Review of Literature
The history of diabetes mellitus began with the mention of polyuria (frequent urination) in *Ebers Papyrus* by the physician Hesy Ra (1500 B.C.) (Papyrus Ebers, 1937). Hindus (1000 B.C.) in the *Ayurveda* recorded that insects and flies were attracted to the urine of some people, the urine tasted sweet, and this was associated with certain diseases. The fathers of medicine in India, Sushruta and Charaka of ancient India (600-400 B.C.), described the condition as a form of 'Prameha'. They had noted the sweetness of urine of such patients and described the condition as 'Madhumeha' (rain of honey). They have described all the main symptoms of the disease, namely thirst, voracious appetite, etc., in their compilations *'Charaka Samhita'* and *'Sushruta Samhita'*, respectively (Susruta Samhita, 1916; Charaka Samhita, 1977).

Demetris (276 B.C.) of Apamea defined the diagnosis of diabetes mellitus. According to Caelius Aurelianus (230 B.C.), Apollonius of Memphis coined the term "diabetes". The term diabetes in Greek means 'to flow through a siphon' and was coined by Aretaeus and Celsus in the later half of the first century (Whithington, 1894). Later, the masterly description of severe clinical diabetes by Aretaeus (81-138 A.D.) represents the sum of our knowledge about the disease until the later half of 17th century. He described diabetes as "the melting down of flesh and limbs into urine". Greek physician Galen (164 A.D.) of Pergamum mistakenly diagnosed diabetes as an ailment of the kidneys (Whithington, 1894). Arabian writer Rhazea (865-925 A.D.) translated and shared the information of diabetes mellitus from the Hindus. Avicenna (900-1037 A.D.) prescribed emetics and sudorifics for the disease, and directed that all diuretic foods and drugs be avoided and the patients
engage in exercise (preferably on horseback) to “employ moderate friction”. In the later stages of the disease, he recommended tepid baths and fragrant wine. Cardona (1501-1576 A.D.) who measured the intake and output of fluids found a great discrepancy in the figures and surmised that people with diabetes lose more water than they take in due to some unknown reasons (Leibowitz, 1972).

In 1674, Thomas Willis, a physician, anatomist and Professor of Natural Philosophy at Oxford, rediscovered the finding of Susruta that the urine of diabetic patients tasted sweet (Willis, 1674). Mathew Dobson (1776) of Manchester, England, demonstrated that diabetic patients actually excrete sugar in urine. He evaporated urine to dryness by boiling and noted that the residue, a crystalline material, had the appearance and taste of brown sugar. The prevalent view up to that time was that kidney was the central organ affected by the disease, since its most striking signs and symptoms were related to the frequency and degree of urination. Some clinical observers also noted liver enlargement (Dobson, 1776). Cawley (1788) observed a shrivelled pancreas with stones in a diabetic patient at autopsy; this may have been the first published reference to pancreas in relation to human diabetes (Leibowitz, 1972).

John Rollo (1798) applied the discovery of glycosuria to the quantitative metabolic study of diabetes and to the first rational approach to dietary treatment of the disease. He also shifted the then prevalent view that the primary seat of disorder in diabetes is not the kidney but the gastrointestinal tract. According to him, vegetable matter (bread, grain, fruits)
increased glycosuria, whereas animal matter (meat) resulted in a comparatively lower excretion of sugar. He concluded, therefore, that the 'glycosuria' was secondary to the saccharification of vegetable matter and a diet low in carbohydrates and high in fats and proteins was recommended by him for the treatment of the disease (Rollo, 1798). In 1815, Chevreuil showed that blood sugar behaved chemically as if it was grape sugar (dextrose or glucose) (Whithington, 1894).

In France, Claude Bernard (1850) theorized that diabetes mellitus was caused by breakdown of the glycogen stored in the liver (glycogenolysis) and there was a possible role of pancreas in diabetes (Bernard, 1869).

