Introduction
The prevalence of Diabetes Mellitus is increasing globally day by day. The past two decades have seen an explosive global increase in the number of people diagnosed as non-insulin dependent diabetics. In India it is estimated that 19.4 million individuals are affected by non-insulin dependent diabetes mellitus, which is likely to go up to 57.2 million by the year 2025. It was observed that in urban India, prevalence of diabetes has risen to 12.1 percent and there was an equally large pool of individuals with Impaired Glucose Tolerance (IGT), many of them will eventually develop NIDDM in the coming future (Pradeepa et al., 2002). Reports from the WHO indicate that Diabetes mellitus is one of the major killers of our time, with people in south East Asia and Western pacific being most at risk. Diabetes mellitus is a common metabolic and endocrine disorder characterized by chronic hyperglycemic condition and disturbance of carbohydrate, fat and protein metabolism associated with absolute or relative deficiency of insulin secretion or insulin action (Bennet and Joslin, 1998).

**The Role of Insulin**

The major function of insulin is to counter the concerte action of number of hyperglycemia generating hormones and to maintain low blood glucose levels. In addition insulin stimulates lipogenesis, diminishes
lipolysis and increases amino acid transport into cells. Insulin also modulates transcription, altering the cell content of mRNA. It stimulates the growth, DNA synthesis and cell replication. Insulin is synthesized in the B cells of the islets of langerhans and directly infused via the portal vein to the liver, wherein it exerts profound metabolic effects (Geevarghese et al., 1990).

Types of Diabetes

Type 1 Diabetes mellitus (Formerly called Type-I, IDDM or Juvenile Diabetes) is characterized by beta cell destruction caused by autoimmune process usually leading to absolute insulin deficiency (NIH Report, 1995; 1997). The onset is usually acute, developing over a period of a few days to weeks. Over 95% of persons with Type-1 Diabetes mellitus develop the disease before the age of 25, with an equal incidence in both sexes and an increased prevalence in the white population. Though this form of Diabetes accounts for 5 to 10% of all cases, the incidence is rapidly increasing in specific regions.

Type-2 Diabetes mellitus (Formerly called NIDDM, Type II or Adult onset) is characterized by insulin resistance in peripheral tissue and an insulin secretory defect of the beta cells (NIH Report, 1995; 1997). This is
the most common form of Diabetes mellitus and is highly associated with family history of diabetes, older age, obesity and lack of exercise. This type of disease accounts for 90 to 95% of all diabetic patients.

Other types of Diabetes

The other types of Diabetes includes secondary diabetes, a form of diabetes that is secondary to certain conditions and syndromes such as pancreatic disease, hormone disturbances, drug influence, malnutrition and gestation diabetes (Refers to glucose intolerance occurring during pregnancy) (Bennet and Joslin, 1998).

Causes of Diabetes

Heredity: The stronger the family history for prevalence of Diabetes, the greater is the chance of developing diabetes in the family.

Obesity and Malnutrition: A highly refined diet with fiber-depleted carbohydrate is believed to be diabetogenic. The percentage of calories from fat, especially saturated fat in the diet has been shown to be associated with NIDDM as well as to predict the conversion from impaired glucose tolerance to NIDDM (Marshall et al., 1991; 1994). Obesity is another
significant factor as 90% of NIDDM types are obese and obesity plays a major role in the etiology of NIDDM for many patients and is associated with insulin insensitivity (Krot Kiewsk et al., 1983; Hughes et al., 1984; Smith, 1984; Wyngaarden et al., 1992; Campbell and Carlson, 1993).

Lack of Exercise: Regular exercise helps to burn the excessive calories, which prevents the obesity and activates the insulin receptors.

Stress: It was reported that the tension, anxiety or stress can aggravate the prevalence of Diabetes.

Drugs: The use of steroids and diuretics can enhance the occurrence and prevalence of diabetes in several cases.

Repeated infections: The regular occurrence of infections decreases the body resistance and can make any individual susceptible to Diabetes. Epidemiological and experimental evidence has strengthened the hypothesis of a viral etiology of IDDM in some cases (Schroeder et al., 1983; Leslie and Elliott, 1994).

Complications of Diabetes

The occurrence of Diabetes may lead to the development of numerous complications because of the prevalence of hyperglycemia. The likelihood
of developing complications, whether acute or chronic is ultimately a reflection of the level of blood sugar control.

**Acute Complications:** In general, the Diabetis is susceptible to several acute complications:

**Hypoglycemia** – Much more common in type-I Diabetic Ketoacidosis – Caused by lack of insulin leading to build up of ketoacids and can result in metabolic problems and even sometimes lead to coma.

**Non-Ketogenic Hyperosmolar Syndrome:** As a result of profound dehydration, deficient fluid intake or precipitating events such as pneumonia, stroke or with certain drugs such as phenytoin, gluco corticoids and diuretics may lead to this complication.

**Chronic Complications**

In patients suffering with Diabetis for a longer period, the health condition is complicated by repeated elevations in blood glucose levels. There were two primary mechanisms behind the development of most chronic complications of Diabetis i.e. glycosylated proteins and the intracellular accumulation of sorbitol. The binding of glucose to proteins, a process referred to as glycosylation, leads to changes in the structure and
functions of many body proteins. Excessive or no enzymatic glycosylation has many adverse effects such as inactivation of enzymes, inhibition of regulatory molecule binding, cross linking of glycosylated proteins, trapping of soluble proteins by glycosylated extra cellular matrix, decreased susceptibility to proteolysis, abnormalities of nucleic acid function, altered macromolecular recognition and increased immunogenicity (Brownlee et al., 1984). Sorbitol is a by-product of glucose metabolism formed within the cell through the accumulation or impairment of aldose reductase. Aldose reductase, a key enzyme of polyol pathway, catalyzes NADPH-dependent reduction of glucose to sorbitol (Sorbitol pathway) and an excessive accumulation of intracellular sorbitol plays a major role in the development of the chronic complications of Diabetes (Kinoshita et al., 1990; Raskin and Rosenstock, 1987).

