CHAPTER-2

REVIEW OF LITERATURE
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“Diabetes mellitus (DM) is a metabolic disorder that occurs due to multiple etiologies. It is characterized by hyperglycemia in which there is disturbance in carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both” (WHO, 1999. http://www.who.int/diabetes/action_online/basics/en/).

Two basic pathogenic processes are seen to be involved in the development of DM that is (i) Autoimmune destruction of $\beta$-cells of pancreas (ii) Deficient insulin secretion or resistance.

2.1 HISTORY OF DIABETES MELLITUS

People of Egypt and Greece had the knowledge of DM since ancient times. The term "diabetes" is derived from word 'Diab' (meaning to pass through, cycle of heavy thirst and frequent urination) (Singh, 2011).

"Diabetes" (to pass through) was first coined by Araetus of cappodocia (81-133AD) and the word mellitus was added by Thomas Wills (Britain) in 1675 (Ahmed, 2002). Sushruta, Araetus and Thomas Wills were early pioneers, who attempted to treat diabetes. From $5^{th}-6^{th}$ century AD, Sushruta and Charka, two renowned Indian physicians first reported a sweet tasting substance in the urine of the patients of DM with polyuria, strongly attracting ants and called this disease Madhumeha (Pickup and Williams, 2003).

The important facts about diabetes were discovered in nineteenth century when biochemistry and biological sciences developed. Claude Bernard (1813-1878) discovered that pancreatic secretions control glucose level. William Peters (1785-1850), who described diabetic coma, also proved the presence of ketones in urine of diabetic patients (Zajac et al., 2010).

2.2 TYPES OF DIABETES MELLITUS

There are two main types of diabetes:

- Type I Diabetes Mellitus (T1 DM) or Insulin Dependent Diabetes Mellitus (IDDM) seen in childhood and adolescence.

Other categories of diabetes are gestational diabetes which develops during pregnancy and other causes (genetic syndromes, acquired processes like pancreatitis, exposure to certain drugs and unknown cause’s fibrocalculous pancreopathy (malnutrition related diabetes mellitus) (WHO, http://www.staff.ncl.ac.uk.philip.home/who_dmc.htm# Authors).

2.2.1 Type I Diabetes Mellitus

Type I DM is a condition in which β-cells of pancreas are destroyed and leads to absolute insulin deficiency (Ozougwu et al, 2013).

Two types of type 1 diabetes are identified type 1A occurs due to autoimmune attack of pancreatic cells by T lymphocytes and type 1B is less frequent, has no known cause, found in the people of Asian and African descent who have varying degree of Insulin deficiency and sporadic episodes of ketoacidosis (Daneman, 2006).

Type I DM can appear at any age but usually develops in children and adolescents. Mutation in genes as well as environmental factors are responsible for type I DM (WHO, www.who.int/diabetes/action_online/basics/en). Mutations on HLA-DQ and DR, chromosome 6, Insulin gene on chromosome 11 and cytotoxic T-lymphocyte antigen gene on chromosome 2 are observed to be associated with the development of this type of DM (Lenmark, 1999). Patients of Type I DM require lifelong injections of Insulin to manage and show severe symptoms like coma, ketoacidosis and are at the high risk of microvascular and macrovascular complications (WHO, http://www.who.int/diabetes/action_online/basics/en/index.html).

2.2.2 Type 2 Diabetes Mellitus

Type 2 DM is characterized by an high glucose level, as a result of either insulin resistance and/or insulin deficiency. This is the most prevalent type of DM
since 90% patients of DM are of this category (Hassan, 2013). Patients of type 2 diabetes do not require insulin doses to survive. Patients remain undiagnosed for many years because hyperglycemia is often not very high to cause overt symptoms of DM (Mooy et al., 1995), but patients are at risk of development long term macrovascular and microvascular complications (Harris, 1993).

Type 2 DM has heterogeneous etiologies, caused by genetic and some environmental factors result defects in insulin secretion or insulin action. (Kuhlmaan and Puls, 1996).

2.2.3 Gestational Diabetes Mellitus


2.3 PREVALENCE OF DIABETES MELLITUS

Diabetes mellitus is the most common chronic degenerative disease across the world and the number of diabetic patients is continuously increasing. In 2011, 366 million people had diabetes in the world. By the year 2030 it is estimated that 552 million people will be affected by this disease (Whiting et al., 2011).

