Introduction
Diabetes mellitus is a major and growing health problem in most countries and an important cause of prolonged ill health and early death (WHO report, 2000). It was the sixteenth leading cause of global mortality in 1990, accounting for 571,000 deaths (Murray and Lopez, 1998). Diabetes is predicted to continue to grow worldwide at epidemic proportions in the first quarter of the 21st century. The growth will be particularly strong in India and China (King et al., 1998; Roglic et al., 2000), which lead the world in the prevalence of diabetes, with 14.3% and 11.8% of prevalence, respectively in 1995. In USA, which ranks third after India and China in the prevalence of diabetes, the growth rate is expected to be much smaller: from 13.9 million in 1995 to 21.9 in 2025 (King et al., 1998).

Diabetes mellitus is a metabolic disorder with characteristics of hyperglycemia and insufficiency of secretion or action of endogenous insulin leading to disturbances in carbohydrate, fat and protein metabolism (Arulmozhi et al., 2004). There are two types of diabetes Type I and Type 2.

Type I diabetes mellitus also known as insulin-dependent diabetes mellitus (IDDM), usually begins in childhood and is thought to be a result of autoimmune destruction of pancreatic beta cells. Destruction of beta cells results in a complete or almost-complete loss of insulin production, thereby necessitating insulin injections to maintain blood glucose control.

Type 2 also known as non-insulin-dependent diabetes mellitus (NIDDM) is usually diagnosed after 40 years of age. Type 2 diabetes mellitus is frequently associated with insulin resistance and normal or even elevated levels of insulin, although subnormal insulin levels are also seen in some type 2 diabetes (Keen and Ng Tang Cui, 1982; Ziv et al., 1999; Pickup and Williams, 2003). Type 2 diabetes once believed to affect only adults is being diagnosed increasingly among young people.
Introduction

According to recent estimates the human population world wide appears in the midst of epidemic of diabetes (Raman, 2002). The global prevalence of diabetes is estimated to increase from 4% in 1995 to 5.4% by the year 2025. The number of adults suffering from diabetes in India is expected to increase three-fold, from 19.4 million in 1995 to 57.2 million in 2025.

Diabetes is associated with number of significant medical problems. Severe hyperglycemia may result in coma or even death. Milder hyperglycemia, if present for many years, increases the risk of major complications of diabetes, including nephropathy, retinopathy, neuropathy and microvascular and macrovascular damage (Brownlee, 2001; Cullen et al., 1999).

Type 2 diabetes occurs at younger age in Indians giving a ample time for development of chronic vascular complications. There is a wide urban-rural difference in prevalence of diabetes indicating a major role for urbanization in the causation of disease (Ramachndran, 1992). Indians are also susceptible to the major complications related to diabetes like coronary artery disease, neuropathy, nephropathy and retinopathy.

Prevalence of the complications is higher in low socio-economic groups due to lack of good control of glycemia and hypertension and also due to behavioral factors. The direct and indirect costs involved in the treatment of chronic disease especially when associated with the vascular complication are enormous. There is an urgent need to implement preventive measures to reduce the high morbidity and mortality and also to reduce the cost burden to the patients and to the society (Ramachandran, 2002).
Metabolic disturbance in diabetes mellitus:

In diabetes mellitus the changes are mainly the result of low insulin/glucagon ratio. Insulin deficiency decreases the uptake of glucose by cells. High glucagon levels decreases the hepatic fructose 2, 6-bisphosphate level, thereby decreasing the utilization of glucose. The insulin dependent enzymes are also less active. Net effect is inhibition of glycolysis and stimulation of gluconeogenesis leading to hyperglycemia. A reduced insulin activity influences the Pentose Phosphate Pathway. The impairment of Pentose Phosphate Pathway thus lead to a reduced NADPH availability, and negatively influences other enzymes and systems involved in defensive processes against oxidative agents, such as the catalase and glutathione systems (Bono et al., 1987). Hyperglycemia in turn causes activation of sorbitol pathway. This involves reduction of glucose to sorbitol catalyzed by sorbitol dehydrogenase, this has important implications in terms of redox changes of NADP⁺ and NAD⁺ couples and metabolism of glucose by alternative pathways (Jeffrey and Jornval, 1983). Conversion of glucose to sorbitol by aldose reductase requires NADPH and NADP⁺ and thereby competes with other NADPH requiring reactions. Conversion of sorbitol to fructose by sorbitol dehydrogenase is coupled to reduction of NAD⁺ to NADH and this competes with glycolysis at the glyceraldehyde dehydrogenase step for NAD⁺ (Gonzalez et al., 1986).