**Atherosclerosis:** The Diabetic patients have two to three fold higher risk of developing atherosclerosis than a non diabetic person.

**Diabetic Neuropathy:** It is a very frequent complication of long term Diabetes. Loss of peripheral nerve function, tingling sensation, numbness, pain and muscle weakness are the major symptoms of neuropathy. There was a substantial evidence that Diabetic neuropathy usually occurs due to
sorbitol accumulation (Cogan et al., 1984; Wyngaarden et al., 1992). It was also reported that sorbitol accumulation leads to myoinositol loss (Yue et al., 1984) and some studies have shown inositol supplementation to improve nerve conduction velocity (Gegersen et al., 1983).

**Diabetic Retinopathy:** It is a serious eye disease that can result in blindness. One in 20 of Type-I and one in 15 of Type-II Diabetic patients can develop retinopathy. It is reported that after 15 years of insulin dependent diabetes, 80% of them show retinopathy with 25% of patients having more severe proliferative Diabetic retinopathy (Reqqierolopez et al., 1997).

**Diabetic Nephropathy:** This is a common complication and a major cause of death in Diabetes mellitus (Wyngaarden et al., 1992).

**Diabetic Foot Ulcers:** Ischemia and peripheral neuropathy are the key factors in development of Diabetic foot ulcers.

**Oxidative stress:** It results from a cell or tissue, which fails to detoxify the free radicals that are produced during metabolic activity. The oxidative stress is implicated in prevalence of Diabetic vascular and neural diseases (Yorek, 2003).
Treatment of Diabetes Mellitus

The proper and effective treatment of the Diabetic patient requires the careful integration of a wide range of therapies and patients willingness to alter their diet and life style.

Insulin

In juvenile Diabetes and in patients of Type-I Diabetes, soluble insulin is the drug of choice. In all the cases of Diabetic coma soluble insulin is the only life saving drug. Soluble insulin is short span drug. There are some long acting preparations of insulin available now.

Oral Hypoglycemic agents (OHA'S)

The α-Glucosidase inhibitors: The α-glucosidase inhibitors such as acarbose and miglitol functions by interfering with the action of the β-glycosidase present in the small intestinal brush border.

The Sulfonylurea: The sulfonylurea and meglitinide classes of oral hypoglycemic drugs are referred to as endogenous insulin secretagogues because they induce the pancreatic release of endogenous insulin.
The Meglitinides: The meglitinides, repaglinide and nateglinide are non-sulfonylurea insulin secretagogues that are both fast acting and of short duration.

The Biguanides: The biguanides are a class of drugs that function to lower serum glucose levels by enhancing insulin-mediated suppression of hepatic glucose production and enhancing insulin-stimulated glucose uptake by skeletal muscle.

The Thiazolidinediones (TZDs): The TZDs, such as troglitazone and pioglitazone have been proved to be useful in treating the hyperglycemia associated with insulin-resistance in both Type-II Diabetes and non-diabetic conditions.

Nutritional supplements

Providing the diabetic persons with additional key nutrients has been shown to improve blood sugar control as well as help to prevent or ameliorate many of the major complications of Diabetes.

Chromium: It is vital to blood glucose control as it functions as a key constituent of the glucose tolerance factor. Chromium works closely with insulin in facilitating the uptake of glucose into cells. Without chromium
insulin action is blocked and glucose levels will be elevated (Mooradian, 1994). Chromium has been shown to decrease fasting glucose levels, improving the glucose tolerance and decrease the total cholesterol and triglyceride levels and increases HDL levels (Anderson, 1992; Mooradian 1994).

**Vitamin C:** Many Diabetic persons do not have enough intracellular vitamin-C since its transport into cells is facilitated by insulin (Cunningham, 1991). Vitamin-C at high doses has shown to reduce the accumulation of sorbitol in the erythrocytes of Diabetic patients and to inhibit the glycosylation of proteins (Vinson, 1989; Davie et al., 1992).

**Niacin and Niacin amide:** Like chromium it is also an essential component of the glucose tolerance factor making it a key nutrient for hypoglycemia and diabetes (Urberg and Zemel, 1987). The mechanism of action appears to be inhibition of macrophage – and interlocking-1-mediated beta cell damage, inhibition of nitric oxide production along with anti oxidant action (Andersen, 1994).

**Biotin:** Biotin supplementation has shown to enhance insulin sensitivity and increase the activity of the enzyme glucokinase, the enzyme responsible for
the utilization of glucose by the liver (Reddi et al., 1988; Maebashi et al., 1993).

**Vitamin B6:** It inhibits the glycosylation of proteins (Solomon and Cohen, 1989) and useful in gestational diabetes (Coelingh and Schreurs, 1975).

**Vitamin B12:** The Vitamin B-12 deficiency is characterized by numbness of the feet, pins and needles sensations, or a burning feeling, which are symptoms of diabetic neuropathy (Sancetta et al, 1951; Davidson, 1954).

**Vitamin E:** The vitamin E not only improves insulin action, but also exerts a number of beneficial effects that may aid in preventing the long term complications in Diabetes (Paolisso, 1993). The various minerals such as magnesium, potassium, manganese and zinc play vital role in treatment of Diabetes.

**Botanical Medicines**

The use of ethno botanicals has a long folkloric history for the treatment of Diabetes. Prior to the development of insulin, Diabetes was entirely managed with herbal medicines only. Plants are wonderous chemists, they can easily synthesize chiral specific compounds in short time. India is endowed with rich flora because of the extreme variations in
geographical conditions available in the country. The traditional systems of medicines (Ayurvedic, Siddha and Unani) along with folkloric medicines continued to fetch a large portion of the population (Aruna and Sivaramakrishnan, 1990).