Earlier DM was considered a disorder of elderly or affluent but in past 30-40 years the status of diabetes has changed to one of the major causes of morbidity and mortality and affecting much younger people of all continents (Wild et al., 2004). 80% of patients of DM are living in low and middle income countries. The greatest numbers of people with diabetes are 40 and 59 years of age and 50% (183 million)
are undiagnosed. In 2011, 4.6 million deaths occurred due to diabetes in world. (IDF, http://www.idf.org/diabetestats/6e/the global burden). The major reason of the rise of diabetes may be due to the recent increase in obesity. Increased urbanization, access large quantities of food, increased mechanization are the environmental factors responsible for obesity (Huizinga and Rothman, 2006).

The number of adults with diabetes worldwide is estimated to increase by 122% from 135 million in 1995 to 300 million in 2025. In developed countries, it will be a 42% increase but in developing countries this figure is going to be 170% (King et al., 1998). Epidemic diabetes is imposing a double burden on world's poorest countries (http://www.who.int/mediacentre/news/releases/2003/pr86/en). The greatest increase in diabetes is expected in Middle East crescent, Sub Saharan Africa and India. In developing countries most of the people with diabetes are in the 45-61 year range (King et al., 1998).

2.3.1 Diabetes in India

In 2013, 65.1 million people have DM in the country. The crude prevalence rate of diabetes is about 9% in the urban areas of India. DM is affecting Indians at much younger age. It means more chances of long term complications (GDC, http://www.diabetes.co.uk/global_diabetes/diabetes_in_india.html). Genetic susceptibility for diabetes has been found in Asian population which interacts with modern environmental factors like high fat diet, low physical activity to cause the disease with heavy morbidity and mortality. Indians are metabolically obese with normal BMI, less muscle mass, high percent body fat, which make them more susceptible to this disease (Ramchandran et al., 2012).

2.4 PATHOGENESIS OF TYPE 2 DIABETES MELLITUS

T2 DM is the result of a combination of genetic factors related to impaired insulin secretion and resistance as well as environmental factors (KAKU, 2010). Type2 DM progresses from normal glucose tolerance to impaired glucose tolerance (IGT) and then to the overt form (Gastadelli et al., 2004). Type 2 diabetic subjects have disturbances in glucose homeostasis due to impaired insulin secretion or insulin resistance in muscles, liver and adipocytes and abnormalities in glucose
uptake (DeFrenzo, 2004). Type DM is the result of a complex interaction of processes between pancreatic beta cells’ function, glucose uptake by the muscles, secretion of multiple cytokines, hormones like molecules from adipocytes, glucose production by liver and central nervous system (Das and Elbein, 2006).

2.4.1 Genetic Factors Responsible for T2 Diabetes Mellitus

Multiple genes are found to be involved in the development of T2 DM, 27 genes are identified to be responsible for the susceptibility and opon mutation can make the people T2DM patients (Spellman, 2010).

2.4.2 Environmental Factors Responsible for T2 Diabetes Mellitus

Aging, obesity central obesity, insufficient energy consumption, overeating, especially of simple sugars, lack of exercise are some of the factors responsible for the development of T2 DM (Kaku, 2010).

2.4.2.1 Obesity and T2 Diabetes Mellitus

Obesity, particularly abdominal obesity is highly correlated with the diabetes. The possible mechanisms that link obesity to T2 DM are:

(i) Plasma level of free fatty acids (FFA’s) increases in obesity and there is a competition between increased FFA and glucose for oxidation in peripheral cells.

(ii) Production of adipokines and cytokines including tumor necrosis factor $\alpha$ (TNF$\alpha$), resistin and increase in the level of retinol binding protein 4 (RBP4) that cause insulin resistance. But the level of adiponectin decreases (Leong and Wilding, 1999).

(iii) Ectopic fat storage in muscles and liver.

(iv) Decreased mitochondrial functions and high oxidative stress (Quatanani and Lazar, 2007).

In obese people adipose tissue releases increased amount of free fatty acids, glycerol, hormones, inflammatory cytokines responsible for Insulin resistance, which cause $\beta$-cell dysfunction and inadequate insulin secretion owing to decreased
efficiency of liver and muscle glucose uptake Elevated glucose is cytotoxic for β-cell and a vicious cycle arises (Kahn et al., 2006).

Resistin, a cytokine, chiefly derived from the abdominal adipose tissue is also responsible for insulin resistance glucose intolerance and type2 diabetes (McTernan et al., 2002).