When the blood glucose level exceeds the renal threshold, glucose is excreted in urine. Due to osmotic effect, more water accompanies the glucose (polyuria). To compensate for this loss of water, thirst center is activated and more water is taken (polydipsia). The loss and ineffective utilization of glucose leads to breakdown of fat and protein. This leads to loss of weight. To compensate the loss of glucose and protein, patient will take more food (polyphagia). The need for fatty acid breakdown to meet the energy requirements would lead to production of more acetyl CoA. The acetyl CoA cannot be efficiently oxidized by Kerb’s cycle since the availability of oxaloacetate is limited. The stimulation of gluconeogenesis is mainly responsible for the depletion of oxaloacetate. The excess of mitochondrial acetyl
Introduction

Diabetic syndrome

Hyperglycemia

Auto-oxidation of glucose

Generation of free radicals

Excess reactive oxygen species and low antioxidant defense (oxidative stress)

Increased generation of reactive oxygen species from mitochondria

- Activation of PK-C isofoms
- Increased glycation end-product
- Increased glucose flux via aldose reductase pathway
- Increased hexoseamine synthesis
- O-glycation of Sp-1
- Pal-1 expression

Pathological changes in small vessels, arteries and peripheral nerves

Diabetic complications

Figure 1: Hyperglycemia induced oxidative stress and diabetic complications (Tiwari, 2002)
CoA therefore is diverted to ketone bodies leading to ketogenesis. This tendency is more in IDDM.

Both forms of diabetes mellitus are equally devastating with respect to their later complications i.e., nephropathy, neuropathy, retinopathy and aggregated atherosclerosis which leads to cardiovascular disorders (myopathy, coronary vascular disease and hypertension), shortened lifespan of erythrocytes (Lahrman, 1977; Percasmona et al., 1982) and anemia (Gupta et al., 1998).

Vascular complications (Nephropathy):

Chronic elevation of blood glucose in diabetes plays a critical role in development and progression of major diabetic complications. Prolonged exposure to elevated glucose causes both acute reversible changes in cellular metabolism and long-term irreversible changes in stable macromolecules.

The injurious effects of hyperglycemia are characteristically observed in tissues that are not dependent on insulin for glucose entry into the cell (eg. eye lens and kidneys) and, hence, they are not capable of down regulating glucose transport along with the increase of extra cellular sugar concentrations.(Kyselova et al., 2004).

Diabetes is a disease of complications. The vascular complications of DM are divided into microvascular (retinopathy, nephropathy and neuropathy) and macrovascular complications (coronary artery disease, peripheral vascular disease and cerebrovascular disease). Overall 99% of patients having diabetes for more than 15 years will exhibit at least one and usually several of these complications of diabetes with an inexorable course to disability and ultimately premature death.

The cause of microvascular complication is not understood but the most important influence is probably the quality of diabetes control over many years. Small vessel (capillary) basement membrane thickening occurs throughout the body.
Introduction

but manifests itself in two strategically important areas—the eyes and the kidneys (Ryan, 1980).

Diabetes is the leading cause of end stage renal failure and much of the morbidity and mortality of diabetes can be attributed to diabetic nephropathy (Borch johnsen and Kreiner, 1998; Krolewski, 1998; Dazhong, 2003).