In 1869, Paul Langerhans, a senior medical student in Berlin, published a short paper on his medical dissertation on pancreatic histology, in which he reported a previously unknown cell type in the gland. According to him, these cells were situated between the acini and did not communicate directly with the ducts. He described them as occurring in small heaps or islands (Langerhans, 1869).

French physician Bouchardat (1870) argued that pancreatic factor was involved in the aetiology of diabetes. He did meticulous long-term study on human diabetes. He added a very important therapeutic regime, encouraging hard physical labor, having observed the ameliorative effects of muscular work on glycosuria and hyperglycemia. He recognized two different types of diabetes from his clinical experience (Leibowitz, 1972).
1. The severe type in younger persons, which responded poorly to his regime.

2. The type in older obese persons for which the prescribed therapy of diet and physical exertion worked admirably.

The clinical behavior of the two types of diabetes and postmortem findings led Bouchardet to suggest that the severe form, resistant to dietary treatment, was pancreatic in origin (Leibowitz, 1972).

The decisive turning point in the history of diabetes was marked by the experimental work of Vonmering and Minkowski in 1889 (Houssay, 1952). Vonmering was interested in finding the possible role of pancreas in the digestion and absorption of fats. He understood from the then available literature that it was virtually impossible for an animal to survive total pancreatectomy. He counselled with Minkowski and conducted total pancreatectomy in two dogs. Both animals survived the complete pancreatectomy. Within less than a day, these animals exhibited unexpected behaviour, in particular, with frequent and voluminous urination. Minkowski demonstrated clearly in the next two years that the pancreas was a gland of internal secretion and that a small portion of the gland, when implanted upon the skin of freshly depancreatized dog, prevented the appearance of hyperglycemia until the implanted tissue was removed or had degenerated spontaneously (Luft, 1989; Minkowski, 1989).

Between 1891 and 1894, Laguesse conducted studies on the inter-acinar cells of pancreas and christened them as 'Islets of Langerhans', after Paul Langerhans who did the pioneering studies on them. Opie (1901)
detected islet cell lesion in diabetes (Opie, 1900, 1901). German scientist Georg Zuelzer (1908) developed the first injectable pancreatic extract to suppress glycosuria; however, extreme side effects developed due to the treatment (Leibowitz, 1972).

In 1910, Jean de Meyer suggested that the pancreatic secretion that was lacking in the diabetic state should be called 'insulin', to denote its origin from the insulae of Langerhans. Between 1910 and 1920, Frederick Madison Allen and Elliot P. Joslin emerged as the two leading diabetes specialists in the United States (Allen, 1915; Joslin, 1922).

In 1921, Banting with the assistance of Best, Collip and Mac Leod did his research using a variety of different extracts on de-pancreatized dogs. Insulin was discovered in 1921. A de-pancreatized dog was successfully treated with insulin. One of Collip's (1922) insulin extracts first tested on a human being, a 14-year-old boy named Leonard Thompson, in Toronto, was considered a success. Following this great milestone in the history of medicine, rapid strides were made in the extraction and purification of insulin. The focus then shifted to the ability of making this insulin safe, of consistent potency and effective in reversing diabetic symptoms (Banting and Best, 1922).

In 1936, Hagedom discovered that the activity of insulin after injection could be delayed or prolonged with the addition of various basic proteins, such as fish protamine, which kept the insulin in suspension so that it was absorbed more slowly from the subcutaneous sites. In the same year, Scott and Fisher created even better long-acting insulin. They demonstrated that
the addition of Zinc and other heavy metals extended the duration of action of protamine insulin even further. This led to the development of protaminezinc insulin (PZI) (Leibowitz, 1972). PZI could lower the blood glucose level for 48 to 72 hours and, therefore, required to be administered only once a day to achieve good glycemic control in patients. This discovery marked the beginning of “Hagedorn Era” which revolutionized insulin therapy, leading to the once-a-day regimens of intermediate and long-acting insulins in the treatment of diabetes, as opposed to the multiple daily injections of soluble insulin used previously. In subsequent years, other insulin with prolonged action was developed. Isophane insulin, a more stable form of protamine insulin, known today as NPH insulin (neutral protamine hagedorn), was introduced in 1946. Insulin zinc suspensions that contain no added protamine or modifying proteins, referred to as the “lente” (slow acting) series, were developed and introduced in the early 1950’s. The structure of insulin was first elucidated by Fredrick Sanger (Sanger, 1951, 1953, 1959).

