# REVIEW OF LITERATURE

# 2.0 REVIEW OF LITERATURE

The review of literature pertaining to the present study, 'Antidiabetic effect of *Helicteres isora* on streptozotocin-induced diabetes mellitus in rats', is discussed under the following headings:

2.1 Introduction

2.2 Diabetes mellitus

2.3 Diabetic complications

2.4 Oxidative stress and associated diseases

2.5 Allopathic drugs and their adverse effect

2.6 Herbal medicine for treatment of diabetes

## 2.1 Introduction

Diabetes mellitus is found to have affected over 140 million people worldwide and is becoming more prevalent in India. There were more than 30 million people with diabetes mellitus in India in 1999 and by the year 2025, India is predicted to have 80 million numbers of people with diabetes mellitus in the world. The disease has become a real problem of public health in developing countries where its prevalence increases steadily (WHO, 2008).

Diabetes mellitus is a major disease characterised by derangement in carbohydrate, fat and protein metabolism. The hallmark of diabetes is chronic hyperglycemia and it contributes greatly to the vascular complications of diabetes (Wohlrab *et al.*, 2007).

A substantial proportion of the predominant type of diabetes (type 2), can be prevented through the promotion of physical activity, healthy eating and the reduction of obesity. The quality of life of people with diabetes can

be largely preserved, and their risk of long-term complications reduced, through the provision of effective health care and education (IDI, 2008).

**2.2 Diabetes mellitus**

Diabetes mellitus is defined as a state in which homeostasis of carbohydrate and lipid metabolism is improperly regulated by insulin. This results primarily in elevated fasting and postprandial blood glucose levels. If this imbalanced homeostasis dose not returns to normalcy and continues for a protracted period of time, it leads to hyperglycemia, which in due course turns into a syndrome called diabetes mellitus (Tiwari and Rao, 2002). The long term effects of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation and features of autonomic dysfunction, including sexual dysfunction. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease (Varughese and Scarpello, 2006).

There are two main categories of this disease - type 1 (insulin dependent diabetes mellitus, IDDM) and type 2 (non insulin dependent diabetes mellitus, NIDDM). Type 1 diabetes is typically a disease of juvenile onset and is associated with insulin deficiency, usually resulting from autoimmune destruction of pancreatic beta cells. Type 1 diabetic patients are prone to develop ketoacidosis and require insulin therapy to control their hyperglycemia. Type 2 diabetes is typically a disease of adult onset (although it is becoming increasingly recognized in children) and is caused by a combination of defective insulin secretion with reduced insulin sensitivity of the tissues. An increase in body fat is generally associated with an increase in risk of metabolic diseases such as type 2 diabetes mellitus,

hypertension and dyslipidemia (WHO, 2006). This impaired glucose tolerance is usually associated with obesity and physical inactivity. Hyperglycemia in type 2 diabetic patients can be often managed using a combination of dietary modification and oral hypoglycemic drugs. It has become increasingly recognized that there are some diabetic patients who develop diabetes as adults (usually older than 30 years of age), who are initially diagnosed as having type 2 diabetes but who are not overweight and who also show evidence of circulating autoantibodies. These patients are often managed initially using oral hypoglycemic drugs, but they usually progress to insulin therapy. This form of diabetes has now been classified as Latent Autoimmune Diabetes of Adults (LADA), sometimes referred to as type 1.5 diabetes. Juvenile onset type 1 diabetes appears to result from an overwhelming autoimmune response against pancreatic beta cells that rapidly leads to their total destruction. In contrast, LADA seems to result from a more slowly progressive autoimmune process and it takes several years before the beta cell mass has been reduced to an extent whereby normoglycemia cannot be maintained and clinical signs of diabetes become apparent (Catchpole *et al.*, 2008).

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with the onset or first recognition during pregnancy. The definition applies whether insulin or only diet modification is used for treatment and whether or not the condition persists after pregnancy. It does not exclude the possibility that unrecognized glucose intolerance may have antedated or begun concomitantly with pregnancy. Approximately 7 per cent of all pregnancies are complicated by GDM, resulting in more than 200,000 cases annually. The prevalence may range from 1 to 14 per cent of all pregnancies, depending on the population studies and the diagnostic tests

employed. Offsprings of women with GDM are at an increased risk of obesity, glucose intolerance and diabetes in late adolescence and young childhood. Risk assessment for GDM should be undertaken at the first prenatal visit. Women with clinical characteristics consistent with high risk of GDM (marked obesity, personal history of diabetes) should undergo glucose testing. Women with GDM represent a high risk group for cardiovascular disease that can be identified years before the development of adverse events with the incidence of type 2 diabetes increasing at epidemic proportions (Buchanan and Xiang, 2005).

**2.3 Diabetic complications**

Chronic hyperglycemia due to uncontrolled diabetes causes a number of secondary complications like cardiovascular, renal, neurological and ocular disorders. Though various mechanisms have been proposed, several studies suggest that oxidative stress is a major determinant in the pathogenesis of various vascular and non-vascular diabetic complications (Brownlee, 2001).

Type 1 diabetes mellitus (insulin-dependent diabetes mellitus) is associated with a markedly increased risk of vascular disease. The Diabetes Complications and Control Trial (DCCT) Research Group identified hyperglycemia as a risk factor for progression of microangiopathy. Still there is no consensus regarding the causal connection between hyperglycemia and diabetic angiopathy (Vessby *et al.*, 2002).

