1. INTRODUCTION

1.1 Indigenous System of Medicine

Mankind has a long history in the use of herbal medicine. Rigveda and Ayurveda (4500-1600 BC) reveal that ancient Indians had a rich knowledge of the use of medicinal plants. India unquestionably occupies the topmost position in the use of herbal drugs since ancient times utilizing nearly 600 plant species in different formulations. Great majorities of the people in India have been depending on crude drugs for the treatment of various diseases as evidenced from well-documented indigenous systems of medicine namely Ayurveda, Siddha and Unani (Nadkarni, 1955).

The WHO estimates that 65-80% of the world’s population use traditional medicine as their primary form of healthcare and about 85% of traditional medicine involves use of plant extracts. In the last century, roughly 121 pharmaceutical products were formulated based on the traditional knowledge obtained from various sources (Sheetal and Singh, 2008).

India has 2.4% of world’s area with 8% of global biodiversity. The wide range of Indian forests is estimated to harbor 90% of India’s medicinal plants. Around 25,000 effective plant based formulations are used in traditional and folk medicine; over 1.5 million practitioners are using the traditional medicinal system for healthcare in India. It is estimated that over 7800 Indian manufacturing units have been involved in the production of natural health products and traditional plant based formulations which requires more than 2000 tonnes of medicinal plant raw material annually (Aneesh et al., 2009).

1.2 Diabetes mellitus

Diabetes mellitus (DM) 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, polydipsia and polyphagia (Shoback, 2011).
There are three main types of DM. Type 1 DM results from the body's failure to produce insulin, and hence requires the person to inject insulin or wear an insulin pump. This form was earlier referred to as "Insulin-Dependent Diabetes Mellitus" (IDDM) or "Juvenile diabetes".

Type 2 DM results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency. This form was earlier referred to as ‘Non Insulin-Dependent Diabetes Mellitus’ (NIDDM) or "Adult-onset diabetes". The third form, Gestational diabetes occurs when pregnant women without a previous diagnosis of diabetes, develop a high blood glucose level. It may precede development of type 2 DM (Merck Manual, 2010).

Diabetes increases the risk of long-term complications. These typically develop after many years (10-20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular diseases (Emerging Risk Factors Collaboration, 2010).

1.3 Diabetes related complications

Diabetes also causes microvascular complications damage to the small blood vessels. Diabetic retinopathy, which affects blood vessel formation in the retina of the eye, can lead to visual symptoms, reduced vision and potentially blindness. Diabetic nephropathy, the impact of diabetes on the kidneys can lead to scarring changes in the kidney tissue, loss of small or progressively larger amounts of protein in the urine and eventually chronic kidney disease requiring dialysis.

Diabetic neuropathy is the impact of diabetes on the nervous system, most commonly causing numbness, tingling and pain in the feet and also increasing the risk of skin damage due to altered sensation. Together with vascular disease in the legs, neuropathy contributes to the risk of diabetes-related foot problems (such as diabetic foot ulcers) that can be difficult to treat and occasionally require amputation (Boussageon, 2011).
### Table 1.1 Different forms of Diabetes mellitus (ADA, 2010)

#### I. Type 1 diabetes
(cell destruction, usually leading to absolute insulin deficiency)

- A. Immune-mediated
- B. Idiopathic

#### II. Type 2 diabetes
(may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)

#### III. Other specific types of diabetes

- A. Genetic defects of cell function characterized by mutations in
  1. Hepatocyte nuclear transcription factor (HNF) 4 (MODY 1)
  2. Glucokinase (MODY 2)
  3. HNF-1 (MODY 3)
  4. Insulin promoter factor-1 (IPF-1; MODY 4)
  5. HNF-1 (MODY 5)
  6. NeuroD1 (MODY 6)
  7. Mitochondrial DNA
  8. Subunits of ATP-sensitive K⁺ channel
  9. Proinsulin or insulin sequence conversion
- B. Genetic defects in insulin action
  1. Type A insulin resistance
  2. Leprechaunism
  3. Rabson-Mendenhall syndrome
  4. Lipodystrophy syndromes
- C. Diseases of the exocrine pancreas
- D. Endocrinopathies
- E. Drug or chemical-induced
- F. Infections
- G. Uncommon forms of immune-mediated diabetes—"stiff-person" syndrome, anti-insulin receptor antibodies

#### IV. Gestational diabetes mellitus (GDM)
1.4 Epidemiology of diabetes

Globally, as of 2012, an estimated 346 million people have type 2 DM making up about 90% of DM. Its incidence is increasing rapidly and by 2030, this number is estimated to almost double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase is expected to occur in Asia and Africa, where most patients will probably be found by 2030. The increase in incidence in developing countries follows the trend of urbanization and lifestyle changes, perhaps due to the “Western-style” diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented.