Ten to twenty per cent of all patients with insulin dependent diabetes develop proteinuria, the hallmark of diabetic nephropathy within 10 years of diagnosis. This complication is the first manifested as an increase in urinary albumin excretion (micro albuminuria), which progress to overt albuminuria and then to renal failure (Mogensen, 1983).

Diabetic nephropathy is more rapidly labile to functional deterioration compared with other types of chronic renal disease and finally progress to renal failure. Several mechanisms have been proposed to the pathogenesis of diabetic vascular complications that include nephropathy, such as hyperfiltration, increased production of advanced glycation end products, activation of protein kinase-C, enhanced polyol pathway and enhanced oxidative stress. Enhanced oxidative stress might induce mtDNA damage result in subsequent mtDNA mutation in kidney of diabetic subjects, and this might be involved in the pathogenesis of diabetic nephropathy (Maiko et al., 2002).

Oxidative stress in diabetic complications:

Oxidative stress is the imbalance between production and removal of ROS. Increased oxidative stress, which contributes to the pathogenesis of diabetic complications, is the consequence of either enhanced ROS production or attenuates ROS scavenging capacity. The level of ROS scavenging mechanisms are altered in diabetes and therefore, the ineffective scavenging of free radicals play a crucial role in determining tissue injury (Wohaieb and Godín, 1987).
Abnormalities in tissue antioxidants-oxidant balance may be important in the pathogenesis of both macro and micro angiopathic complications of diabetic patients (Godin, 1988; Baynes, 1991). Hyperglycemia alone does not cause diabetic complications. It is rather the detrimental effect of glucose toxicity due to chronic hyperglycemia, which is mediated and complicated through oxidative stress (Tiwari, 2002). Diabetes mellitus was found to be inextricably connected with increased oxidative stress both in diabetic humans and hyperglycemic animals (Baynes, 1991; Cameron, 1995; Dai and Mc Neill, 1995; Kowluru and Kennedy, 2001). Increased free radical production is said to mediate tissue injury in a wide range of diseases and diabetes mellitus is no exception (Halliwell and Gutteridge, 1990; Stankora et al., 1997).

ROS can attack vital cell components like polyunsaturated fatty acids, proteins and nucleic acids. To a lesser extent carbohydrates are also the target of ROS. These reactions can alter intrinsic membrane properties like fluidity, ion transport, loss of enzyme activity, protein cross-linking, inhibition of protein synthesis, DNA damage ultimately resulting in cell death (Halliwell and Gutterdie, 1990). Some of well known consequences of generation of free radicals in vivo are DNA strand scissions, protein oxidation (Stadman, 1990) and lipid peroxidation (LPO) (Hliwell and Gutteridge, 1990).

Besides all these deleterious effects of free radicals, the cell possess some innate mechanism by which it tries to combat oxidative insult by increasing by its reserve antioxidants. Cellular antioxidant enzymes and free radical scavengers protect cell from the toxic effect of free radicals.

Several mechanisms, including autooxidative glycosylation, formation of advanced glycation end products and increased polyol pathway activity contribute to increased oxidative stress.
**Introduction**

**Autooxidative Glycooxidation:**

Under physiological conditions free radicals can be generated in glucose oxidation, which is believed to be the main source of free radicals. In its enediol form, glucose is oxidized in a transition-metal-dependent reaction to an enediol radical anion that is converted into reactive ketoaldehydes and to superoxide anion radicals. Which if not degraded by catalase or glutathione peroxidase, and in the presence of transition metals, can lead to production of extremely reactive hydroxyl radicals (Jiang et al., 1990). Superoxide anion radicals can also react with nitric oxide to form reactive peroxynitrate radicals. Hyperglycemia is also found to promote lipid peroxidation of low density lipoproteins (LDL) by a superoxide-dependent pathway to generate free radicals (Tsai et al., 1994).

Increased oxygen free radical activity can initiate peroxidation of lipids which in turn stimulates glycation of proteins, inactivation of enzymes and alterations in the structure and functions of collagen, basement and other membranes and play a role in the long term complications of diabetes. It has also been suggested that there is a link between development of macrovascular and microvascular diabetic complications and free radical damage (Giugliano, 1996; Low, 1997; Bayne, 1999).