Improvement in the purity of commercially available insulin has resulted in a marked decrease in the medical problems attributed to immunogenicity of the insulin preparations. In 1977, Ulrich and associates successfully cloned the insulin gene. In 1980, human insulin was introduced, and its use has increased steadily. In 1982, Lilly Company came up with recombinant DNA insulin, by enzymatic conversion of porcine insulin sequence into the human insulin sequence. Various developments on this procedure have resulted in a number of insulin available today (Bliss, 1982).
Insulin, with all its recent advancements in availability and efficacy, has its own definite disadvantages, like wide swings in blood sugar levels, subcutaneous lipodystrophy at the injection site, insulin allergy, insulin resistance and insulin neuropathy (Rang and Dale, 1991; Anuradha et al., 2004).

Insulin being inactivated in oral administration, research work was done for orally effective hypoglycemic agents. It was observed that SYNTHALIN-A (Decamethyl Di Guanidine), a higher homologue of Guanidine, produced similar effects as Guanidine in animals, and they responded to i.v. glucose therapy. Synthalin was, thus, used in the treatment of patients with glycosuria and acetonuria, and the results came to be hailed by many, even after the advent of insulin in 1921, as a great advancement in the treatment of diabetes. The toxic effect of the drug on the liver, and the availability of physiologically sound and usable insulin ended the synthalin era (Schafer, 1983).

The oral hypoglycemic action of some alkyl derivatives of biguanides, which were chemically related to synthalin A were reported. Many analogues of biguanides, including dimethyl biguanide (Metformin), have since been synthesized. The unfavourable results in the early trials using these drugs were attributed to the unwise selection of patients and over-enthusiasm shown, disregarding the mode of action of the drug (Holman and Turner, 1991; Bailey, 1992). With the development of the timed disintegration form of phenformin, many of these side-effects were reduced. For the biguanide products there appears to be no single decisive mechanism of action but acts
unlike insulin and sulphonylurea, and does not lower blood glucose levels in normal persons. Hypoglycemic action has been attributed to decreased gluconeogenesis, increased glucose utilisation by aerobic glycolysis and decreased rate of intestinal glucose absorption (Akhtar and Iqbal, 1991; Bailey, 1992).

The early impetus given by Loubatieres (1947) in the study of hypoglycemic sulfonamides led to the discovery of the modern oral antidiabetic agent carbutamide, a sulphonylurea compound. Sulphonylureas are a class of compounds containing the sulphonylurea moiety that are related to sulphonamide drugs. The discovery of its hypoglycemic action was made serendipitically in 1942, when the original analogue (glyprothiazole) was used to treat patients with typhoid fever. Subsequent modification of the compound (by elimination of an amino moiety on the benzene ring, and opening of heterocyclic nitrogen ring) enhanced the hypoglycemic activity and reduced the toxicity (Loubatieres, 1957). This led to the development of so-called first generation sulphonylureas (Tolbutamide, Acetohexamide, Tolazamide and Chlorpropamide). The introduction of cyclohexyl group to replace the aliphatic side-chain and the addition of another ring structure linked to glycine at the other end of the molecule created the so-called second generation sulphonylureas (Glypizide, Glibenclamide and Glycazide). The antidiabetic mechanism of action of all sulphonylureas is similar. But the second-generation agents have much greater intrinsic activity (Gerich, 1985; Groop et al., 1985). The presence of a sulphonylurea-binding site on the surface of β-cells was initially suggested for all sulphonylureas except glibenclamide (Jackso and Bressler, 1981). The sulphonylurea receptor has a
high affinity for second-generation sulphonylureas (Lebovitz and Feinglos, 1978). The hypoglycemic effect of sulphonylurea compound depends mainly on its ability to stimulate the release of endogenous insulin by the β–cells of pancreas and to a smaller extent through the inhibition of glucose formation from liver glycogen (Goth, 1985; Ivorra et al., 1988; Siyem et al., 2002; Subramoniam et al., 1996).