Ancient Concept of Diabetes

A study of ancient literature indicates that Diabetes was fairly well known and well conceived as an entity in ancient India. The knowledge of the system of Diabetes mellitus, as the history reveals, existed with the Indians since prehistoric age. Its earliest reference (1000 BC in the Ayurvedic literature) is found in mythological form where it is said to have originated by eating Havisha (Charak Samhita Nidan) a special food which is offered at the times of yagna organized by Dakshaprajapati. The disease was known as Asrava during Vedic era (6000 BC) and a detailed description of it is available in Brahattrai viz. Charak Samhita, Sushruta Samhita and Vagbhatta. Asthanga Haridaya (600 AD) is the first medical treatise in which one gets clear definition of Madhumeha/Diabetes mellitus by mentioning Glycosuria (Madhviv mehati-honey like urine). The word Prameha (Diabetes) is derived from the root ‘miha sechane’ meaning watering. In reference to disease of human beings, it may have a meaning
of passing urine, qualified by prefix ‘pra’ meaning excess in both frequency and quantity (Prameha = Pra {Excessive + Meha (Urination}) (Kohli and Singh, 1993). This derivation of word is again substantiated when the clinical features of “Prameha” are described as prabhuta-mutrata and Avil mutrata i.e. excessive urination with increased turbidity of urine. Also discussed by ancient Hindu physicians like Charaka, Shushruta, Vagbhata etc. as ‘Madhumeha’ (Honey urine), Diabetes mellitus is:

"Mudhura Yachch Mehesu Proyo Madhvint Maihati"

"Sarve Api Madhumehachya Madhuyachchi Manorath" Madhav nidan

It means, Madhumeha is a disease in which a patient passes sweet urine and exhibits sweetness all over the body i.e. in sweat, mucus, breath, blood etc. The ancient Hindu physicians knew of the fact that the urine of a Madhumeha Patient tastes sweet. They have recorded in their observations that, - ‘if too many ants swarm around a spot of urine, one can state that Prameha (Diabetes) of any variety, if neglected will finally lead to ‘Madhumeha’ and in due course become incurable. The whole description of prameha from the aetiology, pathogenesis, clinical features, complications and management all look to be comparable with the syndrome of Diabetes mellitus as known in modern medicine(Kar et al.,1997).
Classifications of Prameha in Ayurveda

Prameha i.e. Diabetes mellitus in Ayurvedic literature has been studied extensively and classified under several classes depending upon its aetiology, constitution, management, and therapy. Aetiological classification describes Diabetes as either i) Sahaj of genetic origin with lean, thin and emaciated physical state (IDDM) or ii) Apathyanimittaja of dietary irregularities, lack of exercise (NIDDM) (Sushrut Samhita) Charaka has categorized Prameha according to doshik prakritis (viz. Vataja, pittaja and kaphaja) and also by its prognosis. The later involving three types as sadhya (Curable), yapa (Pliable) and asadhya (Incurable). Charak also emphasizes constitutional and managerial differences. Sthula/balvan (Obese) patient needs Sodhana therapy (Weight control) and Krisha paridurbala (Asthenic) patient requires Brimhana therapy to provide him strength.

Dietary Management of Madhumeha

Ayurvedic antidiabetic herbs improve digestive power, increasing one of the Rasas (Gastric secretions), being Laghu, gets easily digested in the body and being Ruksha, decreases output of overall body fluids e.g. urine, sweat etc. "Ushna virya" helps further to decrease 'Kapha' in the body and also to alleviate burning sensation in all extremities. Katu veepaka helps
improve digestion and also has ‘Medaghna’ property (Acharya et al., 1996). Thus use of food items which are madhumehaghna (Antidote) is an important underlying principle of therapy for the prameha patient. Food items which try to correct the metabolic imbalance by their action e.g. rasa, katu, laghu, medaghna, properties are old cereals, roasted cereals, barley, jawar, ragi, mung dal, horsegram, tur dal, drumstick leaves, bitter gourd, jamun, amla, fig, raw papaya, milk etc. Acharya et al., (1996) reported that the Aahar chikitsa (Dietary management) is highly effective in early onset of diseases and in case of kapha dosha predominant non-insulin dependent Diabetes mellitus (NIDDM). Dietary management is a supportive/accessory treatment for vata dosha predominant and insulin dependent diabetes mellitus patients, which requires a long-term follow-up.

Present Status and Future Prospects

Diabetes is becoming something of a pandemic and despite the recent surge in new drugs to treat and prevent the condition, its prevalence continues to soar. Perhaps the most worrying aspect of all is that the rise is even reflected in children. Although several drugs targeted for carbohydrate hydrolyzing enzymes (Pseudosaccharides), release of insulin from pancreatic β-cells (Sulphonyl urea), glucose utilization (Biguanides insulin
sensitizers, PPARg agonists (Glitazones) are in clinical practice, the growing diabetes market observes a number of changes. The glitazones are meant to target the problem of insulin resistance and enhance insulin action at the cellular level, however, some of these drugs are linked to liver toxicity (Troglitazone), including a number of deaths from hepatic failure (Stern, 1999; Krishe, 2000) and raising the symptoms and risk factors of heart disease leading to heart failure (Rosiglitazone) (Gale, 2001). The long term risk and effect on the complications of Diabetes related with these drugs are not yet clear, as reported by De Soza et al., (2006) all the agents currently available for control of Type-II diabetes have several drawbacks like, they cannot correct all the metabolic disorders, show development of tolerance and produce various side effects as mentioned above, hence there is a need to search for alternative therapies.

Vegetables are among the numerous plant adjuncts tried for the treatment of the Diabetes mellitus. A few vegetables that are commonly consumed in India have been claimed to possess antidiabetic potency. In recent years, there has been a renewed interest to screen such plant food materials, for a possible beneficial use. Considerable amount of work has been carried out in this regard with bitter gourd i.e. *Momordica charantia* (Kavi Kumar et al., 1997) and ivy gourd i.e. *Coccinia indica* (Kamble et al.,
both in experimental animals and human Diabetic subjects. The hypoglycemic influence is claimed to be mediated through an insulin secretagogue effect or through an influence on enzymes involved in glucose metabolism. The limited number of studies on other vegetables such as cabbage (*Brassica oleracea*), capsicum (*Capsicum annum*) green leafy vegetables, beans and tubers have shown the beneficial hypoglycemic influence in both experimental animals and humans (Patel and Shrinivasan, 1995). Since diet forms the mainstay in the management of Diabetes mellitus, there is scope for exploiting the antidiabetic potency of vegetables to the maximum extent. Such plant food adjuncts possessing hypoglycemic activity appear to hold promise as potential antidiabetic agents.