**Advanced glycation end products:**

Under hyperglycemic conditions, part of the excess glucose reacts nonenzymatically with proteins or other tissues or blood constituents, thus increasing the physiological rate of non enzymatic glycation (Brownlee, 1996). Chronic, irreversible abnormalities unaffected by normalization of blood glucose levels primarily involve long lived molecules including extra cellular matrix, eye lens crystallins and chromosomal DNA. Due to their characteristic chemical properties, advanced products of non enzymatic glycation play a critical role in the evolution of diabetic complications. Another factor that contributes to the complications of diabetes is a process called glycation of proteins (Kyselova et al., 2004).
Introduction

Glycation reaction also known as non enzymatic glycation or Maillard reaction, is the reaction that free amino groups of proteins react slowly with carbonyl groups of reducing sugars to yield Schiff base intermediates, which undergo Amadori rearrangement to stable ketoamino derivatives. These Schiff-bases and Amadori products subsequently degrade to α-dicarbonyl compounds such as deoxyglucosone, methylglyoxal and glyoxal, which are more reactive than the parent sugars with respect to their ability to react with amino group of proteins to form inter and intra molecular cross-links of proteins called advanced Maillard products or advanced glycation end products (AGEs) (Wells-Knecht et al., 1996; Monnier et al., 1996; Bucal, 1999).

Tissue accumulation of AGEs is associated with a number of toxic effects. These include cross-linking of long lived proteins such as collagens and other matrix proteins, increasing of vascular permeability and promotion of mononuclear cell influx. The cross-linked proteins will be more persistent and could be a reactive site for putative reducing and oxidizing molecules, which produce free radicals for a long duration (Yim et al., 1999). Additionally advanced glycation end products have been shown to induce genes for growth factors, extra cellular matrix proteins and inflammatory cytokines, as well as to stimulate cell proliferation (Soulis-Liparota et al., 1991; Cohen et al., 1994). AGEs have also been shown to quench nitric oxide, and have been implicated in the pathogenesis of atherosclerosis (Brownlee, 1992; Vlassara, 1994).

Recent studies suggest that these AGEs via their receptors (RAGE) inactivate enzymes and alter their structure and functions, promote free radical formation, induce cellular lipid peroxidation and quench and block anti proliferate effects of nitric oxide. By increasing intracellular oxidative stress, advanced lycation end products activate transcription factor Nuclear factor- kappa B (NF-κB), thus promoting up regulation of various NF-κB controlled target genes. NF-κB enhances production of nitric oxide which is believed to be mediators of islet beta cell damage.
Introduction

In addition, hyperglycemia leads to glycation of antioxidant enzymes and low molecular antioxidants such that they are unable to detoxify free radicals, exacerbating oxidative stress in diabetes. Therefore, the process of glucose oxidation might be responsible not only for increased ROS products but also for decreased ability of antioxidant enzymes.

The AGEs concept proposes that chemical modification and cross linking of tissue proteins, lipids and DNA affect their structure, function and turnover contributing to gradual decline in tissue function and pathogenesis of diabetic complications (Jakus, 2000).

In patients with diabetic nephropathy, high levels of AGEs accumulate in the plasma, and importantly within the sclerosing glomeruli (Makita et al., 1991; Nishino et al., 1995). The latter has been noted to precede the onset of diabetic renal disease and correlates with the course of disease (Beisswenger et al., 1995). In animals, chronic administration of advanced glycation end products to non diabetic rats leads to proteinuria and glomerular changes similar to those seen in diabetic nephropathy (Vlassara, 1994).

Reactive dicarbonyls, products of carbohydrate autooxidation, contribute to covalent attachment of monosaccharide to protein with high cross-linking potential. Indeed, glycation and oxidation are closely connected and the complex process if often referred to as glycooxidation (Baynes, 1991).