Despite the different modes of action, the contra-indication is similar in both groups of drugs. The most common adverse effects associated with sulphonylurea administration are,

i) gastrointestinal problems like nausea, vomiting and non-specific abdominal discomfort;

ii) skin rashes; and

iii) rare cases of hemolytic disorders like hemolytic anemia, agranulocytosis and liver diseases like jaundice, granulomatous hepatitis and immune disorders (UGDP, 1970).

The search for an oral insulin substitute led to several investigations in the field of experimental diabetes. In order to induce permanent experimental diabetes, destruction of β–cells must occur. This may be accomplished by surgical ablation of most or the entire pancreas, administration of a chemical selectively toxic to β–cells like alloxan or streptozotocin (Nukatsuka et al., 1990; Garg et al., 1996; Szkudelski, 2001; Mc Letchie, 2002), injection of diazoxide (a sulphonamide derivative) or continuous administration of glucose or certain diabetogenic hormonal agents.
Streptozotocin

Streptozotocin [2-deoxy-2- (3-(Methyl-3-nitrosoureido)-D-glucopyranose] is synthesized by *Streptomyces achromogenes*, and is used to induce both insulin-dependent and non-insulin dependent diabetes mellitus. Streptozotocin may be given in multiple low doses (Ganda *et al.*, 1976; Szkudelski, 2001). Such treatment is practised predominantly in the mouse, and the induction of IDDM is mediated by the activation of immune mechanisms. NIDDM can easily be induced in rats by intravenous or intraperitoneal treatment with 100 mg/kg body weight of streptozotocin on the day of birth (Portha *et al.*, 1974). Streptozotocin action in β–cells is accompanied by characteristic alterations in blood insulin and glucose concentrations. Two hours after injection, the hyperglycemia is observed with a concomitant drop in blood insulin. About six hours later, hypoglycemia occurs, with high levels of blood insulin. Finally, hyperglycemia develops and blood insulin level decreases (West *et al.*, 1996; Szkudelski, 2001). These changes in blood glucose and insulin concentrations reflect abnormalities in β–cell function. Streptozotocin treatment impairs glucose oxidation (Bedoya *et al.*, 1996), and insulin biosynthesis and secretion (Nukatsuka *et al.*, 1990).
It was observed that streptozotocin at first abolished the β-cell response to glucose. Temporary return of responsiveness then appears which is followed by its permanent loss and cells are damaged (West et al., 1996).

**Alloxan**

![Alloxan molecule](image)

Alloxan (2, 4, 5, 6-tetraoxypyrimidine; 5-6-dioxyuracil) was first described by Brugnatelli in 1818, Wohler and Liebig used the name “alloxan” and described its synthesis by uric acid oxidation (Dunn et al., 1943; Lenzen et al., 1988; McLetchie, 2002). The diabetogenic properties of this drug were reported many years later by Dunn et al. (1943), who studied the effect of its administration in rabbits and reported a specific necrosis of pancreatic islets. Since then, alloxan-diabetes has been commonly utilized as an animal model of insulin dependent diabetes mellitus (Portha et al., 1974; Weaver et al., 1978; Gorus et al., 1982; Boquist et al., 1983; Lenzen and Parten, 1988).