Patients with type 2 diabetes mellitus have a higher risk of developing cardiovascular, cerebrovascular and renal disease than the general population. Although relative hyperglycemia accounts for part of the increased risk, the presence of other factors increases it yet further. The UK's National Service Framework (NSF) for diabetes suggests that upto

70 per cent of patients with type 2 diabetes have raised blood pressure and that more than 70 per cent of patients with type 2 diabetes have raised cholesterol. In type 2 diabetes mellitus, excessive hepatic glucose output contributes to the fasting hyperglycemia. Increased gluconeogenesis is the predominant mechanism responsible for this increased glucose output, while gluconeogenesis has not been shown to be increased in patients with type 2 diabetes (Lowey *et al.*, 2007).

Diabetes increases the risk of ischaemic stroke more than hemorrhagic strokes, resulting in a greater ischaemic to hemorrhagic stroke ratio in the people with diabetes compared with the general population. The high stroke risk in diabetes is due to the complex interplay between the various hemodynamic and metabolic components of the diabetes syndrome. Other than the many recognized risk factors associated with acute stroke (e.g. hypertension, dyslipidemia and atrial fibrillation), specific risk factors attributable to diabetes have also been reported. Components of the metabolic syndrome such as insulin resistance, central obesity, impaired glucose tolerance and hyperinsulinemia, both individually and collectively, are associated with an excess risk of stroke disease, while decreased high-density lipoprotein (HDL) cholesterol is an important predictor of stroke risk in the general population. Data from the UK Prospective study support the likelihood of a shared pathogenesis of atherosclerosis and retinopathy (van Hecke *et al.,* 2006) and diabetic retinopathy is associated with an increased risk of ischaemic stroke and lacunar infarcts (Idris *et al.*, 2006).

The strong relationship between diabetes mellitus and hypertension with implications for cardiovascular disease (CVD) risk was also well recognized (Jonas *et al.*, 2003). Interestingly, the close association between diabetes mellitus and hypertension had also been demonstrated

(Hippisley-Cox and Pringle, 2004; Czupryniak *et al.*, 2006) and the huge benefits of statin drug therapy in addition to correction of dyslipidemia in this select group of patients could not be emphasised any further. Diabetes mellitus has also been shown to be a strong and independent risk factor for the development of dysrhythmias such as atrial fibrillation in addition to CVD (Costa *et al.*, 2006), such as ventricular tachycardia as well as ventricular dysrhythmias (Chen-Scarabelli and Scarabelli, 2006).

There is a genetic predisposition to autoimmune destruction of beta cell and it is also related to environmental factors that are still poorly defined. Although there are patients with this type of diabetes, the presence of obesity is not incompatible with diagnosis. These patients may also have other autoimmune disorders such as Graves's disease, Hashimoto's thyroiditis and Addison's disease (Varughese *et al.*, 2006).

Several forms of the diabetes state may associate with monogenic defects in β-cell function, frequently characterized by onset of mild hyperglycemia at an early age (generally before age 25 years). They are usually inherited in an autosomal dominant pattern. Patients with these forms of diabetes, formerly referred to as maturity onset diabetes of the young (MODY), have impaired insulin secretion with minimal or no defect in insulin action (Bonnycastle *et al.*, 2006).

The two most common life threatening complications of diabetes mellitus include diabetic ketoacidosis (DKA) and hyperglycemic hyperosmolar syndrome (HHS). Although there are important differences in their pathogenesis, the basic underlying mechanism for both disorders is a reduction in the net effective concentration of circulating insulin coupled with a concomitant elevation of counter regulatory hormones namely glucagon, catecholamines, cortisol and growth hormone. These

hyperglycemic emergencies continue to be important causes of morbidity and mortality among patients with diabetes. DKA was reported to be responsible for more than 100,000 hospital admissions per year in the United States and accounted for 4-9 per cent of all hospital discharge summaries among patients with diabetes. Most patients with DKA have type 1 diabetes; however, patients with type 2 diabetes are also at risk during the catabolic stress of acute illness (Umpierrez and Kitabchi, 2003). Contrary to popular belief, DKA is more common in adult than in children. DKA is the initial manifestation of diabetes in 20 per cent of adult patients and 30-40 per cent of children with type 1 diabetes. In patients with establishing diabetes, precipitating factors for DKA include infections, intercurrent illness, psychological stress and poor compliance with therapy. Infection is the most common precipitating factor for DKA, occurring in 30-50 per cent of cases. Urinary tract infection and pneumonia account for the majority of infections. Other acute conditions that may precipitate DKA include cerebrovascular accident, alcohol/drug abuse, pancreatitis, pulmonary embolism, myocardial infarction and trauma. Drugs that affect carbohydrate metabolism, such as corticosteroids, thiazides, sympathomimetic agent and pentamidine, may also precipitate the development of DKA. Cerebral oedema is a rare serious complication of DKA. It was reported to occur in ~1 per cent of episodes of children with DKA (Umpierrez *et al.*, 2002).

Insulin is formed from the precursor molecule, preproinsulin, which is then cleaved to proinsulin. Further maturation results in the conversion of proinsulin and a smaller peptide called C-peptide. Insulin promotes glycogen synthesis (glycogenesis) in the liver and inhibits its breakdown (glycogenolysis). It promotes protein, cholesterol and triglyceride synthesis and stimulates formation of very low density lipoprotein cholesterol. It also

inhibits hepatic gluconeogenesis, stimulates glycolysis and inhibits ketogenesis. Liver is the primary target organ for glucagon action, where it promotes glycogenolysis, gluconeogenesis and ketogenesis. Hyperglucagonemia has been shown to augment increased rates of hepatic glucose output, probably through enhanced gluconeogenesis (Murray *et al.*, 2006)

