</td>
</tr>
<tr>
<td><strong>Nigella sativa</strong> L</td>
<td>Seeds</td>
<td>Hypoglycemic, antihyperlipidemic, Antioxidant effect.</td>
</tr>
<tr>
<td><strong>Ocimum sanctum</strong> 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><strong>Panax ginseng</strong> C.A. Mey Araliacea</td>
<td>Roots, stems, leaf and fruits</td>
<td>Hypoglycemic, Anti-hyperglycemic, Antidiabetic Hypolipidemic effects.</td>
</tr>
<tr>
<td><strong>Phyllanthus emblica</strong> L. Euphorbiaceae</td>
<td>Fruits</td>
<td>Hypoglycemic, Antihyperlipidemic and Antioxidant effect.</td>
</tr>
<tr>
<td><strong>Pterocarpus marsupium</strong> Roxb. Fabaceae</td>
<td>Bark, Wood</td>
<td>Hypoglycemic activity, Anti-hypertriglyceridaemic, hyperinsulinaemic and Antidiabetic effect.</td>
</tr>
<tr>
<td><strong>Punica granatum</strong> L. Punicaceae</td>
<td>Seeds Flower</td>
<td>Hypoglycemic, Antidiabetic effects 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, Hypcholesterolemic effects.</td>
</tr>
</tbody>
</table>

The changing faces of macro vascular disease in non-insulin dependent diabetes mellitus, an epidemic progress.

**1.14. Inflammation**

Inflammation is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process. Inflammation is not a synonym for infection, even in cases where inflammation is caused by infection. Although
infection is caused by a microorganism, inflammation is one of the responses of the organism to the pathogen. However, inflammation is a stereotyped response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity, which is specific for each pathogen.

Without inflammation, wounds and infections would never heal. Similarly, progressive destruction of the tissue would compromise the survival of the organism. However chronic inflammation can also lead to a host of diseases such as hay fever, atherosclerosis, rheumatoid arthritis, periodontitis and even cancer. (e.g: gallbladder carcinoma). It is for that reason that inflammation is normally closely regulated by the body.

Inflammation can be classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process.

Acute inflammation is a short-term process, usually appearing within a few minutes or hours and ceasing upon the removal of the injurious stimulus. It is characterized by five cardinal signs.

The acronym that may be used for this is "PRISH" for Pain, Redness, Immobility (loss of function), Swelling and Heat.

The traditional names for signs of inflammation come from Latin:

- Dolor (pain)
- Calor (heat)
- Rubor (redness)
- Tumor (swelling)
- Function laesa (loss of function)
The first four (classical signs) were described by Celsus while loss of function was added later by Galen even though the attribution is disputed and the origination of the fifth sign has also been ascribed to Thomas Sydenham and Virchow.

Redness and heat are due to increased blood flow at body core temperature to the inflamed site; swelling is caused by accumulation of fluid; pain is due to release of chemicals that stimulate nerve endings. Loss of function has multiple causes.

These five signs appear when acute inflammation occurs on the body's surface, whereas acute inflammation of internal organs may not result in the full set. Pain only happens where the appropriate sensory nerve endings exist in the inflamed area e.g., acute inflammation of the lung (pneumonia) does not cause pain unless the inflammation involves the parietal pleura, which does have pain-sensitive nerve endings.