2.4.2.2 Role of Diet in the Pathogenesis of T2 Diabetes Mellitus

Diets high in saturated fat predispose people to weight gain, insulin resistance and hyperinsulinemia (Arslanian et al., 2000).

2.5 SYMPTOMS AND COMPLICATIONS OF DIABETES MELLITUS

The overt and frequent symptoms of type I diabetes are polyphagia, polydipsea and Polyuria, ketoacidosis and hypoglycemic episodes. In Type 2 DM, patient is asymptomatic may with polyuria, polydypsia, weakness, loss of body weight. Long term complications of DM are atherosclerosis, nephropathy, neuropathy, retinopathy and infections (Reema et al., 1995). Both microvascular (neuropathy, nephropathy, retinopathy) and macrovascular (cardiovascular diseases) complications are the long term effects of hyperglycemia (Amed et al., 2010). Factors responsible for vascular complications in T2DM are hyperglycemia, insulin resistance, advance glycation end products (AGE’s) accumulations, impaired vasodilatory response due to NO inhibition and chronic inflammation (Todd, 2008).

2.5.1 Pathogenesis of Diabetes Related Problems

(i) Polyol pathway: In the condition of hyperglycemia, enzyme aldose reductase reduces the glucose into sorbitol. This enzyme requires NADPH. NADPH is also a cofactor for regeneration of reduced glutathione (antioxidant). Hence polyol pathway increases cellular oxidative stress responsible for diabetes related complications (Lorenzi, 2007).

(ii) Hyperglycemia increases the production AGE’s responsible for the damage of endothelial cells of blood vessels (Brownlee, 2005).

(iii) Hyperglycemia increases the production of protein kinases responsible for vasoconstriction. Consistent hyperglycemia affects heart and blood vessels
eyes, kidneys, nerves and teeth. People with diabetes have high risk for developing infections (Rahman et al., 2007).

(iv) **Oxidative Stress and Diabetes:** There is a close association between hyperglycemia, oxidative stress and diabetic complications. High blood glucose level increases the production of reactive oxygen spices (free radicals) in the mitochondria which oxidizes cellular DNA, protein and lipids of the body (Piconi et al., 2005, Johansen et al., 2005).

Free radicals are also produced by NADP oxidase, xanthine oxidase uncoupling of lipoxyxenasates, cytochrome 450, monoxygenase and glucose autooxidation (Niedowicz and Daleke, 2005). Glucose stimulated Insulin secretion (GSIS) mechanism also enhances the ROS production in pancreatic β-cell and is responsible for further β-cell dysfunction and apoptosis (Chang and Chung, 2010).

### 2.5.2 Diabetes and Cardiovascular Diseases

Diabetes is the strong risk factor for cardiovascular disease (CVD). Correlation between diabetes and CVD is complex and multifactorial (Dokken, 2008). About 65% of the people with diabetes die from heart disease and stroke. (National Diabetes Education Program (NDUP), http://www.nedp.nih.gov/media/cvd_factsheet.pdf) Myocardial ischemia due to coronary atherosclerosis is a common problem in diabetic patients (Wingard et al., 1993). Hyperglycemia is also responsible for low level of nitric oxide (NO) in endothelial cells NO cause vasodilation and protect the blood vessels from thrombosis. Conversely, pro inflammatory transcription nuclear factor kappa B (Nf – kB) enhances monocyte adhesion (Creager et al., 2003). Dyslipidemia is the common feature and major risk factor for CVD in diabetes. In diabetes, concentration of total triglycerides (TG) and low density lipoproteins (LDL) cholesterol becomes high and level of HDL cholesterol decreases due to insulin resistance (Moordian, 2009).

In Insulin resistance fat cells release free fatty acids which promote the triglyceride and VLDL production in the liver and thus cause hepatic fat accumulation (Frayan, 2001). In diabetes, LDL particles are small and dense and more pathogenic than normal LDL's because they can easily penetrate the vessels
and more prone to oxidation (Betsy, 2008). LDL Particles are glycated in diabetics. Glycated LDL have long half life and behave like oxidized LDL and promote platelet aggregation (Napolic et al. 1997).