Risk factors for worsening albuminuria are HbA1c, baseline albuminuria level, triglyceride and body mass index (BMI). Among normo, macro and microalbuminuric patients, coronary heart disease event rates were 7, 12, and 22 per cent respectively. There was a 56 per cent incidence of new retinopathy over 7.5 years for those without retinopathy initially; risk factors were the duration of diabetes, HbA1c, albuminuria, triglyceride, fibrinogen, von Willenbrand factor (vWF) and γ-glutamyl transpeptidase (GGTP). Neuropathy, as assessed by symptoms, abnormal deep tendon reflexes, autonomic function, or vibration perception (measured with a bioesthesiometer) developed over 7.5 years in 24.6 per cent of the patients, with independent risk factors of age, duration, HbA1c, triglyceride and BMI. For all complications, there appeared to be a long-linear relationship to glucose without evidence of glycemic threshold. Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20-74 years. During the first two decades of the disease, nearly all patients with type 1 diabetes and >60 per cent of patients with type 2 diabetes were found to have retinopathy (Fong *et al.*, 2004).

Diabetic retinopathy is a highly specific vascular complication of both type 1 and type 2 diabetes. The prevalence of retinopathy is strongly related to the duration of diabetes. After 20 years of diabetes, nearly all patients with type 1 diabetes and 60 per cent of patients with type 2 diabetes were

found to have some degree of retinopathy. Diabetic retinopathy poses a serious threat to vision. In younger-onset group, 86 per cent of blindness was attributable to diabetic retinopathy. In the older-onset group, where other eye diseases were common, one third of the cases of legal blindness were due to diabetic retinopathy. Overall, diabetic retinopathy is estimated to be the most frequent cause of new cases of blindness among adults aged 20-74 years. Vision threatening retinopathy virtually never seemed to appear in type 1 patient in the first 3-5 years of diabetes or before puberty. Over the subsequent 2 decades, nearly all type 1 patients were found to develop retinopathy. Upto 21 per cent of patients with type 2 diabetes have been found to have retinopathy at the time of first diagnosis of diabetes, and most develop some degree of retinopathy over subsequent decades. In general, the progression of retinopathy is orderly, advancing from mild non-proliferative abnormalities, characterized by increased vascular permeability, to moderate and severe non - proliferative diabetic retinopathy, characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. Pregnancy, puberty and cataract surgery are found to accelerate these changes. Vision loss due to diabetic retinopathy results from several mechanisms. First, central vision may be impaired by macular edema or capillary non-perfusion (American Diabetes Association, 2002).

Diabetic nephropathy also known as Kimmelstiel-Wilson syndrome and intercapillary glomerulonephritis, is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is characterized by nephrotic syndrome and nodular glomerulosclerosis. It is due to longstanding diabetes mellitus and is a prime cause for dialysis in many western countries. The syndrome can be seen in patients with chronic diabetes (15 years or more after onset) and therefore the patients are usually

of older age (between 50 and 70 years old). The disease is progressive and may cause death two or three years after the initial lesions and is more frequent in men. Diabetic nephropathy is the most common cause of chronic kidney failure and end-stage kidney disease in the United States. People with both type 1 and type 2 diabetes are at risk. The risk is higher if blood glucose levels are poorly controlled. Further, once nephropathy develops, the greatest rate of progression is seen in patients with poor control of their blood pressure. Also people with high cholesterol level in their blood have much more risk than others. Kidney failure provoked by glomerulosclerosis leads to fluid filtration deficits and other disorders of kidney function. There is an increase in blood pressure (hypertension) and of fluid retention in the body (oedema). Other complications may be arteriosclerosis of the renal artery and proteinuria (nephrotic syndrome). Throughout its early course, diabetic nephropathy has no symptoms. They develop in late stages and may be a result of excretion of high amounts of protein in the urine or due to renal failure (Wahren *et al.*, 2007).

Diabetic neuropathies are neuropathic disorders that are associated with diabetes mellitus. It is assessed by symptoms such as abnormal deep tendon reflexes, autonomic function or vibration perception (Zachary and Bloomgarden, 2002). With important risk factors of age, duration, HbA1c, triglycerides and body mass index in some patients, focal neurological signs (hemiparesis, hemianopsia) and seizures (partial motor seizures more common than generalised) may be the dominant clinical features. These conditions are thought to result from diabetic microvascular injury involving small blood vessels that supply nerves (vasa nervorum). Relatively common conditions which may be associated with diabetic neuropathy include third nerve palsy, mononeuropathy, mononeuropathy

multiplex, diabetic amyotrophy, a painful polyneuropathy, autonomic neuropathy and thoracoabdominal neuropathy (Wong *et al.*, 2007).

Diabetes mellitus is associated with increased cardiovascular morbidity and mortality. Epidemiological studies have shown that the risk of coronary artery disease increased two to six-fold in patients with type 2 diabetes compared with those without the disease and thus it is considered to be the leading cause of morbidity and mortality (Peter *et al.*, 2008). Cluster of hyperinsulinemia, hypertriglyceridemia, low HDL cholesterol and obesity are considered to be the best predictors of cardiovascular disease. The increasing coronary events are greater for more severe outcomes such as myocardial infarction and sudden death (Rani *et al.*, 2005).

The dyslipidemia seen in type 2 diabetes mellitus is a cluster of elevated triglyceride level, a high LDL cholesterol level and low HDL cholesterol. Thus the highly atherogenic dyslipidemia is found to be associated with insulin resistance (Cardium Study, 2007).

Accumulation of visceral fat is associated with insulin resistance and the development of atherosclerosis. Lipid deposits in the subendothelial extracellular matrix lead to the recruitment of blood monocytes. These cells are the precursors of lipid filled foam cells that are the hallmarks of atherosclerosis (Mohan, 2007). Many of the established risk factors for atherosclerosis are more prevalent in the diabetic population including hypertension, visceral obesity, low plasma HDL and increased plasma LDL (Goldberg, 2004).