**Development of an Effective Formulation**

The new formulation is developed with some medicinal plants which are known to have antidiabetic activity as per folkloric claims and Ayurvedic texts and these are combined with some well known cereals, pulses, millets commonly used by diabetic patients along with other ingredients. Combination products form an important part of the phytomedicines. They are widely accepted by patients and medical professionals. The combination products have great potential and they should be explored further for fixing
the specifications of their standardization parameters, as they possess some extra advantages as indicated below.

The different constituents of a combination may influence the different symptoms of a single syndrome. A combination of different constituents with the same active principle or with different active principles leading to the same effect will achieve cumulative effect. In combining with other substances, the dosage of a single substance can be reduced. The indication of a single compound may be different from that of the combination, but it may enhance the efficacy of the total combination. Further the criteria could be an improvement in tolerance and compliance, a simplification of the dosage scheme or avoidance of pharmaceutical incompatibilities (Ivorra et al., 1989).

Germination

Germination of cereals and pulses is an age old process to improve the nutritional factors. Germination enhances nutritional quality through the biosynthesis of vitamins, essential amino acids and proteins through improving protein digestibility, enhancing micro nutrient bioavailability and degrading anti nutritional factors (Barakoti and Bains, 2007; Tatala et al., 2007; Abdelrahaman et al., 2007). McCue et al., (2005) reported that
sprouting and dietary fungal bioprocessing of soya been improved the antidiabetic potential through modulation of the phenolic profile and further suggested that enzyme inhibitory activity may be linked to phenolic antioxidant mobilization during sprouting and bioprocessing. Dixit et al., (2005) showed more significant antioxidant activity with germinated fenugreek seeds in comparison with dried seeds, due to the improvement in polyphenols, flavonoids and other constituents content which are measured by HPLC analysis in the study. Veena et al., (2007) reported the increase in total dietary fibre content in legumes after the germination process.

Review of Literature

Traditional medicinal plants with various active principles and properties as discussed earlier are being used since ancient times by physicians and laymen to treat a great variety of human diseases such as Diabetes, Coronary heart disease and cancer safely. Ivorra et al., (1989) has extensively reviewed antidiabetic activity of active natural principles (polysaccharides, protein, flavonoids and related compounds, steroids, terpenoids and alkaloids) and crude extracts of various plant species, which have been experimentally studied in last few decades. The use of roughage in foods has been receiving attention more recently, since the establishment
of therapeutic benefits of fibers. It is shown to be very much useful in controlling Diabetes. Among the unconventional dietary fibers, guar gum and pectin have been recommended to be more useful (Jenkins et al., 1977; Smith and Holm, 1982). Akhtar and Iqbal (1991) determined the hypoglycemic activity of *Achyranthes aspera* (Amaranthea) in normal as well as in Diabetic rabbits. Suryanarayana et al., (2004) reported the inhibition of aldose reductase by constituents of *Emblica officinalis* both *in vitro* and in lens organ culture. They demonstrated that the hydrolysable tannoids of *E. officinalis* were responsible for AR inhibition, as enriched tannoids of *E. officinalis* exhibited remarkable inhibition against both rat lens and human AR with IC₅₀ of 6 and 10 µg/ml respectively. The inhibition of AR by *E. officinalis* tannoids is 100 times higher than its aqueous extract and comparable to or better than quercetin. Rao et al., (2005) have shown strong free radical scavenging activity and also strong inhibition of the production of advanced glycosylated end products by amla extracts. Oral administration of amla extracts to the Diabetic rats slightly improved body weight gain and also significantly alleviated various oxidative stress indices of the serum of the Diabetic rats. The elevated serum levels of hydroxymethylfurfural, which is a glycosylated protein that is an indicator of oxidative stress, were significantly reduced dose-dependently in the Diabetic
rats fed with amla. Similarly, the serum level of creatinine, yet another oxidative stress parameter, was also reduced. Furthermore, thiobarbituric acid-reactive substances levels were significantly reduced with amla, indicating a reduction in lipid per oxidation. In addition, the decreased albumin levels in the Diabetic rats were significantly improved with amla. Amla also significantly improved the serum adiponectin levels. These results form the scientific basis supporting the efficacy of amla for relieving the oxidative stress and improving glucose metabolism in Diabetes.

Gray and Flatt (1998) in their study incorporated *Eucalyptus globulus* in the diet and drinking water which reduced the hyperglycemia and associated weight loss of streptozotocin-treated mice. This study revealed that an aqueous extract of *Eucalyptus* enhanced 2-deoxy-glucose transport by 50%, glucose oxidation by 60% and incorporation of glucose into glycogen by 90% in mouse abdominal muscle and enhancement of insulin secretion from the clonal pancreatic beta-cell line. Venkateswaran and Pari (2002) reported the antioxidant effect of an aqueous extract of *Phaseolus vulgaris* pod in rats with streptozotocin-induced diabetes. On oral administration of *Phaseolus vulgaris* pod extract resulted in a significant reduction in thiobarbituric acid reactive substances and hydroperoxides. The extract also caused a significant increase in reduced glutathione, superoxide
dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in the liver and kidneys of rats with streptozotocin-induced Diabetes. These results clearly show the antioxidant property of *Phaseolus vulgaris*.