2.5.3 Microvascular Diseases in Diabetes Mellitus:

After the discovery of insulin, deaths due to acute complications have dramatically decreased but microvascular complications like retinopathy, nephropathy and neuropathy have now been the major problem in diabetic patients (Ohkubo et al., 1995). Diabetic retinopathy, nephropathy and neuropathy are leading cause of blindness, end stage renal disease (ESRD) and amputations (ADA, http://www.diabetes.org/diabetes_basis). Four main mechanisms have been identified in glucose mediated vascular damage; polyol pathway, increased intracellular formation of advanced glycation end products (AGE’s), activation of protein kinase C and hexosamine pathway. Each of these pathway cause high production of super oxidations in the vascular cells. (Brownlee, 2001).

2.5.3.1 Diabetic Retinopathy (DR)

Progressive damage of retina due to hyperglycemia is called diabetic retinopathy. Diabetic retinopathy occurs due to the damage of blood vessels that nourish the retina by the sugar. (ADA, http://www.diabetes.org/diabetes_basis). Diabetic retinopathy is the most frequent cause of blindness among diabetics. During the first two decades of disease nearly all patients of type1 and more than 60% patients of type2 diabetes have retinopathy. (Fong et al., 2004). Diabetic retinopathy involves the anatomical changes in retinal vessels. Sorbitol accumulation in the retinal vessels due to polyol pathway increases the osmotic damage, fructose produced by polyol pathway degraded in AGE’s (Tarr et al., 2013). Diabetic retinopathy progresses from mild non proliferative abnormalities characterized by vascular closure to proliferative diabetic retinopathy (PDR) characterized by the growth of new blood vessels on retina and vitreous (aneurism) (Opara,2006). New blood vessels of PDR may bleed (Estacio et al., 2000).

Polyol pathway also increases the thickness of retinal capillary basement membrane and adhesion of leucocytes to endothelial cells. (Roy and Lorenizi, 1996).
Endothelial cell damage due to various factors disturbs the blood retinal barrier and increases vascular permeability resulting in extracellular fluid accumulation in macula and aneurism (Ciulla, 2003).

2.5.3.2 Diabetic Nephropathy (DN)

Diabetic nephropathy is the most common cause of end stage renal disease (ESRD). Between 20% to 40% of patients of diabetes develop nephropathy (ADA, http://www.diabetes.org/diabetes_basis).

DN is characterized by albuminuria and reduced GFR. (Bakris, 2011). Diabetic nephropathy has many stages of development. Functional changes occur in glomerulus like glomerular hyperfiltration and hyperfusion and subsequent thickening of glomerular basement membrane, glomerular hypertrophy (Dronavalli et al., 2008). Hyperglycemia is responsible for production and activation of abnormal protein kinase C (PKC) and advanced glycation end products. (Schena and Gesualdo, 2005). Tranforming growth factor β, a platelet derived growth factor has also been found to responsible for the diabetic nephropathy in diabetics (Parchwani and Upadhyah, 2012). AGE's are responsible for inflammation and accumulation of monocytes (Rohilla et al., 2011). Mitochondrial derived ROS are also responsible for apoptosis and renal injury (Brownlee, 2007).

2.5.3.3 Diabetic Neuropathy-

About 50% of the diabetics have some extent of nerve damage (ADA, http://www.diabetes.org/living with diabetes/complication/neuropathy). The diabetic neuropathies are heterogeneous affecting various parts of the nervous system. Most common are chronic sensor metadistal symetric polyneuropathy (DPN) and autnomic neuropathies. (Boulton et al.,2004, 2005). Several possible causes have been found responsible for DN, ie altered metabolism of polyol, of lipid and amino acids, vascular insufficiency, increased superoxide induced free radical formation, impaired axonal transport or reduced neutrophism (Messmer et al., 2010, Feldman et al., 1997) .Hyperglycemic neurons have high oxidative stress which damage the DNA and membranes of mitochondria and impair the cell functions and cause
neuron degeneration (Said, 2007). Hyperglycemia increases the production of nitrogen reactive species which in turn increase the severity of symptoms.

2.6 MANAGEMENT OF DIABETES MELLITUS

There are three major components of treatment of diabetes –

1. Insulin treatment is used to lower blood glucose level where absolute deficiency of insulin is there in the body (Alwan, 1994).
2. Oral hypoglycemic therapy
3. Lifestyle modification.

Minimization of diabetes related complications and maximization of quality of life is also important in the management or treatment of DM. (Imam, 2012).

