INTRODUCTION

Diabetes mellitus represents a major medical problem affecting millions of people all over the world. The human population worldwide appears to be in the midst of an epidemic of diabetes. Aretaeus, a Cappadocian physician of the second century A.D., wrote: “The epithet diabetes has been assigned to the disorder, being something like passing of water by a siphon”. He perceptively characterized diabetes as being a melting down of the flesh and limbs into urine. Diabetes named for the excessive urination in the disease and mellitus a Latin word meaning “sweetened with honey”, refers to the presence of sugar in the urine of patients having the disease.

Diabetes mellitus, often simply referred to as diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). It is a group of heterogeneous, hormonal and metabolic disorder characterized by hyperglycemia and glycosuria, with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.

The percentage of diabetic patients all over the world is increasing day by day. Diabetes is the third widespread and serious disorder after cardiovascular disease and cancer. Globally, the estimated incidence of diabetes mellitus and projection for the year 2010, as given by International Diabetes Federation is 239 million. According to the International Diabetes Federation (2011) the number of people living with diabetes is expected to rise from 366 million in 2011 to 552 million by 2030. India leads the way with its largest number of diabetic subjects than any other country. It is estimated that the total number of people living with diabetes in 2010 to be around 50.8 million in India, rising to 87.0 million by 2030 (International Diabetes Federation, 2009).

Glucose is a simple sugar found in food and is an essential nutrient that provides energy for the proper functioning of the body cells. Carbohydrates are broken down in...
the small intestine and glucose in digested food is absorbed by the intestinal cells into the bloodstream and is carried to all the cells in the body. However, glucose cannot enter the cells alone; it needs insulin for its transport into the cells. Without insulin, the cells starve for energy despite the presence of abundant glucose in the bloodstream. In certain types of diabetes the inability of cells to utilize glucose gives rise to an ironic situation of starvation in the midst of abundant quantum of unutilized glucose which is wastefully excreted in the urine.

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 both. Several pathogenic processes are involved in the development of diabetes. 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 basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is due to the deficient action of insulin on target tissues. Inadequate insulin secretion and/or diminished tissue responses to insulin results in deficient insulin action at one or more points in the complex pathways of hormone action.
Acute, life-threatening consequences of uncontrolled diabetes are hyperglycemia with ketoacidosis or the non-ketotic hyperosmolar syndrome. Long-term complications of diabetes include retinopathy with potential loss of vision; nephropathy leading to renal failure; peripheral neuropathy with risk of foot ulcers, amputations, and Charcot joints; and autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction. Patients with diabetes have an increased incidence of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular disease. Hypertension and abnormalities of lipoprotein metabolism are often found in people with diabetes. 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.

1.2 Classification of Diabetes mellitus

Diabetes mellitus is a heterogeneous clinical disorder with numerous causes. The two distinct forms of diabetes mellitus are type I, juvenile or insulin-dependent diabetes mellitus (IDDM) and type II, adult onset or non insulin-dependent diabetes mellitus (NIDDM).

1.2.1 Type 1 - Insulin Dependent Diabetes Mellitus (IDDM)

Type 1 diabetes mellitus (formerly called type I, IDDM or juvenile diabetes) is characterized by beta cell destruction caused by an autoimmune process, usually leading to absolute insulin deficiency. The onset is usually acute, developing over a period of a few days to weeks. Over 95 percent of persons with type 1 diabetes mellitus develop the disease before the age of 25, with an equal incidence in both sexes and an increased prevalence in the white population. A family history of type 1 diabetes mellitus, gluten enteropathy (celiac disease) or other endocrine disease is often found. Most of these patients have the “immune-mediated form” of type 1 diabetes mellitus with islet cell antibodies and often have other autoimmune disorders such as Hashimoto's thyroiditis, Addison's disease, vitiligo or pernicious anemia. A few patients, usually those of African or Asian origin, have no antibodies but have a similar clinical presentation;
consequently, they are included in this classification and their disease is called the “idiopathic form” of type 1 diabetes mellitus (National Diabetes Data Group, 1995).

1.2.2 Type 2- Non-Insulin Dependant Diabetes Mellitus (NIDDM)

Type 2 diabetes mellitus (formerly called NIDDM, type II or adult-onset) is characterized by insulin resistance in peripheral tissue and an insulin secretory defect of the beta cell (National Diabetes Data Group, 1995). This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, older age, obesity and lack of exercise. It is more common in women, especially women with a history of gestational diabetes, and in blacks, Hispanics and Native Americans. Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance. Defective beta cells become exhausted, further fueling the cycle of glucose intolerance and hyperglycemia. The etiology of type 2 diabetes mellitus is multifactorial and probably genetically based, but it also has strong behavioral components.