Periodontal (gum) disease is more common in people with diabetes. Among young adults, those with diabetes have about twice the risk of those without diabetes. Almost one-third of people with diabetes were reported to

have severe periodontal diseases with loss of attachment of the gums to the teeth measuring 5 millimeters or more (Silva *et al.*, 2007).

**2.4 Oxidative stress and associated diseases**

Free radicals may play an important role in the causation and complication of diabetes mellitus. During diabetes mellitus, persistent hyperglycemia causes an increased production of free radicals via auto-oxidation of glucose and non-enzymic protein glycation, which may lead to disruption of cellular functions and oxidative damage to membranes (Shi *et al.*, 2007).

Oxidant or free radicals are atoms or molecules capable of independent existence that contain one or more unpaired electrons, making these species highly reactive. Exogenous source of free radicals includes tobacco smoke, ionizing radiations, toxic gases like ozone, certain pollutants, organic solvents and pesticides. While the main sources of endogenous oxidants are inflammatory cells, the generation of free radicals can bring about thousands of reactions and thus cause extensive tissue damage. Lipids, proteins and DNA are susceptible to attack by free radicals. These agents may cause direct tissue oxidation, release of endogenous oxidants and inactivation of antioxidant defence mechanisms (Raghunath *et al.*, 2006).

Numerous epidemiological studies have shown that free radicals are the leading cause of oxidative stress related diseases like cancer, cardiovascular diseases and neurological degenerative disorders. Free radicals and other reactive oxygen species cause the oxidation of biomolecules which leads to cell injury and death. The increased oxidative stress and decrease in antioxidants may be related to the causation of diabetes mellitus (Iniaghe *et al.*, 2008).

Several studies have proposed the mechanism for the role of free radicals in the pathogenesis of various diseases including diabetes mellitus. Oxygen free radicals are formed disproportionately in diabetes by glucose oxidation, non-enzymatic glycation of proteins and the subsequent oxidative degradation of glycated proteins. Recent reports indicate that diabetic complications are associated with overproduction of free radicals and accumulation of lipid peroxidation by-products. Enhanced oxidative stress has been well documented in both the experimental and the human diabetes mellitus (Maritim *et al.*, 2003).

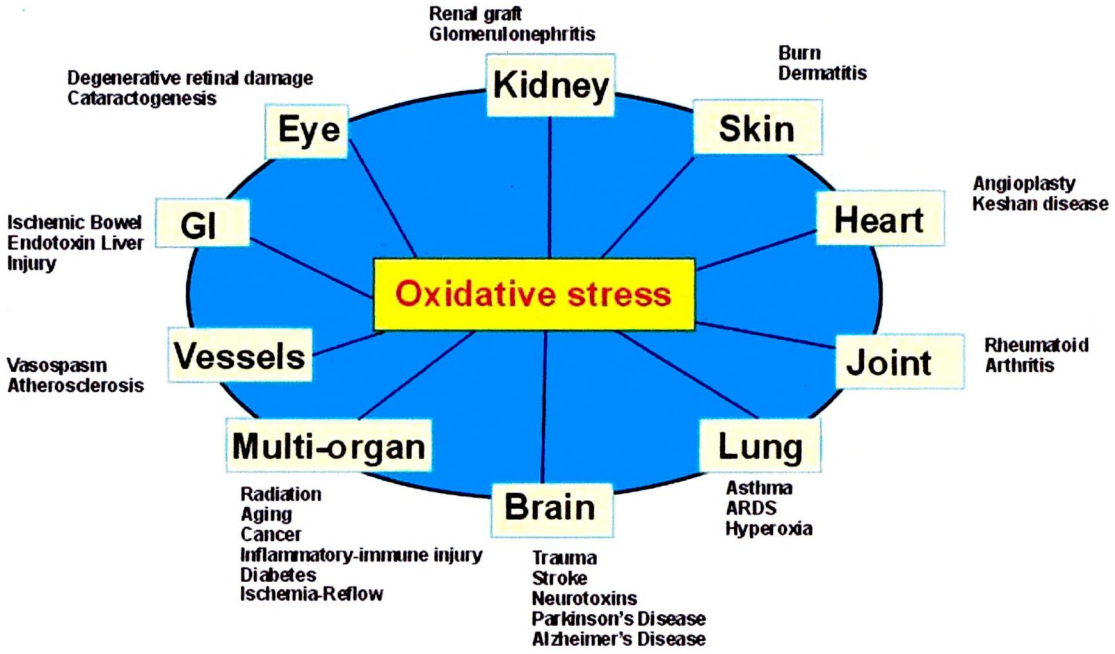
High levels and/or inadequate removal of Reactive Oxygen Species (ROS) may cause severe metabolic imbalance and oxidative damage to biological macromolecules. Oxidative stress *in vivo* is of importance, since it can not only damage receptors, enzymes, signal transduction pathways and transport proteins but also give rise to secondary damage to other biomolecules. The oxidatively modified proteins may be recognized as foreign by the immune system, triggering antibody formation. It may be both a cause and an effect of tissue damage, both a primary and secondary source of diabetic pathology. Oxidative stress is dependent on the balance between oxygen free radical production and antioxidant capacity of the cell in view of the degree of this imbalance; it may induce reversible or irreversible myocardial damage (Halliwell and Gutteridge, 1999).