India has the highest diabetics than any other country in the world, according to the International Diabetes Foundation, although more recent data suggest that China has even more. The disease affects more than 50 million Indians, nearly 7.1% of the nation's adults and kills about 1 million Indians a year. The average age of onset is 42.5 years. The high incidence is attributed to a combination of genetic susceptibility plus adoption of a high-calorie, low-activity lifestyle by India's growing middle class (Chan et al., 2009).

1.5 Pathogenesis of type 1 diabetes

Type 1 diabetes accounts for 5-10% of diabetes and results from autoimmune-mediated destruction of the cells of the islet leading to total or near total insulin deficiency. Although traditionally considered a disease of children and adolescents, type 1 diabetes resulting from autoimmune cell destruction can occur at any age. The concordance of type 1 diabetes in genetically identical twins is 40-60%, indicating a significant genetic component. The major genetic risk (40-50%) is conferred by HLA class II genes encoding HLA-DR and HLA-DQ (and possibly other genes with the HLA locus).

The first physiological abnormality that is detectable in affected subjects is loss of the first phase of glucose-stimulated insulin secretion. Prior to this, islet cell
autoantibodies can be detected in the serum (known autoantigens include insulin, glutamate decarboxylase and protein tyrosine phosphatase IA-2[ICA-512]. The initiating or triggering stimulus for the autoimmune process is not known, but most favour exposure to viruses (enterovirus, etc.) or other ubiquitous environmental agents.

Histological examinations of human pancreas during the prediabetic period and at presentation are quite limited, but animal models of type 1 diabetes show a T cell infiltrate with a predominance of CD8+ cells (insulitis). The cell destruction is cell mediated, and there is also evidence that infiltrating cells produce local inflammatory agents such as TNF-\(\alpha\), IFN-\(\gamma\), and IL-1, all of which can lead to \(\beta\) cell death. The \(\beta\) cell destruction occurs over a period of months to year. When >80% of the cells are destroyed, hyperglycemia ensues and the clinical diagnosis of type 1 diabetes is made (Von et al., 2007).

1.6 Pathogenesis of type 2 diabetes

The pathogenesis of type 2 diabetes mellitus is complex and the condition is best thought of as a heterogeneous syndrome of dysregulated glucose homeostasis associated with impaired insulin secretion and insulin action. Overweight or obesity is a common correlate of type 2 diabetes that occurs in ~ 80% of affected individuals. Increased lipid accumulation in depots in the abdomen, skeletal muscle cells and hepatocytes has been linked to some of the common impairments. For the vast majority of persons developing type 2 diabetes, there is no clear inciting incident, but rather the condition is thought to develop gradually over years with progression through identifiable prediabetic stages.

In fundamental terms, type 2 diabetes results when there is insufficient insulin action to maintain plasma glucose levels in the normal range. Insulin action is the composite effect of plasma insulin concentrations (determined by islet cell function) and insulin sensitivity of key target tissues (liver, skeletal muscle and adipose tissue). These sites of regulation are all impaired to variable extents in patients with type 2 diabetes (Figure 1.1).
The etiology of type 2 diabetes has a strong genetic component (Das and Elbein, 2006; Grant et al., 2009). It is a heritable condition with a relative 4-fold increased risk of disease for persons having a diabetic parent or sibling, increasing to 6-fold if both parents have type 2 diabetes. Consistent with this, the concordance rates of diabetes in monozygotic twins are 2 to 3-fold of those in dizygotic twins. Based on linkage analysis, candidate gene searches and genome-wide association studies, type 2 diabetes appears to be a complex multigenic condition, with many loci of susceptibility contributing to the ultimate phenotype.

Although more than 20 genetic loci with clear associations to type 2 diabetes have been identified through recent genome-wide association studies, the contribution of each is relatively small. The genetic locus with the largest relative risk is the transcription factor TCF7L2. Most of the genes currently associated with type 2 diabetes have a relevant connection to cell function with fewer linked to the action of insulin in target cells.
1.7 Goals of therapy for diabetes

The goals of therapy for diabetes are to alleviate the symptoms related to hyperglycemia (fatigue, polyuria, etc.) and to prevent or reduce the acute and chronic complications of diabetes. Accomplishment of these goals requires a multidisciplinary team (physicians, nurse educators, pharmacists) with expertise in pharmacology, nutrition and patient education. Central to the treatment plan is the patient who must actively participate in the care of his or her diabetes.