Sathishsekar and Subramanian (2005) investigated the antioxidant activities of the aqueous extract of seeds of two varieties, namely a country and hybrid variety of *Momordica charantia* (MCSEt1 and MCSEt2) respectively in streptozotocin induced Diabetic rats. The oral administration of both the seed extracts at a concentration of 150 mg/kg body weight for 30 days showed a significant decrease in fasting blood glucose, hepatic and renal thiobarbituric acid reactive substances and hydroperoxides. The treatment also resulted in a significant increase in reduced glutathione, superoxide dismutase, catalase, glutathione peroxidase and glutathione-S-transferase in the liver and kidney of Diabetic rats. The results clearly suggest that seeds of *Momordica charantia* may effectively normalize the impaired antioxidant status in streptozotocin induced Diabetes than the Glibenclamide treated groups. The extract exerted rapid protective effects against lipid peroxidation by scavenging of free radicals there by reducing the risk of Diabetic complications.
Ahmed et al., (2004) also reported the beneficial effects and mechanism of action of the juice of *Momordica charantia* in streptozotocin (STZ) induced Diabetes mellitus in rats. Daily oral administration of *M. charantia* juice to STZ-induced Diabetic rats significantly reduced (p < 0.01) the Na+- and K+-dependent absorptions of glucose by the brush border membrane vesicles of the jejunum compared to the responses obtained in STZ-induced diabetic rat. Either insulin (100 MM) or the fruit juice lyophilised extract (5 μg x ml (-1)) can stimulate 14C-D-glucose uptake in L6 myotubes. These effects were completely blocked by wortmannin, an inhibitor of phosphatidylinositol 3-kinase. High concentrations (10-200 μg x ml (-1)) of *M. charantia* juice extract inhibited 14C-D-glucose uptake in L6 myotubes compared to the control response. The effect of *M. charantia* treatment was also investigated on myelinated fibre abnormalities in the tibial nerve of STZ-induced diabetic and control rats. The results show that Diabetes was associated with significant (P < 0.05) reduction in the mean cross-sectional myelinated nerve fibres, axonal area, myelin area and maximal fibre area compared to end controls. Treatment of STZ-induced Diabetic rats with *M. charantia* juice normalized the structural abnormalities of peripheral nerves. The results indicate that *M. charantia* can exert marked beneficial effects in diabetic rats, and moreover, it can regulate glucose
uptake into jejunum membrane brush border vesicles and stimulate glucose uptake in to skeletal muscle cells similar to the response obtained with insulin.

Hannan et al., (2006) reported that *Plantago ovata* has reduced postprandial glucose concentrations in Diabetic patients. The study reported that the administration of *P. ovata* significantly improved glucose tolerance in normal, Type-1 and Type-2 Diabetic rat models. When the extract was administered orally with sucrose solution, it suppressed postprandial blood glucose and retarded small intestinal absorption without inducing the influx of sucrose into the large intestine. The extract significantly reduced glucose absorption in the gut during *in situ* perfusion of small intestine in non-diabetic rats. It can be concluded that, aqueous extracts of *P. ovata* reduces hyperglycaemia in Diabetes via inhibition of intestinal glucose absorption and enhancement of motility.

Mathews et al., (2006) carried out work on aqueous extract of *Asparagus adscendens* and shown to induce a significant non-toxic 19-248% increase in glucose-dependent insulin tropic actions (P < 0.001) in the clonal pancreatic beta cell line, BRIN-BD11. In addition, the extract produced an 81% (P < 0.0001) increase in glucose uptake in 3T3-L1 adipocytes.
Asparagus adscendens also produced a 21% (P < 0.001) decrease in starch digestion in in vitro. This study has revealed the presence of insulin tropic, insulin-enhancing activity and inhibitory effects on starch digestion by Asparagus adscendens. Maiti et al., (2005) observed significant attenuation of hyperglycemia by measuring FBG, glycogen level and glucose-6-phosphatase activity along with monitoring of intravenous GTT and serum insulin level with administration of Tamarindus indica extract. Similarly, correction of hyperlipidemia in Diabetic rats after this extract supplementation was confirmed by significant reduction in the levels of above-mentioned hyperlipidemic indicators. Intravenous GTT was performed that highlights the antidiabetic action of this extract is not due to its effect on the intestinal rate of glucose absorption but may be due to modulation of intracellular glucose utilization in target organs. This study reveals the efficacy of this extract for the management of experimental Diabetes in rat model, which may shed some light on the scientific basis of ancient herbal therapy in this line using this seed. Arulselvan and Subramanian (2007) evaluated the possible protective effects of Murraya koenigii leaves extract against beta-cell damage and antioxidant defense systems of plasma and pancreas in streptozotocin induced diabetes in rats. The levels of glucose and glycosylated hemoglobin in blood and insulin,
Vitamin C, Vitamin E, ceruloplasmin, reduced glutathione and TBARS were estimated in plasma of control and experimental groups of rats. To assess the changes in the cellular antioxidant defense system such as the level of reduced glutathione and activities of superoxide dismutase, catalase and glutathione peroxidase were assayed in pancreatic tissue homogenate. The levels of glucose, glycosylated hemoglobin, insulin, TBARS, enzymatic and non-enzymatic antioxidants were altered in diabetic rats. These alterations were reverted back to near control levels after the treatment of *M. koenigii* leaves extract. Transmission electron microscopic studies also revealed the protective nature of *M. koenigii* leaves on pancreatic beta-cells. These findings suggest that *M. koenigii* treatment exerts a therapeutic protective nature in Diabetes by decreasing oxidative stress and pancreatic beta-cell damage. The antioxidant effect of the *M. koenigii* extract was compared with glibenclamide, a well-known hypoglycemic drug and Kaleem et al., (2006) observed that oral administration of ethanol extract of *Nigella sativa* seeds to streptozotocin induced Diabetic rats significantly reduced the elevated levels of blood glucose, lipids, plasma insulin and improved altered levels of lipid peroxidation products (TBARS and Hydroperoxides) and antioxidant enzymes like catalase, superoxide dismutase, reduced glutathione and glutathione peroxidase in liver and kidney. The results confirm the
antidiabetic activity of *N. sativa* seeds extract and suggest that because of its antioxidant property, its administration may be useful in controlling the Diabetic complications in experimental Diabetic rats. Kanter et al., (2004) have also evaluated the possible protective effects of *Nigella sativa* L. (NS) against beta-cell damage from streptozotocin (STZ)-induced Diabetes in rats. The *Nigella sativa* treatment has shown to provide a protective effect by decreasing lipid peroxidation and serum nitric oxide and increasing antioxidant enzyme activity. Islet cell degeneration and weak insulin immunohistochemical staining was observed in rats with STZ-induced Diabetes. Increased intensity of staining for insulin, and preservation of beta-cell numbers were apparent in the *Nigella sativa* treated Diabetic rats. These findings suggest that *Nigella sativa* treatment exerts a therapeutic protective effect in Diabetes by decreasing the oxidative stress and preserving pancreatic beta-cell integrity. Consequently, *Nigella sativa* may be clinically useful for protecting beta-cells against oxidative stress.