Oxidative stress is thought to contribute to the development of a wide range of diseases including Alzheimer's disease, Parkinson's disease, the pathologies caused by diabetes, rheumatoid arthritis and neurodegeneration in motor neuron diseases. In many of these cases, it is unclear whether oxidants trigger the disease, or they are produced as a consequence of the disease and cause the disease symptoms; as a plausible alternative. A

neurodegenerative disease might result from defective axonal transport of mitochondria, which carry out oxidation reactions. One case in which this link is particularly well-understood is the role of oxidative stress in cardiovascular disease. Here, low density lipoprotein oxidation appears to trigger the process of atherogenesis, which results in atherosclerosis and finally cardiovascular disease (Zafrilla *et al.,* 2006). The diseases associated with oxidative stress are given in Figure 1.

**FIGURE 1**

**OXIDATIVE STRESS AND ASSOCIATED DISEASES**




(www.cstl.nist.gov/div831/DNATechologies/imgs/DNA_Damage_Repair.jpg)

Lipid peroxidation is the oxidative degradation of polyunsaturated fatty acids and involves formation of lipid radicals leading to membrane

damage. Free radicals induce lipid peroxidation in polyunsaturated lipid rich areas like brain and liver. Initiation of lipid peroxidation by ferrous sulphate takes place through hydroxyl radical by Fenton's reaction. The inhibition could be caused by the absence of ferryl-perferryl complex or by scavenging the hydroxyl radical or the superoxide radicals or by changing the $Fe^{3+}/Fe^{2+}$ or by reducing the rate of conversion of ferrous to ferric or by chelating the iron itself (Baskar *et al.*, 2007).

Antioxidants are agents that are capable of effectively neutralizing deleterious effects of free radicals. Natural enzymic antioxidants that are present in the body are superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) and glutathione -S- transferase (GST) and non-enzymic antioxidants are vitamin A, vitamin C (ascorbic acid), vitamin E (α-tocopherol) and reduced glutathione (Lavhale and Mishra, 2007).

Antioxidants play an important role in inhibiting and scavenging radicals, thus providing protection to humans against infection and degenerative diseases such as atherosclerosis, stroke, diabetes, Alzheimer's disease and cancer (Khalaf *et al.*, 2008). Antioxidants are compounds that help to inhibit many oxidation reactions caused by free radicals such as singlet oxygen, superoxide, peroxyl radicals, hydroxyl radicals and peroxy nitrate and thereby preventing or delaying damages to the cells and the tissues. There is some synthetic antioxidant compounds, such as butylated hydroxy toluene (BHT) and butylated hydroxyanisole (BHA), commonly used in processed foods. However, it has been suggested that these compounds have side effects. Medicinal plants possessing natural antioxidant polyphenolics such as anthroquinones, flavonoids, aromatic acids and tannins have been shown to have scavenging effect on lipid

peroxidation preventing effects on ROS (Odukaya *et al.*, 2007). In addition, it has been reported that there is an inverse relationship between dietary intake of antioxidant rich foods and the incidence of human diseases. Therefore, research for the identification of the natural antioxidants source is important (Karthikumar *et al.*, 2007).

As a defence system, plants in turn enhance the activation of enzymic and non-enzymic antioxidants to combat with the oxidative stress injury under extreme temperatures. The steady state concentrations of AOS (Active Oxygen Species) are kept low by the operation of the antioxidant defences which comprise enzymes such as superoxide dismutase, catalase, ascorbate peroxidase and glutathione reductase together with low molecular weight antioxidants such as α-tocopherol, ascorbate, glutathione and carotenoids (Karthikeyan and Rani, 2003).

**Enzymic antioxidants**

Three groups of enzymes namely superoxide dismutase, catalase and glutathione reductase play a significant role in protecting cells from oxidant stress (Ahmed *et al.*, 2006).

Superoxide anion ($O^{2-}$) is the most abundantly produced free radicals. The biologically generated superoxide anion dismutases into molecular oxygen and hydrogen peroxide in the presence of protons and this reaction are highly favored in the presence of superoxide dismutase. Catalase is a hemeprotein, localized in the peroxisomes or the microperoxisomes. This enzyme catalyses the decomposition of $H_2O_2$ to water, thus protecting the cell from oxidative damage by $H_2O_2$ and $OH^-$ It has one of the highest turnover rates of all enzymes; one molecule of catalase can convert millions

of molecules of hydrogen peroxide to water and oxygen per second (Venukumar and Latha, 2002).

Glutathione reductase also plays a key role in the antioxidant defence processes, by reducing oxidized glutathione reaction, which consumes NADPH, thus allowing a high GSH/GSSH ratio to be maintained. Glutathione -S- transferase and glutathione peroxidase are the most abundant and ubiquitous detoxification enzyme families in the plant system. These enzymes play a pivotal role in inhibiting the cellular damage produced by a wide variety of stresses (Kretchmer *et al.,* 2004).

**Non - enzymic antioxidants**

Non - enzymic antioxidants such as reduced glutathione, vitamin C, vitamin E, flavonoids and carotenoids play an excellent role in protecting the cells from oxidative damage (Ramprasath *et al.*, 2006).

Glutathione is the most abundant low molecular weight thiol substance with sulfhydryl (-SH) group. The sulfhydryl (-SH) group, which gives the molecule its electron donating character, comes from the cysteine (generated from methionine) residue. It is a significant component of collective antioxidant defenses and a highly potent antioxidant and antitoxin in its own right. The –SH group of GSH is important for many facets of cell function. Observations from hereditary GSH synthesis deficiencies confirm that GSH is essential both to the functionality and the structural integrity of the tissues and the organ systems. The glutathione status of a cell (that is excess of reduced over oxidized glutathione) will perhaps turn out to be the most accurate single indicator of the health of the cell (Agarwal, 2007).