Glycemic control is assessed using both short-term (blood glucose self-monitoring) and long-term metrics (A1C, fructosamine). Using capillary blood glucose measurements, the patient assesses capillary blood glucose on a regular basis (fasting, before meals, or postprandially) and reports these values to the diabetes management team. A1C reflects glycemic control over the prior 3 months; glycosylated albumin (fructosamine) is a measure of glycemic control over the preceding 2 weeks.

Approaches to diabetes care are sometimes termed intensive insulin therapy, intensive glycemic control and tight control. The term comprehensive diabetes care is used to describe optimal therapy, which involves more than glucose management and includes aggressive treatment of abnormalities in blood pressure and lipids and detection and management of diabetes related complications.

Table 1.2 shows the ADA recommended treatment goals for comprehensive diabetes care, for glucose, blood pressure and lipids (Brunzell et al., 2008). Improved glycemic control reduces the complications when started relatively early in the course of both type 1 and type 2 diabetes, but very intensive glucose lowering (with A1c near 6.0) that not shown benefit in individuals with type 2 diabetes and atherosclerotic disease (Duckworth et al., 2009; Holman et al., 2008; Skyler et al., 2009).
Table 1.2: Goals of therapy in diabetes (ADA, 2010)

<table>
<thead>
<tr>
<th>Index</th>
<th>Goal $^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A. Glycemic control</strong> $^b$</td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td>$&lt;7.0%$ $^c$</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>3.9-7.2 mmol/L (70-130 mg/dL)</td>
</tr>
<tr>
<td>Peak Postprandial capillary plasma glucose</td>
<td>10.0 mmol/L ($&lt;180$ mg/dL) $^d$</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>$&lt;130/80$ mmHg</td>
</tr>
<tr>
<td><strong>B. Lipids</strong> $^e$</td>
<td></td>
</tr>
<tr>
<td>Low-density lipoprotein</td>
<td>$&lt;2.6$ mmol/L ($&lt;100$ mg/dL) $^f$</td>
</tr>
<tr>
<td>High-density lipoprotein</td>
<td>$&gt;1.1$ mmol/L ($&gt;40$ mg/dL) $^g$</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>$&lt;1.7$ mmol/L ($&lt;150$ mg/dL)</td>
</tr>
</tbody>
</table>

$^a$ As recommended by the ADA goals should be individualized for each patient. Goals may be different for certain patient populations.

$^b$ A1C is primary goal.

$^c$ While the ADA recommends an A1C $<7.0\%$ in general, it recommends that an appropriate goal for the individual patient based on age, duration of diabetes, life expectancy, other medical conditions, cardiovascular disease).

$^d$ One to two hours after beginning of a meal.

$^e$ In decreasing order of priority

$^f$ In individuals with coronary artery disease, an LDL $<1.8$ mmol (70 mg/dL) is the goal.

$^g$ For women, some suggest a goal that is 0.25 mmol/L (10 mg/dL) higher.
1.8 Insulin resistance

Insulin sensitivity is a quantifiable parameter that is measured as the amount of glucose cleared from the blood in response to a dose of insulin. The failure of normal amounts of insulin to elicit the expected response is referred to as insulin resistance. This is a relative term because there is inherent variability of insulin sensitivity among cells, tissues and individuals.

Insulin sensitivity is affected by many factors including age, body weight, physical activity levels, illness and medications. Furthermore, insulin sensitivity varies within individuals over time and across groups or populations of subjects, even among healthy adults. Thus, insulin resistance is a relative designation but has considerable pathological significance because persons with type 2 DM or glucose intolerance have reduced responses to insulin and can easily be distinguished from groups with normal glucose tolerance.

The major insulin-responsive tissues are skeletal muscle, adipose tissue and liver. Insulin resistance in muscle and fat is generally marked by a decrease in transport of glucose from the circulation. Hepatic insulin resistance generally refers to a blunted ability of insulin to suppress glucose production. Insulin resistance in adipocytes causes increased rates of lipolysis and release of fatty acids into the circulation, which can contribute to insulin resistance in liver and muscle, hepatic steatosis and dyslipidemia.