Alloxan exerts its diabetogenic action when it is administered parenterally: intravenously, intraperitoneally or subcutaneously. The most frequently used intravenous dose of this drug to induce diabetes in rats is 65 mg/kg body weight (Gruppuso et al., 1990). When alloxan is administered intraperitoneally or subcutaneously its effective dose must be 2-3 times higher. The intraperitoneal dose below 150 mg/kg body weight may be insufficient for inducing diabetes in the rat (Katsumata et al., 1992; Szkudelski et al., 1998).
The action of alloxan in the pancreas is preceded by its rapid uptake by the β-cells (Weaver et al., 1978; Boquist et al., 1983). Rapid uptake by insulin secreting cells has been proposed to be one of the important features determining alloxan diabetogenicity. Another aspect concerns the formation of reactive oxygen species (Heikkila and Fischer, 1982; Takasu et al., 1991; Sakurai and Ogiso, 1995). A similar uptake of alloxan also takes place in the liver. However, the liver and other tissues are more resistant to reactive oxygen species in comparison to pancreatic β-cells and this resistance protects them against alloxan toxicity (Tiedge et al., 1997; Malaisse et al., 1982). The formation of reactive oxygen species is preceded by alloxan reduction. In β-cells of the pancreas, its reduction occurs in the presence of different reducing agents. Since alloxan exhibits a high affinity to the SH-containing cellular compounds, reduced glutathione, cysteine and protein-bound sulfhydryl groups are very susceptible to its action (Malaisse, 1973; Lenzen and Munday, 1991). However, other reducing agents such as ascorbate may also participate in this reduction (Zhang et al., 1992). It was proposed that one of the -SH containing compounds essential for proper glucose-induced insulin secretion is glucokinase (Lenzen et al., 1987). Alloxan reacts with two -SH groups in the sugar binding site of glucokinase, resulting in the formation of disulfide bond and inactivation of the enzyme. Glucose can protect glucokinase against the inactivation, hindering the access of alloxan to the-SH groups of the enzyme (Lenzen et al., 1988; Lenzen and Mirzaie-Petri, 1991).

Dialuric acid is formed as a result of alloxan reduction. It is then re-oxidised back to alloxan, establishing a redox cycle for the generation of
superoxide radicals (Munday, 1988). The reaction between alloxan and dialuric acid is a process in which intermediate alloxan radicals and an unidentified “Compound 305” is formed. The latter appears when alloxan is reduced by GSH (Sakurai and Ogiso, 1995). Superoxide radicals are able to liberate ferric ions from ferritin and reduce them to ferrous ions. Fe$^{3+}$ can also be reduced by alloxan radicals (Sakurai and Ogiso, 1995). Moreover, superoxide radicals undergo dismutation to hydrogen peroxide.

$$\text{O}_2^- + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2$$

This reaction may occur spontaneously or may be catalysed by superoxide dismutase. In the presence of Fe$^{2+}$ and hydrogen peroxide, highly reactive hydroxyl radicals are then formed according to the Fenton reaction (Grankvist, 1981; Munday, 1988).

$$\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^-$$

One of the targets of the reactive oxygen species is DNA of pancreatic islets. Its fragmentation takes place in β-cells exposed to alloxan (Takasu et al., 1991; Sakurai and Ogiso, 1995).

It has been proposed that disturbances in intracellular calcium homeostasis constitute an important step in the diabetogenic action of alloxan (Park et al., 1995). This effect arises from several events: alloxan-induced calcium influx from extracellular fluid, exaggerated calcium mobilization from intracellular stores and its limited elimination from the cytoplasm. The calcium influx may result from the ability of alloxan to depolarize pancreatic β-cells (Dean and Mathews, 1972; Katsumata et al., 1992). Depolarisation of the cell
membrane opens voltage-dependent calcium channels and enhances calcium entry into cells. Alloxan was also found to exert a stimulatory effect on mitochondrial Ca\(^{2+}\) efflux with simultaneous inhibitory action on Ca\(^{2+}\) uptake by mitochondria (Nelson and Boquist, 1982; Lenzen et al., 1992). The effects of alloxan on intracellular calcium concentration seem to be mediated, at least partially, by H\(_2\)O\(_2\) since hydrogen peroxide itself exerts a similar effect on calcium concentration in \(\beta\)-cells (Park et al., 1995).