Ascorbic acid or vitamin C is found in a large variety of foods but particularly in fruits and vegetables. It is actively taken up in high concentration by secretory cells of the islets of Langerhans where it is

believed to play a role in antioxidant defence (Wahab *et al.*, 2002). In diabetes mellitus, vitamin C metabolism is abnormal and the subjects have been shown to have low vitamin C. It is a potent inhibitor of protein glycation, which has pronounced effects on the structure and function of proteins that contribute to the pathogenesis and long-term complications of diabetes. It reduces blood pressure and arterial stiffness in type 2 diabetes and thus it may therefore be a useful and inexpensive adjunctive (Mullen *et al.*, 2002).

Vitamin E is the most important antioxidant and an earlier line of defence in lipid peroxidation. It is a scavenger of peroxyl radicals. The major function of vitamin E is its role as a physiological membrane bound antioxidant, protecting cell membrane lipids from oxidative damage initiated by reactive oxygen metabolites. Epidemiological evidence suggests that low vitamin E intake is a risk factor for the development of type 2 diabetes (Metin *et al.*, 2002).

**2.5 Allopathic drugs and their adverse effect**

Currently available therapy for diabetes includes insulin and various oral antidiabetic agents such as sulfonylurea, metformin, α-glucosidase inhibitors and thiazolidinediones. These drugs are used as monotherapy or in combination to achieve better glycemic control. Each of the above oral agents suffers from a number of serious adverse effects (Zhang and Moller, 2000).

Sulfonylurea remains the most popular group of medications today. A drawback of sulfonylurea is that, on average, they lose effectiveness for 44 per cent of patients within six years of the beginning of their use. Hypoglycemia and weight gain are the two most frequent side effects of these drugs (Proks *et al.*, 2002).

Metformin can be used as a first line of therapy. It is useful for patients who are obese because it does not cause the weight gain seen with sulfonylureas; it may even bring about some degree of weight loss. Metformin is also as capable as the sulfonylureas in reducing HbA1c. An additional benefit of metformin is its positive effect upon lipid metabolism - it reduces blood triglyceride and LDL cholesterol levels by about 10 per cent and also lowers fatty acids. Side effects can be a problem with metformin. Upto 30 per cent of patients develop gastrointestinal complaints, though these may be mild and temporary, especially if dosages are brought up slowly. The largest concern with metformin is the potential to produce a build up of lactic acid. Contraindications for this drug include evidence of kidney disease, significant liver disease, chronic alcoholism or congestive heart failure (Ketz, 2001).

The thiazolidinediones (TZDs) enhance insulin action in muscle, fat and other tissues and are known as insulin sensitizers. TZDs are effective in reducing HbA1c. They are also effective in combination with either sulfonylureas or metformin. The major side effect, seen with troglitazone, the first TZD to be approved by the FDA, is liver damage. The effects observed range from an elevation in liver enzymes, which is reversible, to liver failure, which has caused death in a small number of patients (Yale *et al.*, 2001).

Glucosidase inhibitors are most useful in combination with other drugs. Gastrointestinal side effects are common in this, affecting upto 30 per cent of patients. Bloating, flatulence, diarrhoea, abdominal discomfort and pain are the major complaints. As a consequence, there continues to be a high demand for new oral antidiabetic drugs (Kameswararao *et al.*, 2001).

## 2.6 Herbal medicine for treatment of diabetes

Medicinal plants, which form the backbone of traditional medicine, have in the last few decades been the subjects for very intense pharmacological studies; this has been brought about by the acknowledgement of the value of medicinal plants as potential sources of new compounds of therapeutic value and as a source of lead compounds in the drug development. In developing countries, it is estimated that about 80 per cent of the population rely on traditional medicine for the primary health care. There arises a need therefore to screen medicinal plants for bioactive compounds as a basis for further pharmacological studies (Sampathkumar *et al.*, 2006). In recent times, there is a focus on natural products derived from plants in search of new drugs by indicating new modes of pharmacological action. Traditional knowledge on herbal systems is being widely used in pharmaceutical industry and primary health care systems in developing countries. Recent studies have also imparted the identification and isolation of new therapeutic compounds of medicinal importance from higher plants for specific diseases. The most important bioactive constituents of these plants are alkaloids, tannins, flavonoids and phenolic compounds (Kumar *et al.*, 2007a).

Many plants synthesize substances that are useful to the maintenance of health in humans and other animals. These include aromatic substances, most of which are phenols or their oxygen-substituted derivatives such as tannins (Lai, 2004). Many are secondary metabolites, of which at least 12,000 have been isolated, a number estimated to be less than 10 per cent of the total. In many cases, these substances (particularly the alkaloids) serve as plant defense mechanisms against predation by microorganism's insects and

herbivores. Many of the herbs and spices used by humans to season food yield useful medicinal compounds (Tapsell *et al.*, 2006).

Herbal remedies from medicinal plants have been used traditionally in many parts of the world where access to formal healthcare is limited. There are several reasons why the uses of medicinal plants should be studied; herbal remedies may have recognizable therapeutic effects; they may also have toxic side effects. Indian system of medicine uses herbal remedies extensively for the treatment of diabetes. In the international scenario, there is a renewed interest in herbal medicines. In Unani medicine, diabetes is treated with formulations containing different plant materials. Global estimates suggest that the world population cannot afford the products of allopathic medicine and, thus have to rely on the use of traditional medicines, which are largely derived from plants (Hu *et al.*, 2003).

In recent years, many studies have shown that plants containing high content of antioxidant phytochemicals can provide protection against various diseases (Buricova and Reblova, 2008). Dietary measures and traditional plant therapies as prescribed by Ayurvedic and other indigenous systems of medicine are used commonly in India. The WHO has also recommended the evaluation of the plants effective in conditions where safe modern drugs are lacking. Recently an intensive search for novel types of antioxidants has been carried from numerous plant materials (Ramkumar *et al.*, 2007).