2.6.1 Oral Hypoglycemic Agents

Six different classes of hypoglycemic agents are available for the treatment of type 2 diabetes. Sulphonylureas, biguanides, alpha glycosidase inhibitors, glinides, thiazolidinediones and dipeptidyl petipdase-4 inhibitors, (Takamoto and Kadowaki, 2011). These drugs act in two ways increase the peripheral glucose uptake or increase exocytosis of insulin in pancreatic $\beta$ cells.

But these drugs are not free from side effects like lactic acidosis, myocardial infarction, congestive heart failure, anemia, weight gain increased risk of fractures, renal failure and hypoglycemia. (Hamnvic and McMahon, 2009). Control of hyperglycemia and maintenance of Hb AIC value <6 percent help in the prevention of acute and long term complications of diabetes (Stratton et al., 2000).

2.6.2 Life Style Intervention:

Body weight loss, intake of fat <30% energy, intake of saturated fats <10% energy increase of dietary fibers≥ 15g/1000 kcal and increase in physical activity help to control the long term complications of type 2 diabetes. (Tuomilehto et al.,2011, Knowler et al.,2002).
2.7 TRADITIONAL MEDICINES FOR THE TREATMENT OF DIABETES

From thousands of years spices, herbs and indigenous plants have been used for treating diabetes in Egypt, India and China (Lasker et al., 2010). Traditional medicines derived from medicinal plants are used by about 60% of world’s population (Modak et al., 2007). Ayurveda is the Indian medical systems of traditional healing, known for nearly 5000 years (Morgan, 2002). In modern world 70-95% of the population relies on herbal medicines for primary treatment of different diseases. In fact, 80% of the Indian population is dependent on phytotherapy (Chawla et al., 2013). Phytotherapy is defined as the utilization of different plant parts for the treatment of diseases. Drugs prepared from plants are called herbal drugs. In the past few years, herbal medicines are gaining popularity in developed and developing countries due to their low cost and very few side effects. (Grover et al., 2002).

Since free radicals and AGE’s, along with hyperglycemia, are the major causative factors in the pathogenesis of diabetes and related to long term diabetic complications (Oberlay, 1988) (Brownlee, 1995).

As diabetes is a multifactorial disease and thus calls for multifactorial treatment. Efforts are on to find suitable antidiabetic and antioxidant therapy for diabetes (Modak et al., 2007). Neglect of holistic care by modern medicine is one of important reason behind the increasing support for alternative care and phytomedicines (Eisenberg et al., 1993). About 800 plants have been found to show antidiabetic potential. Plants contain different bioactive compounds like alkaloids, glycosides, galactomannans, gum, polysaccharides, peptidoglycans, hypoglycans, guani-dine, steroids, carbohydrates glycopetides, terpenoids, amino acids and inorganic ions (Patil et al., 2011). Antidiabetic or hypoglycemic effect of Acacia arabica, Aegle marmelos, Allium stativum, Aloe vera, Azadirachta indica, Caesalpinia bonducella, Coccinia indica, Eugenia jambolana, Momordica charantia has been explored and proved. (Modak, 2007)
2.7.1 *Cinnamomum verum* (cinnamon)


*Cinnamomum verum* grown in Srilanka and India. It is obtained by drying central part of bark and is marketed as quills or powder. (Lee and Balick, 2005). *Cinnamomum verum* is different from *Cinnamomum cassia* (Chinese cinnamon). Both bark and leaves are aromatic, plant grows around 7-10 mt. height and bears yellowish white flowers and dark purple berries (Araar, 2009). In Ayurvedic system, cinnamon bark is used as flu preventive as well as for indigestion and flatulence control. It is also used for the treatment of pain associated with amenorhea. (Asolkar et al., 2004). The bioactive compounds found in cinnamon are cinnamaldehyde, gum, tannins, mannitol, coumarins, aldehydes, eugenol, pinene (www.hillgreen.com/pdf/cinnamon.verum).

### 2.7.1.1 Antidiabetic Activity of Cinnamon

Interest in cinnamon as a potentially useful treatment for the type 2 diabetes mellitus began almost 20 years ago. An unidentified factor isolated from cinnamon has been termed as insulin potentiating factor (IPF). This IPF may be involved in the alleviation of the signs and symptoms of diabetes and other diseases related to insulin resistance (Khan et al., 1990).