Figure 1.2. Type 1 and Type 2 diabetes

1.2.3 Other specific types

Types of diabetes mellitus of various known etiologies are grouped together to form the classification called “other specific types.” This group includes persons with genetic defects of β-cell function (this type of diabetes was formerly called MODY or maturity-onset diabetes in youth) or with defects of insulin action; persons with diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis; persons with dysfunction associated with other endocrinopathies; and persons with pancreatic dysfunction caused by drugs, chemicals or infections (National Diabetes Data Group, 1995).
1.2.4 Gestational diabetes mellitus (GDM)

Gestational diabetes mellitus is an operational classification (rather than a pathophysiologic condition) identifying women who develop diabetes mellitus during gestation. Women with diabetes mellitus before pregnancy are said to have “pre-gestational diabetes” and are not included in this group. Women who develop type 1 diabetes mellitus during pregnancy and women with undiagnosed asymptomatic type 2 diabetes mellitus that is discovered during pregnancy are classified with gestational diabetes mellitus. However, most women classified with gestational diabetes mellitus have normal glucose homeostasis during the first half of the pregnancy and develop a relative insulin deficiency during the last half of the pregnancy, leading to hyperglycemia. The hyperglycemia resolves in most women after delivery but places them at increased risk of developing type 2 diabetes mellitus later in life.

1.3 Risk factors for Diabetes mellitus

Diabetes mellitus is now considered as a very common lifestyle disease. Although it can be triggered by genetic susceptibilities and viruses, there are many other factors that can increase the risk of diabetes as well. Knowing what these factors are very important because they can help to come up with measures on how to prevent the disease from ever occurring. Some of the most common factors that trigger and make more susceptible to diabetes mellitus are as follows.

1.3.1 Risk Factors for Type 1 Diabetes

The primary risk factor for type 1 diabetes is a family history of this lifelong, chronic disease.

1.3.1.1 Genetics and family history

Anyone with a parent or sibling with type 1 diabetes has a slightly increased risk of developing the condition.

1.3.1.2 Diseases of the pancreas

Injury or diseases of the pancreas can inhibit its ability to produce insulin and lead to type 1 diabetes.
1.3.1.3 Infection or illness

A range of relatively rare infections and illnesses can damage the pancreas and cause type 1 diabetes. Exposure to Epstein-Barr virus, coxsackie virus, mumps virus or cytomegalovirus may trigger the autoimmune destruction of the islet cells, or the virus may directly infect the islet cells.

1.3.2 Risk Factors for Type 2 Diabetes

Risk factors for developing type 2 diabetes include the following

1.3.2.1 High blood Cholesterol and high blood pressure

People with unregulated blood cholesterol levels and high blood pressure have increased risk of diabetes. This is mainly because high blood glucose levels can increase the viscosity of the blood, resulting to increased pressure in the vessels. It can also cause damage to the blood vessels themselves.

1.3.2.2 Gestational diabetes

Women who manifest this condition can have a very high risk of diabetes well after they have delivered their babies. Gestational diabetes begins when hormones from the placenta cause the mother’s cells to be insulin resistant.

1.3.2.3 Unhealthy diet

This is one of the most common factors that increase the risk of diabetes. Eating a lot of high sugar, high carbohydrate and high fat foods can trigger the condition and can worsen existing cases of the disease.

1.3.2.4 Sedentary lifestyle

This is also a very common factor that can increase the risk of diabetes. Exercise is one of the most important pillars to health. The lack of physical activity can lead to obesity which as mentioned before can also increase the risk of diabetes. Muscle cells generally have more insulin receptors than fat cells or any other cells in the body. Hence, having more of these types of tissues and less of fat can help in regulating the amount of glucose in the body.
1.3.2.5 Obesity or being overweight

Obesity has been declared as the number one factor that contributes to the risk of diabetes in most of the reported cases. Studies have revealed that obese and overweight patients are 55% more susceptible to acquiring diabetes mellitus compare to people who are non-obese.

1.3.2.6 Ethnic background

Diabetes occurs more often in certain groups, such as Hispanic/Latino Americans, African-Americans, Native Americans, Asian-Americans, Pacific Islanders, and Alaska natives.

1.3.2.7 Aging

Increasing age is a significant risk factor for type 2 diabetes. Risk begins to rise significantly at about the age of 45 years, and rises considerably after the age of 65 years. Medical researchers and scientist hypothesize that the capacity of the pancreas to function may decrease as the body ages. Thus, the organ’s ability to produce and pump in insulin into the body systems becomes less and less efficient as well. Ageing cells can become more and more resistant to insulin overtime which can contribute to the progression of diabetes.

1.3.2.8 Impaired glucose tolerance

Impaired glucose tolerance (IGT) is also referred to as pre-diabetes or impaired fasting glucose (IFG). It is a milder form of diabetes and is a major risk factor for developing type 2 diabetes and cardiovascular complications.

1.3.2.9 Family history

Diabetes mellitus risk factors are high, if there is a family history of diabetes particularly when a close relative had type 2 diabetes.

1.3.2.10 Polycystic ovary syndrome

Women with polycystic ovary syndrome (PCOS) are at higher risk of type 2 diabetes. All of the factors associated with Insulin Resistance, Polycystic Ovarian Syndrome and Pre-diabetes are interrelated.
1.4 Symptoms of Diabetes mellitus

1.4.1 Symptoms of type 1 diabetes

Symptoms are often dramatic and appear suddenly. Type 1 diabetes is usually recognized in childhood or early adolescence, often in association with an illness such as urinary tract infection. The extra stress can cause diabetic ketoacidosis with Symptoms of nausea and vomiting. Without treatment, ketoacidosis can lead to coma and death.