The use of herbal medicine is widespread. There are various medicinal plants in the world, which are the potential sources of the drugs. Traditionally various plants are being used to treat diabetic patients. It is believed that herbal medicine has little side effects as well as it requires no cost in few cases. So the herbal medicine can solve the economic problem for the poor. Nowadays, scientists and researchers are very much busy on

research of natural plant products all over the world and a large number of evidences have shown the immense potential of medicinal plants used traditionally. Diabetes mellitus is a major endocrine disorder affecting nearly 10 per cent of the population all over the world (Burke *et al.*, 2003). It is a deadly disease that has affected an estimated 135 million people worldwide; the numbers are increasing in rural and poor populations throughout the world (Roberts, 2001). Habib *et al.* (2005) tested some plants, which are being used to control blood glucose level.

*Tinospora cordifolia* Meris *(Menspermiaceae)* commonly known as Guduchi (Sanskrit) and Giloy (Hindi) is a glabrous, climbing, succulent herb commonly found in hedges and is a plant of India and thrives easily in tropical regions. It is widely used in Ayurveda as vitaliser, antidiabetic, hepatoprotective, antipyretic, antistress, antiulcer and immunomodulatory agent (Singh *et al.*, 2003).

*Psidium guajava* (guava) leaves have been used as herbal medicine for the treatment of various human ailments such as wounds, ulcers, cholera, and cough (Begum *et al.*, 2002). It also possesses antimicrobial, antipyretic, antidiarrhoeal and antimutagenic activities (Rattanachaikunsopon and Phumkhachorn, 2007).

*Cyperus rotundus* L. *(Cyperaceae)*, vernacularly called "Nagarmotha" is an erect perennial glabrous grass like sedge with slender subterranean stolons ending ovaid or cylindrical brown edible tubers. It is reported to contain oils, alkaloids, glycosides, saponins, flavonoids, tannins, starch and carbohydrate. *C.rotundus* is used in ancient medicine in India for fever, dysentry, purities, pain, vomiting, various blood disorders and diabetes (Raut and Gaikwad, 2006).

*Cassia auriculata* L. (avaram) is widely used in traditional medicine for rheumatism, conjunctivitis and diabetes. The tea prepared from the flowers is used for diabetic complaints (Joshi, 2000). In addition, it is widely used in Ayurvedic medicine as "Avarai panchaga choornam" and as constituent of kalapa herbal tea. It is also reported to possess antiperoxidative and antihyperglycemic effect in streptozotocin diabetic rats (Pari and Latha, 2002). The flower and the leaf extract have antipyretic activity (Kumaran and Karunakaran, 2007).

*Pteris multifida* Poiret (spider fern) is used as antipyretic, detoxifying, anti-inflammatory, antibiotic, heat clearing, antimutagenic activities and mainly used as folk medicine for the treatment of cholera, dysentry and entero-hemorrhoids (Wang *et al.*, 2007).

*Mentha piperita* Linn. commonly called peppermint, is aromatic and has stimulant and carminative properties and is used for allaying nausea, flatulence and vomiting. Mentha extract has been shown to have antioxidant and antibacterial properties. The extracts of mentha could enhance error-free repair of DNA damage and hence could be antimutagenic. *M.piperita* has a chemopreventive effect against gamma-induced carcinogenesis, which could be due to antimutagenic properties. Among the various polyphenolic compounds in the mint family having antioxidant properties, rosmarinic acid is the most abundant caffeic acid ester (Petersen and Simmonds, 2003; Chakraborty *et al.*, 2007).

*Cleome gynandra* (African cabbage) a common weed that grows throughout India, West Africa, Tanzania, Uganda and Nigeria is an erect herbaceous annual herb which has long been used as a household remedy for a variety of ailments including inflammation. Its leaves contain excessive amount of proteins, vitamins A and C and minerals. The leaves and seeds of

this plant are used in many countries for ear ache, epileptic fits, stomach ache, constipation and inflammation. Fresh leaves of *C. gynandra* are used in Ayurveda and Siddha medicine for a variety of disease conditions (Heever and Venter, 2006).

The medicinal uses of garlic, Allium sativam have a long history. Garlic is used in traditional treatment in many countries, notably the near East China and India. It is used as a remedy for heart disease, tumors and headaches. Recent studies have validated many of the medicinal properties attributed to garlic and its potential to lower the risk of disease. Epidemiologic studies show an inverse correlation between garlic consumption and reduced risk of gastric and colon cancer (Thomson *et al.,* 2007). It has been shown to have antithrombotic activity, lower blood lipids and have a cardioprotective effect. The mechanisms of garlic have been ascribed to its potent antioxidant action, its ability to stimulate immunological responsiveness and its modulation of prostanoid synthesis (Anwar and Meki, 2003).