The aqueous extract of cinnamon, potentiated insulin activity more than 20 folds higher than any other compounds tested at comparable dilutions in vitro in epididymal cells. Cinnamon extract found to improve insulin receptor functions by activating the enzyme that causes insulin to bind to cells (insulin receptor kinase) and inhibiting the enzyme that block this process (insulin-recepto phosphatase) leading to maximal phosphorylatin of insulin receptor, which is associated with increase insulin sensitivity (Imparl-Radosevich et al., 1998). The unidentified factor present in cinnamon as methyl hydroxy chalcone polymer (MHCP) has been characterized and investigated for its ability to function as insulin mimetic in 3T3-L1 adipocytes. (Jarvill-Taylor et al., 2001) (Gruenwald et al., 2010). The study found that MHCP stimulated the auto
phosphorylation of Insulin receptor (IR), unregulated glucose uptake, glycogen synthesis and glycogen synthase (GS) activity in 3T3-L1 adipocytes and down regulated glycogen synthase Kinase- 3 β (GSK-3 β) activity. Glycogen synthesis stimulation is through class I Phosphatidylinositol (PI) 3-Kinase dependent pathway. These events are all characteristic of 3T3-L1 adipocyte response to insulin. Anderson et al. (2004) demonstrated that in vitro insulin-potentiating activity found in cinnamon (Cinnamomum cassia) was present in the aqueous fraction. They suggested that the major active components in cinnamon are water soluble doubly linked porocyanidin type-A polymers.

Compounds found to be responsible for in vitro insulin enhancing activity in epididymal fat cells were polyphenols (Anderson et al., 2004). Cinnamon reported to reduce the blood glucose level in non insulin dependent diabetics. Experimental studies have proved the potential of cinnamaldehyde as an anti diabetic agent. Cinnamaldehyde inhibits aldolase reductase, a key enzyme involved in the 'polyol' pathway. This enzyme catalyses the conversion of glucose to sorbitol and responsible for chronic complications of diabetes such as cataract, neuropathy and retinopathy (Lee, 2002). In addition to improving cellular glucose metabolism cinnamon may also provide additional benefits for the diabetic patients through its antioxidant activity.

2.7.1.2 Antioxidant Activity of Cinnamon

Antioxidants are essential to human body to neutralize free ROS. In vitro antioxidant activity of methanol and acetone extract of cinnamon was checked. DPPH, ABTS and hydroxyl radical scavanging properties of both extracts were found. Phenolic compounds such as hyroxy-cinnamaldehyde and hydroxyl-cinnamicacid present in the cinnamon extract act as scavengers of peroxide radicals and prevent oxidative damage (Rani et al., 2010) Antioxidative activity of cinnamtannin B1 isolated from Cinnamomum zeylanium was checked. Cinnamtannin exhibited anti oxidant activity. Specific antioxidants and phytochemicals that have been identified in cinnamon include epicatechin, camphere, eugenol, gamma-terpiene, phenol, salicylic acid and tannins (Duke, 2013).
2.7.1.3 Studies on the Antidiabetic effects of Cinnamon

A human study conducted by Anderson et al. (2004) in which three groups of type 2 diabetic subjects were supplemented with 1,3 and 6 g. cinnamon (*Cinnamomum cassia*) per day for 40 days and there were significant decrease in fasting blood serum glucose (18-29%) triglycerides (23-30%) total cholesterol (12-26%) LDL cholesterol (7-27%).

Advanced glycation end products (AGEs) are the major pathogenic factors in diabetic complications and other related health disorders, such as atherosclerosis. Effect of cinnamon bark proanthocyanidins, catechin, epicatechin and procyanidin B2 on the formation of specific AGE was also analysed. These compounds exerted inhibitory effects on the formation of AGE's. Proantho-cyanidins exerted protective effects on glucose consumption in 3T3-L1 fat cells (Peng et al., 2010).

The effect of cinnamon doses on blood serum glucose was tested in type 2 diabetic subjects. For 60 days, 1 g, 3 g and 6g cinnamon doses/day, significantly reduced the mean fasting serum glucose levels. (Safdar et al., 2004)

1 g, 3g, 6g cinnamon doses/day significantly reduced mean serum TG and cholesterol of diabetic subjects. Cinnamon doses significantly reduced serum LDL also (khan et al., 2003).

Regarding the role of cinnamon (*Cinnamomum zeylanicum*) in reducing oxidative stress was checked in healthy subjects. Cinnamon (100mg) once daily was given to 18 healthy subjects for 10 days. Lipid peroxidation level (LPO), total antioxidant power (TAP) and total thiol molecules (TTM) were measured. Cinnamon significantly reduced LPO (Ranjbar et al., 2007).