More generally the role of obesity in the etiology of type 2 diabetes is related to the insulin resistance in skeletal muscle and liver that comes with increased amounts of lipid storage, particularly in specific fat depots. The sensitivity of humans to the effects of insulin administration is inversely related to the amount of fat stored in the abdominal cavity; more visceral adiposity leads to more insulin resistance (Kahn, 2003). Similarly, intrahepatocyte or intramuscular fat, both commonly associated with obesity are strongly linked to insulin resistance. Intracellular lipid or its byproducts may have direct effects to impede insulin signaling (Savage et al., 2007).
1.9 Treatment of diabetes mellitus

Treatment of DM depends upon the type of diabetes. Insulin therapy is prescribed for IDDM while oral hypoglycemic agents such as sulphonyl ureas, biguanides, alpha-glucosidase inhibitors, thiazolidinediones and meglitinides are used in NIDDM. The present treatment of diabetes is focused on controlling and lowering blood glucose to a normal level. The mechanisms of both Western medicines and the Indian traditional medicines to lower blood glucose are,

- to stimulate β-cell of pancreatic islet to release insulin,
- to resist the hormones which rise blood glucose,
- to increase the number or rise the appetency and sensitivity of insulin receptor site to insulin,
- to decrease the leading-out of glycogen,
- to enhance the use of glucose in the tissue and organ,
- to clear away free radicals, resist lipid peroxidation and correct the metabolic disorder of lipid and protein and
- to improve microcirculation in the body.

Based on the above-mentioned mechanisms, the drugs clinically used to treat diabetes can be mainly divided into insulin, insulin-secretagogues, insulin sensitivity improvement factor, insulin-like growth factor, aldose reductase inhibitor, α-glucosidase inhibitors and protein glycation inhibitor, almost all of which are chemical and biochemical drugs and the effect of these drugs is only aimed to lower the level of blood glucose. Moreover, in most cases, side-effect such as hypoglycemia, lactic acid intoxication and gastrointestinal upset appear after patients take these medicines (Fauci et al., 2008).
Table 1.3: Comparison of agents used for treatment of diabetes

<table>
<thead>
<tr>
<th>Category</th>
<th>Mechanism of action</th>
<th>Examples</th>
<th>Agent-specific advantages</th>
<th>Agent-specific disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Hepatic glucose production</td>
<td>Metformin</td>
<td>Weight neutral, do not cause hypoglycemia, inexpensive</td>
<td>Diarrhea, nausea, lactic acidosis</td>
</tr>
<tr>
<td>Glucosidase inhibitors&lt;sup&gt;c&lt;/sup&gt;</td>
<td>GI glucose absorption</td>
<td>Acarbose, Miglitol</td>
<td>Reduce postprandial glycemia</td>
<td>GI flatulence, liver function tests</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 inhibitors&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Prolong endogenous GLP-1 action</td>
<td>Saxagliptin, Sitagliptin, Vildagliptin</td>
<td>Do not cause hypoglycemia</td>
<td></td>
</tr>
<tr>
<td>Insulin secretagogues-Sulfonylureas&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Insulin secretion</td>
<td>Glibenclamide Glimepiride</td>
<td>Inexpensive</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Insulin secretagogues-Non-sulfonylureas&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Insulin secretion</td>
<td>Repaglinide Nateglinide</td>
<td>Short onset of action, lower postprandial glucose</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td>Thiazolidinediones&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Insulin resistance, glucose utilization</td>
<td>Rosiglitazone, Pioglitazone</td>
<td>Lower insulin requirements</td>
<td>Peripheral edema, CHF, weight gain, fractures, macular edema. Rosiglitazone may increase risk of CV disease</td>
</tr>
<tr>
<td>Bile acid sequestrants&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Bind bile acids; mechanism of glucose-lowering not known</td>
<td>Colesevelam</td>
<td>Constipation, dyspepsia, abdominal pain, nausea, triglycerides, interfere with absorption of other drugs, intestinal obstruction</td>
<td></td>
</tr>
</tbody>
</table>

<sup>c</sup>Used for treatment of type 2 diabetes
1.9 Diabetes dyslipidemia

By the year 2025, there will be more than 300 million type 2 diabetes sufferers worldwide. This epidemic will be followed by a wave of cardiovascular disease. Diabetes is in fact a serious vascular disease with poor prognosis, and not a disease characterized by elevated blood glucose level. If adequate attention were paid to this, it would be much easier to relieve the burden of cardiovascular disease in type 2 diabetes (Marja, 2002).