1.4.2 Symptoms of type 2 diabetes

Symptoms are often subtle and may be attributed to aging or obesity. A person may have type 2 diabetes for many years without knowing it. People with type 2 diabetes can develop hyperglycemic hyperosmolar nonketotic syndrome. Type 2 diabetes can be precipitated by steroids and stress. If not properly treated, type 2 diabetes can lead to complications such as blindness, kidney failure, heart disease and nerve damage.

1.4.3 Common symptoms of both type 1 and type 2 diabetes

1.4.3.1 Fatigue, constantly tired

In diabetes, the body is inefficient and sometimes unable to use glucose for fuel. The body switches over to metabolizing fat, partially or completely, as a fuel source. This process requires the body to use more energy and it results in feeling fatigue or constantly tired.

1.4.3.2 Unexplained weight loss

People with diabetes are unable to process many of the calories in the foods they eat. Thus, they may lose weight even though they eat an apparently appropriate or even an excessive amount of food. Losing sugar and water in the urine and the accompanying dehydration also contributes to weight loss.

1.4.3.3 Excessive thirst (polydipsia)

A person with diabetes develops high blood sugar levels, which overwhelms the kidney's ability to reabsorb the sugar as the blood is filtered to make urine. Excessive
urine is made as the kidney spills the excess sugar. The body tries to counteract this by sending a signal to the brain to dilute the blood, which translates into thirst. The body encourages more water consumption to dilute the high blood sugar back to normal levels and to compensate for the water lost by excessive urination.

1.4.3.4 Excessive urination (polyuria)

Another way the body tries to rid the body of the extra sugar in the blood is to excrete it in the urine. This can also lead to dehydration because a large amount of water is necessary to excrete the sugar.

1.4.3.5 Excessive eating (polyphagia)

The body is resistant to the action of insulin in type 2 diabetes. One of the functions of insulin is to stimulate hunger. Therefore, higher insulin levels lead to increased hunger. Despite increased caloric intake, the person may gain very little weight and may even lose weight.

1.4.3.6 Poor wound healing

High blood sugar levels prevent white blood cells, which are important in defending the body against bacteria and also in cleaning up dead tissue and cells, from functioning normally. When these cells do not function properly, wounds take much longer to heal and become infected more frequently. Long-standing diabetes also is associated with thickening of blood vessels, which prevents good circulation, including the delivery of enough oxygen and other nutrients to the body tissues.

1.4.3.7 Infections

Certain infections, such as frequent yeast infections of the genitals, skin infections and frequent urinary tract infections, may result from suppression of the immune system by diabetes and by the presence of glucose in the tissues, which allow bacteria to grow. These infections can also be an indicator of poor blood sugar control in a person known to have diabetes.

1.4.3.8 Altered mental status and blurry vision

Agitation, unexplained irritability, inattention, extreme lethargy, or confusion can all be signs of very high blood sugar, ketoacidosis, hyperosmolar hyperglycemia
nonketotic syndrome and hypoglycemia. Blurry vision is not specific for diabetes but is frequently present with high blood sugar levels.

1.5 Complications of diabetes

The complications of diabetes mellitus are far less common and less severe in people who have well-controlled blood sugar levels. Wider health problems accelerate the deleterious effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure and lack of regular exercise.

1.5.1 Acute complications

Diabetes can contribute to a number of acute (short-lived) medical problems.

1.5.1.1 Hypoglycemia

Hypoglycemia or low blood sugar occurs intermittently in most people with diabetes. It can result from taking too much diabetes medication or insulin (sometimes called an insulin reaction), missing a meal, exercising more than usual, drinking too much alcohol, or taking certain medications for other conditions. It is very important to recognize hypoglycemia and be prepared to treat it at all times. Headache, feeling dizzy, poor concentration, tremor of the hands and sweating are common symptoms of hypoglycemia. A person can faint or have a seizure if blood sugar level becomes too low.

1.5.1.2 Diabetic ketoacidosis

Diabetic ketoacidosis is a serious condition in which uncontrolled hyperglycemia (usually due to complete lack of insulin or a relative deficiency of insulin) over time creates a buildup of ketones (acidic waste products) in the blood. High levels of ketones can be very harmful. This typically happens to people with type 1 diabetes who do not have good blood glucose control. Diabetic ketoacidosis can be precipitated by infection, stress, trauma, missing medications like insulin, or medical emergencies such as a stroke and heart attack.

1.5.1.3 Hyperosmolar hyperglycemic nonketotic syndrome

Hyperosmolar hyperglycemic nonketotic syndrome is a serious condition in which the blood sugar level gets very high. The body tries to get rid of the excess blood
sugar by eliminating it in the urine. This increases the amount of urine significantly and often leads to dehydration so severe that it can cause seizures, coma and even death. This syndrome typically occurs in people with type 2 diabetes who are not controlling their blood sugar levels, who have become dehydrated, or who have stress, injury, stroke or taking certain medications like steroids.