*Aegle marmelos (Rutaceae)* commonly known as bael is indigenous to India and grown throughout the sub-continent as well as in Burma, Pakistan and Bangladesh. People use leaves and fruits of this plant to treat diabetes mellitus. Preliminary reports indicate blood glucose lowering activity in green leaves. The alkaloid extract prepared from the leaves and crude leaf extract exhibits hypoglycemic effects in alloxanized diabetic rats (Kamalakannan and Prince, 2003; Ravi *et al.*, 2009)

*Pongamia pinnata* Linn. popularly known as " Karanj or Karanja" in Hindi, is a medium sized glabrous tree, found throughout India further distributed eastward, mainly in littoral regions of Southeastern Asia and Australia. Different parts of this plant have been recommended as a remedy

for various ailments such as bronchitis, whooping cough, rheumatic joints, inflammatory and infectious diseases and to quench dyspepsia in diabetes in Ayurvedic and traditional medicine in India (Srinivasan *et al.*, 2001). The leaves are hot, digestive, laxative and antihelmintic and cure piles, wounds and other inflammations (Kirthikar and Basu, 1995). A hot infusion of leaves is used as a medicated bath for relieving rheumatic pain and for cleaning ulcers in gonorrhoea and scrofulous enlargement. In addition, phytochemical examination of this plant indicated the presence of furanoflavones, furanoflavonols, chromenoflavones, flavones, furanodiketones and flavonoid glycosides (Ahmad *et al.*, 2004). It is a well documented fact that most medicinal plants are enriched with phenolic compounds and biflavonoids that have excellent antioxidant property (Shirwaikar *et al.*, 2004).

*Ocimum sanctum (Labiatae)*, known as tulsi in Hindi and Holy basil in English has been extensively used in Ayurvedic system of medicine. Each part of this plant has medicinal value. The juice of the stem and leaves is diaphoretic and expectorant. It relieves ear ache and is used to treat skin disorders (Gupta *et al.*, 2008).

*Rhodiola rosea (Crassulaceae)* commonly known as golden root grows primarily in dry sandy ground. It is rich in phenolic compounds and known to have strong antioxidant property (Khanum *et al.*, 2005).

*Syzygium cumini* Linn. *(Myrtaceae)* is a large evergreen tree attaining 30 m in height and found through out India. The jamun seeds are used in the Ayurveda and Unani system of traditional medicine as an antidiabetic (Helmstadter, 2008)

*Gymnema sylvestre* (Sirukurinchaan), which belongs to the family *Asclepiadaceae* is a large woody climber running over the tops of high trees.

The plant is used in eye complaints, biliousness, bronchitis and asthma in the Indian traditional medicine (Ayurveda). The fresh leaves are chewed to reduce glycosuria (Kirtikar and Basu, 2000). The ethanol extract of leaves produced antimicrobial activity against *Bacillus pumilis, Bacillus subtilis, Pseudomonas aeruginosa* and *Staphylococcus aureus* (Satdive *et al.*, 2003).

*Annona muricata* Linn. *(Annonaceae)* commonly called "Soursop" is a small, upright evergreen tree growing 5 to 6 meters in height. Ethno-botanically, all parts of *A.muricata* tree have been used medicinally in the tropics, including the bark, the leaves, the roots, the fruit and the seeds (Adewole and Martins, 2006). Different properties and uses are attributed to the different parts of the *A.muricata* by the traditional herbal medicine practitioners. Generally, the fruit and the fruit juice are taken for worms and parasites, to cool fevers, to increase mother's milk after child birth and as an astringent for diarrhoea and dysentry. The crushed seeds are used against internal and external parasites, head lice and worms. The bark, the leaves, and the roots are considered sedatives, antispasmodic, hypoglycemic, hypotensive, diuretics and neuralgic (Padma, 2001).

*Diospyros malabarica* (Indian persimmon) is a medium sized evergreen plant found in India. The plant is traditionally used for the treatment of dysentry and menstrual problems; its stem bark is used for the treatment of intermittent fever, and is reported to have hepatoprotective and hypoglycemic activity. The fruit juice is used for the healing of wounds and ulcer. The plant also possesses antifertility activity (Mondal *et al.*, 2005).

*Sphaeranthus indicus* Linn. *(Asteraceae)* popularly known as "Gorakmundi" is cultivated all over India (Warrier *et al.*, 2004) for its medicinal values. Preliminary phytochemical screening of plant has revealed the presence of flavonoids, carbohydrates, alkaloids, gums and mucilage.

The plant is traditionally used for the treatment of rheumatic arthritis. It has antiallergic and anti-inflammatory properties also. Several tribal populations in northern India use this plant to cure diabetes (Yoganarasimhan, 2000; Nadkarni, 2000).

*Helicteres isora* L. *(Sterculiaceae)* is a medicinal plant, widely distributed from Southern China to India, South East Asia and Australia. The plant is a shrub or small tree available in forests throughout the Central and Western India. The roots and the bark are expectorant and demulcent and are useful in colic, scabies, gastropathy, diabetes, diarrhoea and dysentry (Kirthikar and Basu, 1995). The fruits are astringent, refrigerant, stomachic, vermifugal, vulnerary and useful in griping of bowels and flatulence in children (Chopra *et al.,* 1956) and possess an antispasmodic effect (Pohocha and Grampurohit, 2001). From the roots and barks of *Helicteres isora*, betulic acid, daucosterol, sitosterol, isorin (Qu *et al.,* 1991) were isolated. The roots have a significant hypoglycemic effect (Venkatesh *et al.,* 2003). The aqueous extract of the bark showed a significant hypoglycemic effect (Kumar *et al.,* 2006a), hypolipidemic activity (Kumar and Murugesan, 2008), lowering effect of hepatic enzymes (Kumar *et al.*, 2006b) glycoprotein levels (Kumar and Murugesan, 2007) antiperoxidative (Kumar *et al.*, 2007b) and antioxidant activity (Kumar *et al.*, 2008).

Root extracts of *Helicteres isora* possess antihyperglycemic activity in glucose- loaded rats (Venkatesh *et al.,* 2004). It lowers plasma glucose and can nullify the insulin resistance activity. A hypolipidemic activity of *Helicteres isora* has also been reported by Chakrabarti *et al.* (2002). The hepatoprotective (Dhevi *et al.*, 2008) and antimicrobial activity (Venkatesh *et al.,* 2007) of *Helicteres isora* was also reported.