It was reported that *Cinnamon* improves glucose and lipid profiles of people with Type-ii Diabetes (Cao et al., 2007). Water-soluble *Cinnamon* extract and HPLC-purified *Cinnamon* polyphenols with doubly linked procyanidin type-A polymers display insulin-like activity. The results suggest that *Cinnamon* exhibits the potential to increase the amount of
proteins involved in insulin signaling, glucose transport and anti-inflammatory/anti-angiogenesis response. And Suryanarayana et al., (2005) investigated the effect of Curcumin and its source, turmeric, on streptozotocin-induced Diabetic cataract in rats. They reported that both curcumin and turmeric did not prevent streptozotocin-induced hyperglycemia, as assessed by blood glucose and insulin levels, slit lamp microscope observations indicated that these supplements delayed the progression and maturation of cataract. The present studies suggest that curcumin and turmeric treatment appear to have countered the hyperglycemia-induced oxidative stress, because there was a reversal of changes with respect to lipid peroxidation, reduced glutathione, protein carbonyl content and activities of antioxidant enzymes in a significant manner. Also, treatment with turmeric or curcumin appears to have minimized osmotic stress, as assessed by polyol pathway enzymes. Most important, aggregation and insolubilization of lens proteins due to hyperglycemia was prevented by turmeric and curcumin. Turmeric was more effective than its corresponding levels of curcumin. Latha and Pari (2004) studied the effect of an aqueous extract of the plant *Scoparia dulcis* on the polyol pathway and lipid eroxidation were examined in the liver of streptozotocin adult Diabetic male albino Wistar rats. The *Scoparia dulcis*
plant extract administration to Diabetic rats significantly reduced blood glucose, sorbitol dehydrogenase, glycosylated hemoglobin, TBARS and hydroperoxides and significantly increased plasma insulin, GPx, GST and GSH activities in liver. The effect of the extract may have been due to the decreased influx of glucose into the polyol pathway leading to increased activities of antioxidant enzymes and plasma insulin and decreased activity of sorbitol dehydrogenase. These results indicate that the *Scoparia dulcis* was effective in attenuating hyperglycemia in rats and their susceptibility to oxygen free radicals. And Mukhtar et al., (2004) investigated the effect of feeding orally the aqueous extract of beans of *Cyamopsis tetragonoloba* on fasting blood glucose levels in glucose loaded, normal and alloxan-induced Diabetic rats and compared with gliclazide, a reference drug. The aqueous extract of beans significantly lowered blood glucose levels in alloxan-induced Diabetic rats. Investigations were carried out on the antioxidant effect of an ethanolic extract of *Coccinia indica* leaves, an indigenous plant used in Ayurvedic Medicine in India, in Streptozotocin-diabetic rats (Venkatesaran and Pari, 2003). The oral administration of *Coccinia indica* leaf extract resulted in a significant reduction in plasma thiobarbituric acid reactive substances, hydroperoxides, vitamin E and ceruloplasmin. The extract also caused a significant increase in plasma vitamin C and reduced
glutathione, which clearly shows the antioxidant property of *Coccinia*. And Kamble et al (1998) carried out a study on 30 Diabetic patients with dried extract of *Coccinia Indica* and postulated that the ingredients present in the extract of *C. indica*, act like insulin, correcting the elevated enzymes G-6-p (ase), LDH in glycolytic pathway and restore the LPL activity in lypolytic pathway with the control of hyperglycemia in Diabetes.

The aldose reductase inhibitory activity of Diabecon (An herbal drug used for diabetes) was studied together with its effect against sugar-induced lens opacity in organ culture (Moghaddam et al., 2005). Diabecon aqueous extract showed potential inhibitory activity with an IC50 value of 10 μg/ml against rat lens AR. Incubation of goat lens with supraphysiological concentrations of glucose (100 mM) led to the loss of lens transparency associated with increased AR activity, decreased soluble protein and increased protein carbonyls and glycation. Addition of DAE (0.3 mg/ml) to the medium preserved transparency and ameliorated the decrease in lens soluble protein due to hyperglycemia and also prevented the formation of glycated protein. Interestingly extract inhibited aldose reductase activity in lens incubated with 100 mM glucose. And the use of extract decreased the protein carbonyls, prevented the loss of beta (L)-crystallin against 100 mM of glucose. These results suggest that herbal drugs protect the lens against
sugar-induced cataract by multiple mechanisms. And Ravi et al., (2004a) investigated the effect of ethanolic extract of *Eugenia jambolana* seed kernel on antioxidant defense systems of plasma and pancreas in streptozotocin-induced diabetes in rats. They observed a significant increase in the levels of plasma glucose, vitamin-E, ceruloplasmin, lipid peroxides and a concomitant decrease in the levels of vitamin-C, reduced glutathione were observed in Diabetic rats. The activities of pancreatic antioxidant enzymes were altered in diabetic rats. These alterations were reverted back to near normal level after the treatment with *Eugenia jambolana* seed kernel. The histopathological studies also revealed that the protective effect of *Eugenia jambolana* seed kernel on pancreatic beta cells. This study shows that *Eugenia jambolana* seed kernel decreased oxidative stress in Diabetic rats, which inturn may be due to its hypoglycemic property. Further, Ravi et al., (2004b) in another study observed that medicinal herbs used in indigenous medicines for the management of Diabetes mellitus contain both organic and inorganic constituents. Some of these inorganic trace elements possess antidiabetic properties, which accounts for the activity of medicinal herbs. They analyzed the inorganic trace elements present in *Eugenia jambolana* seeds and to evaluate the hypoglycemic activity of the inorganic part of E. jambolana seeds on streptozotocin-induced Diabetes. The seeds of *E.