1.5.1.4 Infections

Many infections are associated with diabetes, and infections are frequently more dangerous in someone with diabetes because the body's normal ability to fight infections is impaired. To compound the problem, infections may worsen glucose control, which further delays recovery from infection.

1.5.2 Chronic complications

Chronic elevation of blood glucose level leads to damage of blood vessels (angiopathy). The endothelial cells lining the blood vessels take in more glucose than normal, since they do not depend on insulin. They then form more surface glycoproteins than normal, and cause the basement membrane to grow thicker and weaker. In diabetes mellitus, the changes results in one or more of the following Complications.

1.5.2.1 Diabetic retinopathy

One of the most devastating microvascular complications of diabetes mellitus is diabetic retinopathy. Over the last decade considerable progress has been made in the understanding of the pathogenesis of diabetic retinopathy and several factors have been implicated in its pathogenesis. These include non-enzymatic glycation, accumulation of advanced glycation end-products, free radical mediated protein damage, up-regulation of matrix metalloproteinases, elaboration of growth factors and secretion of adhesion molecules in the vascular endothelium.

1.5.2.2 Diabetic nephropathy

Diabetic nephropathy accounts for approximately 14% of all deaths in diabetic patients. The earliest functional renal change detected is glomerular hyperfusion. This is followed by renal hypertrophy. At this stage renal morphology is normal although
there may be microalbuminuria which is reversible by strict control of the blood glucose concentration and hypertension, if present. Its importance is that it predicts the development of irreversible renal damage indicated by the development of proteinuria.

1.5.2.3 Diabetic neuropathy

Diabetic neuropathy may affect every part of the nervous system with the possible exception of the brain. Distinct syndromes can be recognized and several different types of neuropathy may be present in the same patient. The most common is peripheral polyneuropathy; the symptoms include numbness and severe pain. Damage to the nerves in lower extremities is a leading cause of foot wounds and ulcers, which frequently lead to foot and leg amputations.

1.5.2.4 Vascular diseases

The excess mortality increased by diabetic patients is mainly due to large blood vessel disease, which is common in diabetic patients and accounts for about 70% of all deaths. The pathological changes associated with atherosclerosis in diabetic patients are similar to those seen in the non-diabetic population but they occur earlier in life and are more extensive and severe. Disease of small vessels is specific to diabetes and is termed diabetic microangiopathy. In microangiopathy there is thickening of the capillary basement with associated increase in vascular permeability throughout the body. These conditions both independently and together with hyperglycemia, increase the risk of heart disease, kidney disease, and other blood vessel complications.

1.6 Metabolic derangements associated with diabetes mellitus

1.6.1 Glucose Metabolism

Uncontrolled diabetes mellitus leads to increased hepatic glucose output. Liver glycogen stores are mobilized and hepatic gluconeogenesis is used to produce glucose. Insulin deficiency also impairs non-hepatic tissue utilization of glucose. In particular in adipose tissue and skeletal muscle, insulin stimulates glucose uptake. This is accomplished by insulin mediated movement of glucose transporter proteins to the plasma membrane of these tissues. Reduced glucose uptake by peripheral tissues in turn leads to a reduced rate of glucose metabolism. In addition, the level of hepatic...
glucokinase is regulated by insulin. The combination of increased hepatic glucose production and reduced peripheral tissues metabolism leads to elevated plasma glucose levels. When the capacity of the kidneys to absorb glucose is surpassed, glycosuria ensures. An increase in renal loss of glucose is accompanied by loss of water and electrolytes. The result of the loss of water leads to the activation of the thirst mechanism. The tissue catabolism leads to an increase in appetite and food intake (Sheriff et al., 1992).

1.6.2 Lipid Metabolism

One major role of insulin is to stimulate the storage of food energy following the consumption of a meal. This energy storage is in the form of glycogen in hepatocytes and skeletal muscle. Additionally, insulin stimulates hepatocytes to synthesize triglycerides and storage of triglycerides in adipose tissue. In opposition to increased adipocyte storage of triglycerides is insulin-mediated inhibition of lipolysis. In uncontrolled diabetes mellitus there is a rapid mobilization of triglycerides leading to increased levels of plasma free fatty acids. The free fatty acids are taken up by numerous tissues (however, not the brain) and metabolized to provide energy. Free fatty acids are also taken up by the liver. In the absence of insulin, mitochondrial oxidation of fatty acids generates acetyl-CoA which can be further oxidized in the TCA cycle. However, in hepatocytes the majority of the acetyl-CoA is not oxidized by the TCA cycle but is metabolized into the ketone bodies, acetoacetate and β-hydroxybutyrate. The increased availability of free fatty acids and ketone bodies exacerbates the reduced utilization of glucose and ensuring hyperglycemia (Sheriff et al., 1992).