The effect of cinnamon on plasma glucose concentration and regulation of 6-phosphofructo-1-Kinase (PFK-1) in the liver and small intestine of streptozotocin induced diabetic rats was investigated. Concentration of glucose, free and esterified cholesterol, triacylglycerol was estimated. These were found to be significantly decreased. The effect of cinnamon was also seen on type I diabetes. Cinnamon was
supplemented for 4 weeks and mean fasting glucose and lipid levels were significantly reduced (Jamal, 2009).

2.7.2 Gymnema sylvestre (Gurmar)

Gymnema sylvestre is the herb native to the tropical forests of Southern and Central India and Sri Lanka. Other names Sanskrit: Meshashringi, madhu shringi, Hindi: Gurmar, G. sylvestre is a slow growing perennial, medicinal woody climber G. sylvestre is a large, more or less pubescent, woody climber. (Kanetkar et al., 2007). Gymnema sylvestre's botanical classification is kingdom – plante, order – gentianales, family – asclepiadaceae, Genus – Gymnema, Species – G. sylvestre. It is a strong antidiabetic plant and used in folk, ayurvedic and homeopathic systems of medicine. It possesses antimicrobial, antihypercholesterolemic, hepato protective and sweet suppressing activities. G. sylvestre leaves contain triterpene, saponins of oleanane and dammarene classes. Oleanane saponines are gymnemic acids and gymnema saponins, while dammarene saponins are gymnemasides (Saneja et al., 2010).

Besides this, other plant constituents are flavones, anthraquinones, hentriocotane, pentatriacotane, α and β chlorophylls, phytin, resin, d-quercitol, tartaric acid, formic acid, butyric acid, lupeol, β-amyrinrelated glycosides and stigma sterols. Leaves yield acidic glycosides and atherosquinoses and their derivatives (Dateo and Long, 1973). Gymnemic acids have antidiabetic, antisweetner and antiinflammatory activities. The antidiabetic array of molecules has been indentified as a group of closely related gymnemic acids. (Liu et al., 1992).

2.7.2.1 Antidiabetic Activity of Gymnema sylvestre

G. sylvestre formulations have also been found reduce obesity. This is thought to be because of gymnemic acids to delay the glucose absorption in the blood. The atomic arrangement of gymnemic acid is similar to that of glucose molecules present in the food, thereby curbing the sugar craving. Gymnemic acid molecules fill the receptors in the absorptive external layers of intestine thereby preventing the glucose molecules’ absorption by intestine, which results in low blood glucose level (Sahu et al., 1996). Gymnema sylvestre leaves have been proved
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to cause hypoglycemia and is therefore used in herbal medicines to help to treat adult onset diabetes mellitus (type-2). Gymnema leaf extract has been found to stimulate pancreas and increase insulin release (Kanetkar et al., 2004). Compounds of *G. sylvestre* have also been found to increase fecal excretion of cholesterol (Persaud et al., 1999).

Gymnema leaf extract components gymnemic acid and gur-marin have been found to suppress the activity of the taste buds on tongue to taste sweet and bitter. By inhibiting the sweet sensation *G. sylvestre* limits the intake of sweet food and this activity may be partially responsible for it antidiabetic effect (Nakamura et al., 1999).

The possible mechanisms by which *G. sylvestre* cause its antidiabetic effects are- Increases the excretion of insulin, enhances regeneration of islet cells and increases utilization of glucose. It also has observed to increase the activities of enzymes responsible for utilization of glucose by insulin mediated pathways, an increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase. *G. sylvestre* also found to be effective in the inhibition of glucose absorption from intestine. (Kanetkar et al. 2007). The leaves are also have been noted to lower serum cholesterol and triglycerides.

2.7.2.2 Studies on Antidiabetic Effect *Gymnema sylvestre*

Extracts of *Gynernema sylvestre* (GS) have been used for the treatment of T2DM in India for centuries. Oral administration of 1g/day extract for 60 days induced significant increase in circulating insulin and c-peptide. Which were associated with significant reductions in fasting and postprandial blood glucose (A1-Romaiyan et al., 2010). In patients, who were supplemented *G. sylvestre* leaves extract for 90 days GS supplementation reduced per preprandial plasma glucose concentration by 11% and postprandial plasma glucose concentrations by 13% and supplement action lowered HbA1c from 8.8% to 8.2% (0.6%) (Joffe and Freed, 2001). In a controlled study, average fasting glucose and HbA1c levels decreased significantly when 400mg/day *G. sylvestre* extract was supplemented to type1 DM patients for 6- 30 months. A significant decrease in the requirement of insulin was
also observed. The average fasting blood glucose decreased from 232 mg/dl to 152 mg/dl in *G. sylvestre* supplemented group (Shanmugasundram et al., 1990).