Thus, the previously mentioned sudden rise in insulin release from \(\beta\)-cells treated with alloxan (Weaver et al., 1978; Kliber et al., 1996) may be one of the effects of alloxan-induced augmentation in cytosolic Ca\(^{2+}\) concentration (Weaver et al., 1978). The exaggerated concentration of this ion contributes to supraphysiological insulin release, and together with reactive oxygen species, causes damage of pancreatic \(\beta\)-cells. To sum up, the selective action of alloxan on pancreatic \(\beta\)-cells, described many years ago by Dunn et al. (1943), are the sum of several processes such as oxidation of essential –SH groups, inhibition of glucokinase, generation of free radicals and disturbances in intracellular calcium homeostasis (Szkudelski et al., 1998; Szkudelski, 2001).

**Indigenous Remedies**

Though different types of oral hypoglycemic agents are available along with insulin for the treatment of diabetes mellitus, there is a growing interest in herbal remedies, due to the side effects associated with the therapeutic agents (Prout, 1974; Gerich, 1985; Groop et al., 1985; Lamer, 1985; Holman and Turner, 1991; Trejo-Gonzalez et al., 1996; Kameswara Rao et al., 1997;
Chakrabarti et al., 2002). Because of their perceived effectiveness, minimal side effects in clinical experience and relatively low costs, herbal drugs are prescribed widely even when their biologically active compounds are unknown (Nagaraju and Rao, 1990; Valiathan, 1998; Kameswara Rao et al., 2001a).

The available literature shows that there are more than 800 plant species showing hypoglycemic activity (Mukherjee, 1981; Oliver-Bever, 1986; Atta-Ur-Rahman and Zaman, 1989; Bailey and Day, 1989; Ivorra et al., 1989; Nagaraju and Rao, 1990; Swanston-Flatt et al., 1990; Handa, 1991; Rastogi and Mehrotra, 1993; Marles and Famsworth, 1994; Rai, 1995; Rajathi and Daisy, 2003; Daisy et al., 2004a, b; Jasmine and Daisy, 2004) and presently several laboratories are involved in isolating new herbal oral hypoglycemic agents. Though some of the plants are reputed in the indigenous systems of medicine for their hypoglycemic activities, it remains to be scientifically established (Kameswara Rao et al., 2001a; Jayakar and Suresh, 2003).

The World Health Organisation has also recommended the evaluation of the effectiveness of plants, in conditions where we lack safe modern drugs (WHO, 1980; Upadhayay and Pandey, 1984; Grover et al., 2001; Ojewole, 2002). The resolution of the 31st WHO Assembly requested a complete inventory, evaluation of the efficacy and safety and standardization of medicinal plants (Famsworth, 1980; Benwahhoud et al., 2001). In India, indigenous remedies have been used in the treatment of diabetes mellitus since the time of Charaka and Sushruta (Grover and Vats, 2001; Grover et al., 2002b). Plants that have been pharmacologically tested and of value in diabetes mellitus are discussed below.
Acacia arabica administered at doses 2, 3 and 4 g/kg body weight exerted a significant hypoglycemic effect in normal rabbits by initiating the release of insulin from pancreatic β–cells (Wadood et al., 1989). Aqueous leaf extract of Aegle marmelos administered orally for 28 days also normalized streptozotocin (45 mg/kg body weight)-induced histopathological alterations in the pancreatic and kidney tissues of rats (Das et al., 1996). Single oral dose of 50 g of juice of Allium cepa residue to 3 diabetic patients significantly controlled post-prandial glucose levels (Mathew and Augusti, 1975). SACS, a sulfur-containing amino acid present in Allium sativum, significantly stimulated insulin secretion in vitro from β–cells isolated from normal rats (Sheela and Augusti, 1992; Sheela et al., 1995). The hypoglycemic effect of Aloe vera and its bitter principle is mediated through stimulation of synthesis and/or release of insulin from the β–cells of Langerhans (Ajabnoor, 1990).