1.6.3 Protein metabolism

Insulin regulates the synthesis of many genes, either positively or negatively that affect the overall metabolism. Insulin has a global effect on protein metabolism i.e., increasing the rate of protein synthesis and decreasing the rate of protein degradation. Thus, insulin deficiency will lead to increased catabolism of protein. The increased rate of proteolysis leads to elevated concentrations of plasma amino acids. These amino acids serve as precursors for hepatic and renal gluconeogenesis. In liver, the increased gluconeogenesis further contributes to the hyperglycemia (Sheriff et al., 1992).
1.7 Insulin and its role in diabetes mellitus

1.7.1 Structure of Insulin

Insulin is a small peptide consisting of fifty-one amino acids synthesized and stored within the pancreas, an organ situated behind the stomach. The protein itself consists of two chains, denoted as A and B, linked by disulfide bridges between cysteine residues (Dewitt et. al., 2003).

![Figure 1.3. Structure of insulin](image)

1.7.2 Synthesis of Insulin

Pre-pro-insulin is synthesized as a random coil on membrane associated ribosomes. After membrane transport the leader sequence is cleaved off by a protease and the resulting pro-insulin folds into a stable conformation. Disulfide bonds forms between cysteine side chains. The connecting sequence is cleaved off to form the mature and active insulin molecule (Bevan, 2001).

![Figure 1.4. Synthesis of insulin](image)
1.7.3 Action of insulin

Insulin is a hormone, produced by the pancreas, which is central to regulating carbohydrate and fat metabolism in the body. Insulin causes cells in the liver, muscle, and fat tissue to take up glucose from the blood, storing it as glycogen in the liver and muscle. As its level is a central metabolic control mechanism, its status is also used as a control signal to other body systems. In addition, it has several other anabolic effects throughout the body.

It is transported in the blood and regulates the activity of certain cells or organs in the body. When blood sugar levels rise following a meal, the pancreas is stimulated to release insulin into the bloodstream. In order for tissues to absorb glucose from the blood, they must first bind insulin. Glucose metabolism is necessary for cell growth and energy needs associated with cell function. When insulin binds to receptors on cell membranes, glucose transporter proteins are released from within the cell to the surface of the cell membrane. On the exterior surface of cells, glucose transporters can carry sugar from the blood into the tissue where it is metabolized. Without insulin, cells cannot absorb glucose.

Figure 1.5. Synthesis and release of insulin from pancreas
The major function of insulin is to counter the concerted action of a number of hyperglycemia-generating hormones and to maintain low blood glucose levels. In addition to its role in regulating glucose metabolism, insulin stimulates lipogenesis, diminishes lipolysis, and increases amino acid transport into cells. Insulin also modulates transcription, altering the cell content of numerous mRNAs. It stimulates growth, DNA synthesis and cell replication, effects that it holds in common with the insulin-like growth factors (IGFs) and relaxin. When control of insulin levels fails, diabetes mellitus will result. As a consequence, insulin is used medically to treat some forms of diabetes mellitus.

1.8 Diagnosis of Diabetes mellitus

Doctors use special tests in diagnosing diabetes and also in monitoring blood sugar level in known diabetics. The health care professional will take a history including information about the patient's symptoms, risk factors for diabetes, past medical problems, current medications, allergies to medications, family history of diabetes, or other medical problems such as high cholesterol or heart disease and personal habits and lifestyle. A number of laboratory tests are available to confirm the diagnosis of diabetes.

1.8.1 Fasting plasma glucose test (FDG)

Fasting Plasma Glucose Test is the most commonly performed diabetes diagnosis test primarily since it is very affordable and convenient. However, it may not be as sensitive and as accurate as the other kinds of diagnostic tests that are available. FPG test is most sensitive during the morning, where normal blood glucose levels can range from 99 mg/dl or below. Those with pre-diabetes can have plasma glucose concentrations from 100-125 mg/dl while those with actual diabetes can have plasma glucose beyond 125 mg/dl. Those who test positive should have a second test performed on a separate day for confirmation.

1.8.2 Oral glucose tolerance test (OGTT)

The Oral Glucose Tolerance Test is a much more reliable and sensitive test compared to the FPG diabetes diagnosis test. But the downside to this diabetes diagnosis test is that it is quite inconvenient to perform. OGTT will require patients to
undergo fasting for 8 hours before the actual test is done. The plasma glucose is tested several times during the procedure. Blood is taken before and after a person drinks a liquid that contains approximately 75g of glucose in water. The result of these two measurements will determine if the patient has diabetes or not. Patients who have blood glucose levels 140-199 mg/dl after 2 hours of taking in the liquid are diagnosed with pre-diabetes, while those with a glucose concentration of 200 mg/dl or more are diagnosed with diabetes. Results need to be confirmed through a second round of tests, done on a separate day.

1.8.3 Glycosylated hemoglobin or HbA1c

Glycosylated hemoglobin is a form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time. It is formed in a non-enzymatic glycation pathway by hemoglobin's exposure to plasma glucose. Normal levels of glucose produce a normal amount of glycosylated hemoglobin. As the average amount of plasma glucose increases, the fraction of glycosylated hemoglobin increases in a predictable way. This serves as a marker for average blood glucose levels over the previous months prior to the measurement. In diabetes mellitus, higher amounts of glycosylated hemoglobin, indicating poorer control of blood glucose levels, have been associated with cardiovascular disease, nephropathy, and retinopathy. Monitoring the HbA1c in type 1 diabetic patients may improve treatment.