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*Jambolana* seeds were reduced to ash and the inorganic elements present were assayed. The hypoglycemic efficacy of the inorganic part was tested by the glucose tolerance test on streptozotocin-induced Diabetes. Elements such as zinc, chromium, vanadium, potassium and sodium, possessing hypoglycemic activity were present in the seed. The *E. jambolana* seed ash-treated Diabetic rats exhibited normoglycemia and better glucose tolerance. And Xue et al., (2007) investigated the *Trigonella foenum-graecum* extracts effects on general properties, blood glucose and blood lipid, and hemorheological parameters in experimental Diabetic rats. Rats treated with *Trigonella foenum-graecum* extract had an increase in body weight and a decrease in kidney/body weight ratio (p<0.05) and had lower blood glucose, hemoglobin, triglycerides, total cholesterol and higher-density-lipoprotein-cholesterol in a dose-dependent manner (P<0.05). The plasma viscosity, whole blood viscosity of high shear rate (200 s-1) and low shear rate (40 s-1), erythrocyte sedimentation rate, whole blood reduction viscosity and platelet conglutination were significantly reduced in diabetic rats treated with high and middle doses of *Trigonella foenum-graecum* extract, but not in those treated with low dose of *Trigonella foenum-graecum* extract. It was concluded that *Trigonella foenum-graecum* extract can lower kidney/body weight ratio, blood glucose, blood lipid levels and improve hemorheological
properties. Hannan et al., (2007a) have studied the antidiabetic properties of a soluble dietary fibre (SDF) fraction of Trigonella foenum-graecum by administration of SDF fraction (0 x 5 g/kg body weight) to normal, Type-I or Type-II Diabetic rats significantly improved oral glucose tolerance. The total remaining unabsorbed sucrose in the gastrointestinal tract of non-diabetic and Type-2 Diabetic rats, following oral sucrose loading (2 x 5 g/kg body weight) and it was significantly increased by T. foenum-graecum (0 x 5 g/kg body weight). The SDF fraction suppressed the elevation of blood glucose after oral sucrose ingestion in both non-diabetic and Type-II Diabetic rats. Intestinal disaccharidase activity and glucose absorption were decreased and gastrointestinal motility was increased by the SDF fraction. The daily oral administration of SDF to Type-II Diabetic rats for 28 days decreased serum glucose, increased liver glycogen content and enhanced total antioxidant status. The glucose transport in 3T3-L1 adipocytes and insulin action were increased by T. foenum-graecum. It indicates that the SDF fraction of T. foenum-graecum seeds exerts antidiabetic effects mediated through inhibition of carbohydrate digestion and absorption and enhancement of peripheral insulin action.