Polyol pathway:

One of the consequence of hyperglycemia in DM is increased metabolism of glucose by polyol pathway consists of two enzymes. The first enzyme, aldose reductase (AR), reduces glucose to sorbitol with the aid of co-factor NADPH and the second enzyme sorbitol dehydrogenase with its co-factor NAD$^+$, converts sorbitol to fructose. Sorbitol is not permeable to cell membrane and tends to accumulates in
cell and cause damage by disturbing osmotic homeostasis. It was thought that osmotic stress, from accumulation of sorbitol, leads to diabetic lesions (Kinoshita and nishimura, 1998). In addition to disturbing osmotic level of cell by aldose reductase activity it also causes oxidative stress (Stephen et al., 2003).

Treatment of diabetic rats with aldose reductase inhibitors (ARI) attenuated the reduction of GSH in their lenses, suggesting that AR activity causes oxidative stress (Gonzale et al., 1998). Treatment with ARI was shown to be effective in preventing the development of various diabetic complications, including cataract, nephropathy and neuropathy (Oates and Mylari, 1999).

Protein kinase C:

In the pathogenesis of diabetic nephropathy have possible role oxidative stress and protein kinase C (PKC). Glucose has been shown to activate glomerular PKC signaling system that enhances phospholipase A₂ activity (De Rubertis and Craven, 1993; De Rubertis and Craven, 1994). The increased free arachidonic acid released by phospholipase A₂ can fuel the enzymatic production of prostaglandins (PGs). Since PG synthesis is well-recognized source for free radicals, the increased PG synthesis, that is known to occur in early stage of diabetes, could also contribute to concomitant occurrence of lipid peroxidation. Lipid peroxides, a product of lipid peroxidation, can in turn further catalyse PG production. Chronic activation of PKC is responsible for the development of abnormal changes in the kidney and increase in oxidative stress associated with diabetes.

As previously stated, convincing evidence is now available about the possible role of oxidative stress in development of diabetic complications including diabetic nephropathy (Giugliano et al., 1996). A causal relationship between oxidative stress and diabetic nephropathy has been established by observation that lipid peroxides and 8-hydroxydeoxyguanosine were increased in the kidney of diabetic rats with albuminuria, high glucose directly increase oxidative stress in glomerular mesangial cells, a target cell of diabetic nephropathy, oxidative stress induces mRNA
expression of Turner growth factor-β1 (TGF-β1) and fibronectin which are the genes implicated in diabetic glomerular injury and inhibition of oxidative stress ameliorates all the manifestations associated with diabetic nephropathy (Ha and Kim, 1999).

Strategies for Treating Diabetes and Preventing Complications:

It is projected that incidence of diabetes is on rise. Control of blood glucose on 24h basis is the desired goal in the management of DM. Appropriate goals in the management of diabetes including maintaining blood glucose levels as close to the normal range as possible, minimizing the adverse effects of free radicals by enhancing antioxidant defenses, and reducing the glycosylation of proteins and the intracellular accumulation of sorbitol. A number of different interventions are currently considered to be in realm of "alternative medicine" have been shown to accomplish one or more of these goals.

Alternative medicine for Diabetes mellitus:

Before the introduction of insulin in 1922, the treatment of DM relied heavily on dietary measures which included the use of traditional plant therapies. But after the advent of insulin and other hypoglycemic drugs (synthetic) this field of work largely remained unexplored. The yawning gap for additional agents to combat hyperglycaemia and its accompanying complications presents an opening to revisit traditional antidiabetic plants (Gray and Flatt, 1997).

Nature has been a source of medicinal treatments for thousands of years, and plants – based systems continue to play an essential role in the primary health care of 80% of the world's underdeveloped and developing countries (King et al., 1998). India is endowed with traditional medicine as is evident from the fact that the Sushruta Samhita differentiated between genetically and acquired forms of diabetes and recommended different treatments for the two types of diseases (Grover and Vats, 2001). Thus, it will be judicious to study the potential of this knowledge in drug
discovery process. Even WHO suggested investigating traditional methods of

Recent decades have seen a resurgent interest in traditional plant treatments
for diabetes. This has pervaded nutrition, the pharmaceutical industry and academic
research, fuelled by a growing public interest and awareness of so called
complementary and natural types of medicine.