The test involves having a small amount of blood drawn. An HbA1c test is the best measurement of blood sugar control in people known to have diabetes. An HbA1c result of 6.0% or less indicates good glucose control. A result of 8% or greater indicates that blood sugar levels are too high. The HbA1c test is the best test for diabetes follow-up care, than to diagnose diabetes. Still, an HbA1c result greater than 6.5% is highly suggestive of diabetes. Generally, a confirmatory test would be needed before diagnosing diabetes.

1.8.4 Diagnosing complications of diabetes

A person with diabetes should be checked regularly for early signs of diabetic complications. A health care professional can order some of these tests; for others, the

References

Antidiabetic activity of Zaleya decandra root extract in diabetes induced rats
patient should be referred to a specialist. The patient should have their eyes checked at least once a year by an eye specialist to screen for diabetic retinopathy, a leading cause of blindness. The patient's urine should be checked for protein (microalbumin) on a regular basis, at least one to two times per year. Protein in the urine is an early sign of diabetic nephropathy, a leading cause of kidney failure. Sensation in the legs should be checked regularly using a tuning fork or a monofilament device. Diabetic neuropathy is a leading cause of lower extremity ulcers in individuals with diabetes, which frequently lead to amputation of the feet or legs. The patient should be screened regularly for conditions that may contribute to heart disease, such as high blood pressure and high cholesterol.

1.9 Management of diabetes mellitus

Diabetes mellitus is a chronic disease which cannot be cured except in very specific situations. Management concentrates on keeping blood sugar levels as close to normal as possible, without causing hypoglycemia. This can usually be accomplished by living a healthy lifestyle, eating healthy, adapting a regular exercise routine and use of appropriate medications. The major components of the treatment of diabetes are:

1.9.1 Diet

Dietary measures such as nutritional counseling and motivating the patient’s compliance to the prescribed dietary plan are important in the management of diabetes mellitus. An estimate is made on the total number of calories needed per day based on ideal body weight. Protein and carbohydrate calories are supplemented with sufficient fat to bring caloric intake to the desired levels.

1.9.2 Oral hypoglycemic therapy

Oral hypoglycemic drugs are used in the treatment of type 2 diabetes. There are four major classes of hypoglycemic drugs.

1.9.2.1 Sulfonylureas

Sulfonylureas are the most widely used drugs for the treatment of type 2 diabetes and appear to function by stimulating insulin secretion. The net effect is increased responsiveness of β-cells to glucose resulting in more insulin being released at
all blood glucose concentrations. Sulfonylureas may also have extra-pancreatic effects, one of which is to increase tissue sensitivity to insulin. Sulfonylureas differ mainly in their potency and their duration of action. Glipizide, glyburide (glibenclamide), and glimepiride are commonly used sulfonylureas.

1.9.2.2 Biguanides

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery, including skeletal muscle. Metformin is the commonly used biguanide and it is effective only in the presence of insulin but, in contrast to sulfonylureas, it does not directly stimulate insulin secretion.

1.9.2.3 Thiazolidinediones

Thiazolidinediones also known as "glitazones," bind to peroxisome proliferator-activated receptor (PPARγ), a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. The final result is better use of glucose by the cells.

1.9.2.4 Alpha glucosidase inhibitors

The alpha glucosidase inhibitors include acarbose (Precose) & Miglitol (Glycet). They inhibit the upper gastrointestinal enzymes that convert dietary starch and other complex carbohydrates into simple sugars which can be absorbed. The result is to slow the absorption of glucose after meals.

1.9.3 Insulin treatment

Insulin is the oldest of the currently available medications and, thereby, the one with the most clinical experience. Although initially developed to treat insulin-deficient type 1 diabetes, it has long been used to treat insulin-resistant type 2 diabetes. It is the most effective drug to decrease glycemia. The total daily dose of insulin, the type of insulin preparation and the number and timing of injections required to achieve satisfactory control without undue risk of hypoglycemia, varies widely and is established by clinical trials.

Currently available therapies for diabetes include insulin and various oral antidiabetic agents such as sulfonylureas, biguanides and α-glucosidase inhibitors which...
are used as monotherapy or in combination, to achieve better glycemia regulation (Sy et al., 2005). Many of these oral antidiabetic agents have a number of serious adverse effects (Zhang and Moller, 2000). Thus, the management of diabetes without any side effects is still a challenge.

1.10 Medicinal plants for the treatment of Diabetes mellitus

Mankind has been continuously using the plants in one or the other way in the treatment of various ailments. In India, the sacred Vedas dating back between 3500 BC and 800 BC give much reference to medicinal plants. One of the earliest works in traditional herbal medicine is “Virikshayurveda”, compiled even before the beginning of Christian era, which formed the basis for medicinal studies in ancient India. The Rig Veda, dating between 3500 BC seems to be the earliest record available on medicinal plants (Ahmad et al., 2003).