Baskaran et al. (1990) administered 400 mg Gymnema extract daily to 22 type2 diabetic subjects for 18-20 months. This group exhibited a significant decrease in average blood sugar and HbA1c level and an increase in pancreatic release of insulin.

*Gymnemna sylvestre* helps to reduce body weight loss through its ability to reduce cravings for sweet and control of blood sugar levels. A standardized *G. sylvestre* extraction combination with niacin bound chromium and hydroxycitric acid has been evaluated for antiobesity activity by monitoring changes in body weight, body mass Index (BMI) appetite, lipid profiles, serum lipid and excretion of urinary fat metabolites. The study showed that combination of *Gymnema sylvestre* extract and hydroxycitric acid, niacin bound chromium can serve as an effective and safe weight loss formula that can facilitate a reduction in excess body weight and BMI while promoting healthy blood lipid levels (Preuss et al., 2004).

The administration of leaf extracts of GS to hyperlipidemic rats for two weeks have been found to show reduction in elevated serum triglycerides (TG) total cholesterol (TC) very low density lipoprotein (VLDL) and LDL cholesterol (Bishayee, 1994).

**2.7.3 Murraya koenigii (The curry tree)**

*Murraya koenigii* spreng. also called 'Cury patta' is native to South East Asia and Australia. It grows wild and found almost throughout India up to height of 1500 to 1655m. If abundtly occurs along outer Himalyas, Assam, Chittgor, Andaman Islands, Maharatra, Tamilnadu, Andhra Pradesh and Forests of western Ghats in Karnataka. The botanical classification of *Murraya koenigii* is, kingdom- Plante, class- Eudicots, order- Sapindales, family- Rutaceae, genus- Murraya, species- *M. koenigii*. The plant has been reported to possess anti-dermatophytic (Vaijayanthimala et al., 2004), immunomodulator (Saha et al., 2004), hepato protective (Gurgune et al., 2003) antidiabetic (Yadav et al., 2002), antioxidant (Patel et al., 1979) properties.
The bark of *M. koenigii* is dark brown and creamish brown in colour and aromatic in odor. Total ash is around 10.15%, acid insoluble ash – 2.8%, water soluble ash 3.65% Moisture content 9.42% foaming index is 111.1 Phytochemicals present in MK bark are alkaloids, glycosides, saponins, flavonoids, coumarin (Kaur et al., 2011).

Mahanimbine, a chemical constituent of *M.koenigii* was isolated from the ether extract of direct plant bark and tested for its antidiabetic effect. The possible mechanism by which mahanimbine decreases blood sugar level may be by potentiating insulin effect either by increasing the pancreatic secretion of insulin from beta cells of islets of langerhans or by increasing the periphral glucose update. Mahanimbine showed appriciable alpha amylase inhibitory effect (Kumar et al., 2010). Carbozole alkaloids a major phytochemical constituent of MK plant, has been found to have various biological activities like anti-oxidant, antidiabetic and lipid lowering (Tembhurne and Sakarkar, 2010).

The status of lipid peroxidation was investigated in rats fed with *M.koenigii*. The concentration of melondiadehyde showed a significant decrease, while hydroperoxide and conjugated dines were significantly increased in the liver and the heart. Glutathione level in liver, heart and Kidney were lowered in rats after administering this plant. Glutathione reducatase, Glutathione Peroxidase, Glutathione Stransferese, SOD and catalase activity showed a sharp increase (Khan et al.,1995). Carbazole alkaloids which were identified as mahanibin, grinimbine, murrayanine and murryaaafoline–A.

To sum up it all, plant, herb and spices are evolutionary companions of human beings. They contain an array of compounds which individually or in combinations have therapeutic and health enhancing properties. Many pharmaceutical drugs are prepared from the plants and even more prepared by getting a clue from the chemistry of active principles of plants. World’s 80% people use plants as medicine varying from small discomforts to severe diseases. Therefore it becomes important to explore the effectiveness of different parts of the plants to prevent and manage diseases of chronic and degenerative kinds with diabetes mellitus, coming the forefront of all such diseases.