The antioxidant effect of fenugreek leaves in the streptozotocin-induced diabetic rat model was reported by Annida et al., (2005). The
antioxidant effect was evaluated by estimating thiobarbituric acid-reactive substances and reduced glutathione and measuring the activities of catalase and superoxide dismutase in liver, heart and kidney in diabetic rats. Fenugreek leaf powder supplementation significantly lowered the lipid peroxidation and significantly increased the antioxidant system in Diabetic rats. The insulin restores all the parameters to near normal values. Thus, fenugreek leaf powder reduces the oxidative stress in experimental Diabetes. The influence of different doses of *Salacia oblonga* extract, an herbal alpha-glucosidase inhibitor, on postprandial glycemic, insulinemic and breath hydrogen responses in healthy adults was demonstrated by Heacock et al., (2005). The study reported that the presence of *S. oblonga* extract tended to lower the postprandial glycemia and significantly reduced the postprandial insulin response. The increase in breath hydrogen excretion suggests a mechanism similar to prescription alpha-glucosidase inhibitors. Yoshikawa et al. (1994) reported a new inhibitor named elatosides E (Which was shown to affect the elevation of plasma glucose level by oral sugar tolerance test in rats) isolated from the root cortex of *Aralia elata* Seem. Together with elatoside F, the structures of elatosides E and F were elucidated on the basis of chemical and physicochemical evidence. The hypoglycemic activities of *oleanolic acid* and nine *oleanolic acid* glycosides obtained from the root
cortex of *Aralia elata* have been examined and some structure-activity relationships have been found. Shanmugasundaram et al., (1990) tested the two water-soluble extracts, GS3 and GS4, obtained from the leaves of *Gymnema sylvestre* in streptozotocin treated rats for their effects on blood glucose homeostasis and pancreatic endocrine tissue. In Diabetic rats, fasting blood glucose levels returned to normal after 60 days of GS3 and after 20 days of GS4 oral administration. Blood collected during the conduct of oral glucose tolerance tests and was used to assay for serum insulin. The GS3 and GS4 therapy led to a rise in serum insulin to levels closer to normal fasting levels. In Diabetic rat pancreas, both GS3 and GS4 were able to double the islet number and beta cell number. This herbal therapy appears to bring about blood glucose homeostasis through increased serum insulin levels provided by repair/regeneration of the endocrine pancreas. And Persaud et al., (1999) have reported that the extracts of *Gymnema sylvestre* have therapeutic potential for the treatment of non-insulin-dependent Diabetes mellitus (NIDDM), they examined the effects of an alcoholic extract of *G. sylvestre* on insulin secretion from rat islets of Langerhans and several pancreatic beta-cell lines. The mechanism of action of insulin secretory action of *Gymnema sylvestre* may be due to permeabilisation of the β-cell membranes, most likely resulting from the
high saponin glycoside content of the extract leading to unregulated loss of insulin from the cells and part of the insulin release may be dependent on channel independent \( \text{Ca}^{2+} \) influx into \( \beta \)-cells, perhaps through the pores formed by plasma membrane disruption and also the hyperglycemic activity in \textit{in vivo} and Dhanabal et al., (2006) evaluated the antidiabetic activity of various subfractions of the alcohol extract of the bark of \textit{Pterocarpus marsupium} Roxb. in alloxan-induced diabetic rats. And also assessed their activity in controlling Diabetes related metabolic alterations. The parameters measured were plasma glucose, total protein, cholesterol, triglycerides, alkaline phosphatase, SGOT and SGPT. The effective role of \textit{Pterocarpus marsupium} on the above mentioned parameters indicating that \textit{Pterocarpus marsupium} can also be used for the control the Diabetes related metabolic alterations apart from controlling the glucose levels and this activity may resemble insulin-like properties. Hoa et al., (2004) investigated the hypoglycemic effect and insulin secretion stimulatory effect of extract of \textit{Anemarrhena asphodeloides}. It is observed that ethanol extract of the roots of \textit{Anemarrhena asphodeloides} contains a substance, TH2, which stimulates insulin secretion both at 3.3 and 16.7 mM glucose in islets of normal Wistar and Diabetic GK rats. The mechanism behind TH2-stimulated insulin secretion involves an effect on the exocytotic machinery of the B-cell,
mediated via pertussis toxin-sensitive Gi-(or Ge-) proteins and Nmila et al., (2000) investigated the insulinotropic effects of different extracts of *Citrullus colocynthis* seed components i.e. RN II (Crude extract), RN VI (Hydro-alcoholic extract), RN X (Purified extract) and RN XVII (Beta-pyrazol-1-ylalanine), the major free amino acid present in the seeds. The insulin secretory effects of these different extracts were evaluated in *in vitro* in the isolated rat pancreas and isolated rat islets in the presence of 8.3 mM glucose. All the tested extracts, when perfused for 20 minutes at 0.1 mg/ml, immediately and significantly stimulated the insulin secretion and the effect was transient. Chattopadhyay (1999) showed the effect of *Azadirachta indica* leaf extract on serotonin inhibition in glucose mediated insulin release in rat pancreas. The *A. indica* leaf extract blocks significantly (*P* < 0.05) the inhibitory effect of serotonin on insulin secretion mediated by glucose. Upadhya et al., (2004) reported hypoglycemic and antioxidant activity of *Aegle marmelos* by decreasing the glutathione-s-transferase in rats. And Kamalakkannan and Prince (2005) elucidated the protective effect of an aqueous extract of *Aegle marmelos* fruits on the histopathology of the pancreas in streptozotocin-induced diabetic rats. The oral administration of *Aegle marmelos* fruit extract at doses of 125 and 250 mg/kg twice daily to Diabetic rats for a period of 30 days resulted in a significant increase in body
weight, weight of the pancreas and insulin levels associated with a significant decrease in fasting blood glucose levels. The fruit extract treated groups showed improved functional state of the pancreatic ss-cells and partially reversed the damage caused by streptozotocin to the pancreatic islets. The findings of the study indicate that *Aegle marmelos* fruit extract exhibits the protective effect and nature on pancreas.

**Mode of Action of Medicinal Plants for Treatment of Diabetes**

From the aforesaid literature review it was evident that the beneficial multiple activities of medicinal plants in treatment of Diabetes were plenty. They can do this by:

i) Manipulating carbohydrate metabolism by various mechanisms

ii) Retarding glucose uptake in the small intestines

- By inhibiting digestive enzymes
- By inhibiting active transport of glucose across intestinal brush border membrane and
- By delaying the gastric emptying rate of gastrointestinal content, there by decreasing the gastric emptying rate and suppressing\delaying the digestion and absorption of carbohydrates
iii) Inhibition of carbohydrate hydrolyzing enzymes i.e. alpha amylase and alpha glucosidase and manipulation of glucose transporters

iv) Preventing and restoring integrity and function of \( b \)-cells

v) Insulin-releasing activity

vi) Improving glucose uptake and utilization

vii) Inhibiting aldose reductase activity and

viii) He antioxidant properties which offer exciting opportunity to develop them into novel therapeutics.

The multifactorial pathogenicity of Diabetes demands a multimodalistic therapeutic approach. Thus, the future therapeutic strategies require the combination of various types of agents. The theories of polyherbal formulation have the synergistic, potentiative, agonistic/antagonistic, pharmacological agents, within themselves due to incorporation of plant medicines with diverse pharmacological actions. These pharmacological principles work together in a dynamic way to produce maximum therapeutic efficacy with minimum side effects. The traditional medicinal preparations therefore should not be considered just as a collection of therapeutic recipes. They should be formulated and prepared keeping in mind the conditions of sickness and the healing properties of individual ingredients (Ashok et al., 2002). Therefore, it is important that
the herbal medicines and preparations should be taken with the consideration of their holistic therapeutic approach. The multiple activities of plant-based medicinal preparations meant for control of Diabetes offer enormous scope for combating the threat of the Diabetic epidemic. In the light of this, the present investigation has been carried out with the following plan of work.

**Plan of Work**

- Selection and collection of plants having antidiabetic property based on preliminary information available in ayurvedic text books and as per folkloric claims.
- Phytochemical analysis of selected plants for determining pharmacological property of selected plants.
- Extraction of selected herbal plants with various solvents.
- Isolation, purification and structural elucidation of some of the constituents present in the plants.
- Pharmacological studies of the selected herbal extracts for confirming the hypoglycemic, antidiabetic, sub-acute toxicity and insulin secretion activity.
- Formulation development by combining herbal extracts with selected germinated cereals, pulses and other excipients for control of Type-II Diabetes.

- Stability studies on the formulation to know the compatibility of the ingredients with various physical, chemical and microbiological parameters.

- Pharmacological studies of the formulation on rabbits to confirm the hypoglycemic and antidiabetic activity.

- Clinical studies to know the potentiality of the formulation to control type-II diabetes.