Table 1.1: List of Medicinal plants reported to possess antidiabetic activity

<table>
<thead>
<tr>
<th>S.No</th>
<th>Plant</th>
<th>Active part/Active compound</th>
<th>Activity demonstrated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Allium cepa</td>
<td>Bulb, allyl propyl disulphide, S-Methyl sulphoxide</td>
<td>Diabetic rats</td>
</tr>
<tr>
<td>2</td>
<td>Allium sativum</td>
<td>Cloves, allicin</td>
<td>Diabetic rabbits</td>
</tr>
<tr>
<td>3</td>
<td>Aloe vera</td>
<td>Whole plant</td>
<td>Diabetic mice, NIDDM patients</td>
</tr>
<tr>
<td>4</td>
<td>Anemarrhena asphodeloides</td>
<td>Rhizome, anemarans</td>
<td>Diabetic mice</td>
</tr>
<tr>
<td>5</td>
<td>Azadirachta indica</td>
<td>Leaves, seeds, nimbidin</td>
<td>Dogs, diabetic rabbits</td>
</tr>
<tr>
<td>6</td>
<td>Bouganvillea spectabilis</td>
<td>Leaves, pinitol</td>
<td>Diabetic mice</td>
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<tr>
<td>7</td>
<td>Coccinia indica</td>
<td>Whole plant, alkaloid</td>
<td>Diabetic rabbits and patients</td>
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<tr>
<td>8</td>
<td>Cymopsis tetragonolobus</td>
<td>Seeds</td>
<td>NIDDM patients</td>
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<td>9</td>
<td>Eugenia jambolana</td>
<td>Fruit pulp seed</td>
<td>Diabetic rats</td>
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### References

<table>
<thead>
<tr>
<th>S.No</th>
<th>Plant</th>
<th>Active part/Active compound</th>
<th>Activity demonstrated</th>
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<tr>
<td>10</td>
<td><em>Ficus bengalensis</em></td>
<td>Bark, leucocyanidin, pellargonidin</td>
<td>Diabetic rats, rabbits and NIDDM patients</td>
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<td>11</td>
<td><em>Gymnema sylvestre</em></td>
<td>Leaves, GS4</td>
<td>Diabetic rats</td>
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<td>12</td>
<td><em>Hamiltonia suaveolens</em></td>
<td>Root</td>
<td>Rabbit</td>
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<td><em>Hedychium spicatum</em></td>
<td>Root</td>
<td>Rats</td>
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<tr>
<td>14</td>
<td><em>Indigophora tinctoria</em></td>
<td>Whole plant including roots</td>
<td>Rats</td>
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<tr>
<td>15</td>
<td><em>Michelia champaca</em></td>
<td>Stem bark</td>
<td>Rats</td>
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<td><em>Momordica charantia</em></td>
<td>Fruit, charantin, kakara Ia,IIia,IIlb</td>
<td>Diabetic rats, rabbits, diabetic patients</td>
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<td><em>Murraya koenigi</em></td>
<td>Leaves</td>
<td>Normal and diabetic dog</td>
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<td>18</td>
<td><em>Musa paradisiaca</em></td>
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<td><em>Panax bipinnatifidum</em></td>
<td>Root</td>
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<td><em>Phyllanthus amarus</em></td>
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<td><em>Potterium ancisoide</em></td>
<td>Tormentic acid</td>
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<td><em>Pterocarpus marsupium</em></td>
<td>Wood, (-)epicatechin marsupin, pterostilbene</td>
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<td><em>Saccharum officinarum</em></td>
<td>Stem, saccharans A,B,C,D,E and F</td>
<td>Diabetic mice</td>
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<tr>
<td>24</td>
<td><em>Salacia prenoids</em></td>
<td>Leaves and stem</td>
<td>Diabetic rats</td>
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<td>25</td>
<td><em>Trichosanthes dioica</em></td>
<td>Seeds</td>
<td>Rabbits</td>
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<tr>
<td>26</td>
<td><em>Trigonells foenum</em></td>
<td>Seeds, trigonelline</td>
<td>Rabbits</td>
</tr>
<tr>
<td>27</td>
<td><em>Zizyphus zujuba</em></td>
<td>Seeds</td>
<td>Rabbits, rats</td>
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</table>

Medicinal plants are frequently used by traditional healers to treat a variety of ailments and symptoms including fever, cold, headache, diabetes and cancer. Plants have been the major source of drugs in Indian system of medicine and other ancient systems in the world. The World Health Organization expert committee on diabetes has...
listed as one of its recommendations that traditional methods of treatment of diabetes should be further investigated. There are many antidiabetic plants which might provide useful sources for the development of drugs which can be used in the treatment of diabetes mellitus. A list commonly used plants with antidiabetic property is given table 1.1.