Many traditional plant treatments for diabetes exist (Bailey and Day, 1989;
Swanston-Flatt et al., 1991; Gray and Flatt, 1997). However, few have received
scientific or medical scrutiny and the WHO has recommended that traditional plant
treatments for diabetes warrant further evaluation (WHO, 1980).

Phyllanthus niruri:

Members of the genus *Phyllanthus* include some 500 species and are
widespread in temperate and tropical climates. *Phyllanthus* species have attracted
the attention of researchers for their hepatoprotective proprieties.

*Phyllanthus niruri* belongs to Family Euphorbiaceae. It is commonly known as
Chanca piedra. In Sanskrit Bhoomya malakee, in Telugu it is called as Nelvusari, in
Hindi Bhuamla, in English it is called as Stone breaker.

*Phyllanthus niruri* is a small, erect, annual herb that grows 30-40 cm in height.
It is indigenous to the rainforest of the Amazon and other tropical areas throughout
world, including the southern India and China.

*Phyllanthus niruri* has been used in Ayurvedic medicine for over 2,000 years
and has a wide number of traditional uses. This includes employing the whole plant
for jaundice, kidney and gallbladder stones, gonorrhea, frequent menstruation and
diabetes and using it topically as a poultice for skin ulcers, sores, swelling and
itchiness. The young shoot of the plant are administered in the form of an infusion for the treatment of chronic dysentery. *Phyllanthus niruri* shows lipid lowering activity, diuretic, hypotensive and antihyperglycemic effect.

Many of the active constituents of *Phyllanthus niruri* are isolated attributed to have medicinal importance include, biologically active lignans (phyllanthine and hypophyllanthine), alkaloids and bioflavanoids (quercetin) elagitannin and phenylpropanoids.

Now traditional use of *Phyllanthus niruri* is supported by scientific studies. Aqueous extract of *Phyllanthus niruri* has inhibitory effect on renal stone formation (Freitas et al., 2002). Tea made from the hole plant *Phyllanthus niruri* has been used in Brazil from many years to treat urinary calculi. Researchers have shown that alkaloids extracted from this plant have antispasmodic activities that relax smooth muscle tissue in urinary tract, thereby facilitating the elimination of urinary calculi.

Extract from *Phyllanthus niruri* has also been shown to have an inhibitory effect on the growth and aggregation of calcium oxlate crystals into canine distal tubular cells. Human subjects who received large oral dose (20 g/day) of *Phyllanthus niruri* as tea experienced no adverse clinical or biochemical effects and good tolerability (Nishiura et al., 2004). *Phyllanthus niruri* has been claimed to be an excellent remedy for jaundice (Kirtikar and Basu, 1935).

An aqueous extract of *Phyllanthus niruri* was demonstrated to exert antheptities B virus effects to varying degrees (Iizuka et al., 2006). Phyllanthine and hypophyllanthine are reported to inactivate Hepatitis-B both in *vitro* and in *vivo*. Preclinical studies demonstrated that an extract of the *Phyllanthus niruri* plant inhibit endogenous DNA polymerase of Hepatitis-B virus and binds to the surface antigen of Hepatitis-B virus (Thyagarajan, 1987). Ethanolic extract of *Phyllanthus niruri* whole plant shows a *in vitro* antiplasmodial activity (Tona et al., 2004). Niruriside is an isolated compound from *Phyllanthus niruri* shows antiviral activity against HIV by
inhibiting the reverse transcriptase enzyme (Qian-Cutrone, 1996). Aqueous extract of *Phyllanthus niruri* was reported to have protective action against cytotoxicity induced by lead nitrate and aluminum sulphate. The frequency of chromosomal breakage, gaps and rearrangements induced by these salts was decreased by *Phyllanthus niruri* treatment compared to control animals (Dhir et al., 1990).