Dyslipidemia has been defined as a total cholesterol, low-density lipoprotein cholesterol (LDL-c), or triglyceride level above the 90th percentile for the general population, or low high-density lipoprotein cholesterol (HDL-c) (Fredrickson, 1971). The dyslipidemia that is associated with type 2 DM, however, does not include an increased LDL-c level. In fact, the prevalence of high concentrations of LDL-c in patients with diabetes is similar to that of the general population. There is however a difference in the distribution of LDL particle sizes, as patients with diabetes have an increased number of small dense LDL particles compared with individuals in the general population (Carmena, 2005). Furthermore, patients with type 2 DM are 2 to 3 times more likely to have elevated triglyceride levels and reduced HDL-c levels than individuals in the general population. A simplified outline of the metabolic pathway of lipids in patients with diabetes is shown in Figure 1.2 (Izkhakov, 2003).

High-density lipoprotein cholesterol

The decrease in HDL-c levels typically observed in patients with type 2 DM is due to the increased catabolism rate of HDL particles. The hypertriglyceridemia that occurs in patients with type 2 DM results in an increased pool of triglyceride-rich lipoproteins, mainly very-low-density lipoproteins (VLDL) that drives the transfer of triglycerides from triglyceride-rich lipoproteins to HDL particles via the enzyme CETP. Lipid enriched HDL particles are more rapidly catabolized, resulting in the reduced plasma levels of HDL-c that is common in this patient population. Triglyceride-rich HDL particles are a good substrate for hepatic lipase, the activity of which results in smaller HDL particles (Verges, 2005).
Low-density lipoprotein cholesterol

The major physiologic role of LDL-C is to provide cholesterol for use in the repair of cellular membranes and for the synthesis of steroid hormones and vitamin D. Patients with type 2 DM usually exhibit normal levels of plasma LDL-C; however, significant changes in the metabolism of LDL-C occur (Figure 1.2). Specifically, the catabolism rate of LDL particles is reduced (possibly because of a reduction of the number of LDL receptors), as is the rate of LDL-C production. These changes result in a reduced turnover of LDL particles, along with an increased LDL-C plasma residence time that may promote cholesterol deposition in the arterial wall.

Furthermore, the hypertriglyceridemia that occurs in patients with type 2 DM may be responsible for the change in the size distribution of LDL particles. The increase in the levels of triglyceride-rich lipoproteins stimulates cholesteryl ester transfer protein (CETP) activity, which promotes the transfer of triglycerides to LDL particles, resulting in the formation of triglyceride rich LDL particles. The hepatic lipase enzyme, which is more active in patients with type 2 DM, converts triglyceride-rich LDL particles into small dense LDL particles (Izkhakov, 2003).
**Triglycerides**

The increase in plasma triglyceride levels observed in patients with type 2 DM is mainly due to an increase in the number of VLDL particles. There is also a reduction in the catabolism rate of VLDL particles as a result of the reduced activity of lipoprotein lipase. Lipoprotein lipase degrades the triglycerides within the VLDL particle. Qualitative abnormalities in the size distribution of VLDL particles have also been observed in patients with type 2 DM specifically; there are increased numbers of large triglyceride and cholesterol-enriched VLDL particles (VLDL1). Increased levels of free fatty acids can result in insulin resistance in muscle and liver tissue. Furthermore, resulting lipotoxicity can impair pancreatic β cell functions in patients with type 2 DM. The increase in plasma triglyceride levels observed in patients with type 2 DM is mainly due to an increase in the number of VLDL particles (Verges, 2005).

Diabetic dyslipidemia is likely to be one of many reasons for the accelerated macrovascular disease in diabetic patients. Nonetheless, treatment of lipid abnormalities has the potential to reduce cardiovascular events more than 50%, to rates that are seen in countries with lower cholesterol and less atherosclerotic burden. This leads to the expectation that treatment of elevated lipid levels will allow patients with diabetes to lead longer and healthier lives.