Plants have been used in treatment of diabetes mellitus all over the world for centuries. Approximately 80% of the world population is almost dependent on traditional medicines (Srinivasan, 2005). The ethnobotanical details and the antidiabetic potential of several plants are known at present, but there is very little information about plants which possess both hypoglycemic and antioxidant properties, which would be very useful as an antidiabetic agent.

1.1 Selected plant and its medicinal properties

Based on the literature survey and traditional values the root of *Zaleya decandra* was selected for screening of antidiabetic potential and antioxidant property. The selected medicinal plant was collected from the Pollachi, Tamil nadu.

1.1.1 *Zaleya decandra* (L.) Burm. f.

Botanical name: *Zaleya decandra*

Synonyms: *Trianthema decandra* L. (Basionym)

Local name: Vellai Sharanai

Classification:

Kingdom: Plantae

Phylum: Tracheophyta

Class: Magnoliopsida

Order: Caryophyllales

Family: Aizoaceae

Sub-family: Sesuvioideae

Genus: Zaleya

Species: *decandra*
Common names:

- Tamil : Vellai Sharanai
- Sanskrit : Punarnavi
- Hindi : Gadabani
- Telugu : Galijeru
- Kannada : Gaijasoppu

Distribution:

It is a prostrate herb distributed in the tropical and sub-tropical regions of the world, and also found abundantly in India. Within India, it is found in the Southern parts of India, Rajasthan, Uttar Pradesh and Haryana.

**Figure 1.6 Zaleya decandra**

Morphological description

*Zaleya decandra* is a prostrate weed belonging to the family Aizoaceae. It is a somewhat succulent, subglabrous, annual herb. Stem spreading, procumbent or prostrate the development of auxiliary buds, subtended by the small leaf of nodal pair. Leaves 10-40 × 5-35 mm in size, opposite, the smaller leaves are narrow, oblong tapering to the base, rounded to apiculate at the apex, long petiolated, flowers small, few-flowered racemes or clusters, inner surface pinkish, operculum retaining 2 seeds, the other two
remaining in lower part of capsule; seed orbicular-reniform, dorsally somewhat ribbed, sides faintly tuberculate, dull black, about 1.5 mm diameter.

**Uses**

The root of this plant is used in the Indian systems of medicine for the treatment of hepatitis, asthma and orchitis and also the decoction of the root’s bark is credited with properties of aperients (Warrier *et al*., 1994). The juice of the leaves is dropped into the nostrils to relieve partial headache (Nadkarni, 1996). Its extract exhibited liver protective effect and also possessed antioxidant activities (Singaravel *et al*., 2009; Balamurugan and Muthusamy, 2008). It is also used in the treatment of various ailments such as inflammation, fever and toothache (Kirtikar and Basu, 1988; Reddy *et al*., 1989).

The present study has been undertaken to identify the antioxidant and antidiabetic effect of *Zaleya decandra* in diabetic rats. The ethanolic root extract was used for isolation of compounds and its characterization.
Diabetes mellitus is a metabolic disease as old as mankind and its incidence is considered to be high all over the world. In spite of the introduction of hypoglycemic agents, diabetes and related complications continue to be a major medical problem. Since time immemorial, diabetes has been treated orally in folk medicine with a variety of plant extracts. In India a number of plants are mentioned in ancient literature for the cure of diabetic conditions and some of them have been experimentally evaluated and the active principles isolated.

The aim of the present study was to explore the antioxidant and antidiabetic potential of the ethanolic root extract of *Zaleya decandra*. To explore this study the following objective were taken up.

**CHAPTER I: Study on the Phytochemical and Antioxidant Properties of *Zaleya decandra* Root Extract**

**Phytochemical screening of extracts**

**Quantification of bioactive compounds**
- Estimation of total phenol content
- Estimation of total flavonoid content
- Estimation of tannin content
- Estimation of total carotenoids
- Estimation of vitamin C
- Estimation of vitamin E

**In vitro radical scavenging assays**
- Reducing power capacity
- DPPH radical scavenging activity
- ABTS radical scavenging activity
- Hydroxyl radical scavenging activity
- Superoxide radical scavenging activity
- Nitric oxide radical scavenging activity
- Inhibition of *in vitro* lipid peroxidation

**HPTLC analysis**
CHAPTER II: Study on the Antidiabetic potential of *Zaleya decandra* Root Extract

- Oral glucose tolerance test
- Changes in body weight and organ weight
- Effect on insulin and C-peptide
- Effect on basic biochemical parameters
- Effect on tissue antioxidants
- Effect on membrane bound enzymes
- Effect on glycoproteins
- Effect on carbohydrate metabolizing enzymes
- Histopathological alteration

CHAPTER III: Isolation and identification of active constituent in the ethanolic root extract of *Zaleya decandra*

- To analyse the crude extract by GC-MS.
- To isolate the compounds by Column chromatography
- To analyse the functional groups of the isolated compound by Fourier transform infrared (FTIR) spectroscopy
- To identify the structure of the compound by Nuclear Magnetic Resonance (NMR) spectroscopy
- To determine the molecular weight of the compound by Mass spectroscopy
- To elucidate the structure of the isolated compound
- Effect of the isolated compound on α - glucosidase activity.