Extract of *Phyllanthus niruri* have been shown to exert hepatoprotective effect against carbon tetrachloride induced liver cell damage in rabbits due to its phyllanthine and hypophyllanthine (Venkata Syamasundar et al., 1985; Vishweshwaran, Santhranii, 1985). *Phyllanthus niruri* pretreated rats showed reduced Paracetmol induced acute liver damage (Tabassum et al., 2005).

Studies of Lizuka et al., (2006) revealed vasorelaxant effect of methyl brevifolin carboxylate isolated from *phyllanthus niruri* leaves on rat aortic rings through the receptor operated Ca\(^{2+}\) channel. Ellagic acid is an isolated compound shows highest inhibitory activity on aldose reductase enzyme, being about 6 times more potent than quercetin, which is a known natural inhibitor of aldose reductase (Shimizu et al., 1989).

As previously stated, convincing evidence is now available about the possible role of oxidative stress in development of diabetic complications. Hence compounds with both antihyperglycemic and antioxidative properties would be useful anti-diabetic agents.

Supplementation with antioxidants as a promising complementary treatment can exert beneficial effects in diabetes (Jakus, 2000). On this matter, it has recently been suggested that antioxidant therapy with vitamin E or other antioxidants is limited to scavenging already-formed oxidants (Cuzzocrea et al., 2001). Thus it is prudent in the current context to identify new and more efficacious antioxidants from vast reserves of phytotherapy.
Introduction

The antioxidant protective effect of natural plants are promising therapeutic drugs for free radical pathologies (Repetto and Llesuy, 2002).

Several phytochemicals were reported to act against the deleterious effects of oxidative stress such as aloe vegetables anthraquinones, total saponins from Pinax ginseng, Tea polyphenols and flavoinds from Siderites reseri anthocyanins from Brassica oleracea

AIM AND SCOPE

A very little information on the antihyperglycemic activity and antioxidant property of Phyllanthus niruri is available (Mazunder et al., 2005) and no biochemical basis related to these properties of Phyllanthus niruri are reported to the best of our knowledge.

Earlier studies in our laboratory demonstrated antihyperglycemic and antilipidimic activities of Phyllanthus niruri in STZ diabetic rats (Vijaya Bharathi et al., 2006). As phyllanthu niruri aqueous extract was reported to have protection against cytotoxicity caused by various toxic salts and its well known hepatoprotective property indicates possible antioxidant potential of this plant. So, the present study was undertaken to investigate the possible antioxidant potential of this plant treatment in the kidney of STZ-induced diabetic rats.

The following systematic study was conducted in STZ-induced diabetic rats; Phyllanthus niruri treated diabetic rats and compared with normal and normal treated rats

- The extent of lipid peroxidation and protein carbonyl content were assessed in kidney of diabetic, diabetic treated, normal and normal treated rats in order to evaluate the protective effect of Phyllanthus niruri aqueous extract against diabetes induced oxidative, alterations in the antioxidant systems was assessed in four experimental groups by measuring renal GSH content and glutathione
dependent and independent antioxidant enzymes viz., glutathione reductase, glutathione peroxidase, glutathione-S-transferase and catalase and superoxide dismutase respectively.

The protective effect of *Phyllanthus niruri* aqueous extract against H$_2$O$_2$, NO and STZ-induced DNA damage of rat lymphocytes was assessed under *in vivo*/*in vitro* conditions.

With the increasing incidence of DM in rural populations throughout the world, the inability of current therapies to control all the metabolic defects of the disease and their pathological consequences, and the great expense of modern therapy, there is a clear need for the development of alternative strategies for diabetes therapy. This work will lead to the development of indigenous botanical resources as inexpensive sources of new antihyperglycemic and antioxidant drugs, and the discovery of novel antihyperglycemic and antioxidant compounds could be used to ameliorate adverse effects of diabetes and its complications, particularly the diabetic nephropathy.