**1.10 Oxidative stress in diabetes**

Oxidative stress has been shown to be a hallmark of many diseases linked with metabolic or vascular disorders. Therefore, diabetes represents an ideal candidate for studying the consequences of oxidative stress and its treatment. Oxidative stress, an imbalance between the generation of reactive oxygen species and antioxidant defense capacity of the body, is closely associated with aging and a number of diseases including cancer, cardiovascular diseases, diabetes and diabetic complications. Indeed diabetes constitutes a multiple source of free radicals, starting very early in the disease process and worsening over the course of disease (Razieh, 2007).
Oxidative stress depicts the existence of products called free radicals (molecules possessing an unpaired electron) and reactive oxygen species (ROS), which are formed, in normal physiology but become deleterious when not being quenched by a cascade of antioxidant systems. This can result either from an overproduction of ROS or from the inactivation of the antioxidant system (AOS), thus shifting the oxidative stress/AOS balance in favour of stress. ROS oxidize various types of biomolecules, leading to cellular lesions by damaging DNA or stimulating apoptosis or cell death. Some ROS are considered more important than others, such as superoxide, hydroxyl radicals or peroxides. However not all oxygen-containing radicals have high oxidative potential (Wiernsperger, 2003).

Hyperglycemia generates oxidative stress (OS) by various mechanisms; excessive levels of glucose reaching the mitochondria lead to an overdrive of the electron transport chain, resulting in overproduction of superoxide anions normally scavenged by mitochondrial superoxide dismutase (SOD).

When the latter fails, OS develops. Recently it was proposed that this mechanism is responsible for the activation of all major pathways underlying the different components of vascular diabetic complications (glycation, PKC activation, and sorbitol pathway). The in vitro supplementation of SOD like drugs corrects most of these defects, supporting the importance of these mechanisms. It has also been proposed that uncoupling mitochondrial NOS by hyperglycemia would be involved. Another mechanism whereby high glucose can stimulate OS is the autoxidation of glucose in the presence of transition metals as well as the generation of ROS during the process of glycation. Indeed the development from Schiff base to Amadori to advanced glycation end products (AGEs) is accompanied by ROS-generating reactions at various steps. It has been proposed that carbonyl stress, rather than OS, involving both sugars and lipids would be the relevant source of OS in diabetes (Mustafa, 2002).

1.11 Mechanism of hyperglycemia-induced oxidative stress

In physiologic concentrations, endogenous reactive oxygen species (ROS) help to maintain homeostasis. However, when ROS accumulate in excess for prolonged periods of time, they cause chronic oxidative stress and adverse effects. This is
particularly relevant and dangerous for the islet, which is among those tissues that have the lowest levels of intrinsic antioxidant defenses. Multiple biochemical pathways and mechanisms of action have been implicated in the deleterious effects of chronic hyperglycemia and oxidative stress on the function of vascular, retinal and renal tissues. Considerably less work has been performed using islet tissue. At least six pathways are emphasized in the literature as being major contributors of ROS.

- Glyceraldehyde autoxidation
- Protein kinase C (PKC) activation
- Glycation
- Sorbitol metabolism
- Hexosamine pathway
- Oxidative phosphorylation

Figure 1.3: Six biochemical pathways along which glucose metabolism can form ROS

Under physiologic conditions, glucose primarily undergoes glycolysis and oxidative phosphorylation. Under pathologic conditions of hyperglycemia, excessive glucose levels can swamp the glycolytic process and inhibit glyceraldehyde catabolism, which cause glucose, fructose-1, 6-bisphosphate, and glyceraldehyde-3-P to be shunted to other pathways (Robertson, 2006).
1.12 Multiple therapeutic approaches of phytochemicals

Phytochemical identified from traditional medicinal plants are presenting an exciting opportunity for the development of new types of therapeutics. This has accelerated the global efforts to harness and harvest those medicinal plants that bear substantial amount of potential phytochemicals showing multiple beneficial effects in combating diabetes and diabetes related complication. As the disease is progressing unabated, there is an urgent need, therefore identifying indigenous natural resources and to procure them, and study in detail, their potential on different newly identified target in order to develop them as new therapeutics (Ashok, 2002).

Today, synthetic drugs and insulin are mainly used for treating diabetes. However, these drugs come with considerable side effects, such as hypoglycemia, drug-resistance, dropsy and weight gain. In contrast, hundreds of traditional folk medicines have demonstrated their potential for the treatment of diabetes with less tolerability and side effects. Thus, there is an increasing need to search for more natural antidiabetic agents from the traditional medicine

Recently, the search for appropriate hypoglycemic agents has been focused on plants used in traditional medicine partly because of leads provided by traditional medicine, to natural products that may be in better for treatments than currently used drugs.

The present research work is therefore, designed to investigate two indigenous plants, namely *Mukia maderspatana* Linn and *Raphanus sativus* Linn for diabetes and diabetes associated dyslipidemia.