Oral administration of methanol extract of aerial parts of Artemisia pallens showed a dose-dependent anti-hyperglycemic effect in glucose-fed hyperglycemic and alloxanised rats (60 mg/kg body weight iv) (Subramoniam et al., 1996). Hydroalcoholic extract of Azadirachta indica showed hypoglycemic and anti-hyperglycemic effect in normal, glucose-fed and streptozotocin diabetic rats (Chattopadhyay et al., 1987). Various glycosides isolated from the root extract of Beta vulgaris have been shown to increase glucose tolerance in rats (Yoshikawa et al., 1996). The leaf extract of Biophytum sensitivum has been shown to exert significant anti-hyperglycemic effect in alloxanised rabbits, possibly by pancreatic β–cell-stimulating action as the plant was effective only in mild to moderate hyperglycemic conditions, and not in severe diabetic state (Puri and Baral, 1998). Oral feeding of
Brassica juncea diet (10%) for 60 days to normal rats showed significant hypoglycemic effect (Khan et al., 1995).

Aqueous and alcoholic extracts of Caesalpinia bonducella seeds exhibited significant hypoglycemic and anti-hyperglycemic activities in normal and streptozotocin-diabetic rats (Simon et al., 1987; Rao et al., 1994). Cooked diet of Cajanus cajan showed significant hypoglycemic effect in healthy human volunteers (Panlasigui et al., 1995). Oral feeding of diet containing Capparis decidua fruit powder (30%) for 3 weeks to alloxanized (80 mg/kg ip) diabetic rats (blood glucose, 450 mg %) produced significant reduction in blood glucose (120-130 mg %) (Yadav et al., 1997). Saponins and glycosidic components of the rind of Citrullus colocynthis bring about hypoglycemic effect (Abdel-Hassan et al., 2000). The hypoglycemic effect of Coccinia indica was partly mediated through suppression of the gluconeogenic enzyme glucose-6-phosphatase (Hossain et al., 1992).

Aqueous extract (0.5 g/L) of Eucalyptus globulus increased peripheral glucose utilization in the mouse abdominal muscle and stepwise enhancement of insulin secretion from the clonal pancreatic beta cell line by 70-160% (Gray and Flatt, 1988; Swanston-Flatt et al., 1990). A glucoside isolated from the bark of Ficus bengalensis showed more potent hypoglycemic action as compared to crude ethanolic extract, and the activity was half that of tolbutamide (Augusti, 1975; Augusti et al., 1994). Oral administration of leucopelarogonidin derivative (100 mg/kg) isolated from bark of Ficus bengalensis exerts significant hypoglycemic activity in normal and moderately alloxanized diabetic dogs (Augusti et al., 1994). Oral
administration of aqueous extracts of Gymnema sylvestre leaves (20 mg/day) for 20-60 days normalized blood sugar level of streptozotocin diabetic rats through β-cell regeneration (Shanmugasundaram et al., 1990a). Daily administration of (250 mg/kg) ethanolic extract of Hibiscus rosa-sinensis produced significant hypoglycemic effect at 30, 90 and 120 min after glucose loading in normal rats (Sachdeva and Khemani, 1999).

Oral administration of Impomoea batatas reduces hyperinsulinemia in Zucker fatty rats by 23, 26, 60 and 50% after 3, 4, 6 and 8 weeks, respectively. In addition, inhibition of blood glucose level after glucose loading was observed after 7 weeks of treatment along with regranulation of pancreatic β-cells and reduction in insulin resistance (Kusano and Abe, 2000). Administration of Lantana camara leaf juice (1500 mg/kg/day for 14 days) showed significant hypoglycemic effect in rats (Garg et al., 1997; Sachdeva and Khemani, 1999). Oral administration of alcoholic extract of the leaves of Memecylon umbellatum (250 mg/kg) caused a significant reduction in the serum glucose levels in normal and alloxanised rats at 30, 60 and 90 min after administration (Amalraj and Ignacimuthu, 1998). Oral feeding of powder of the fruit of Momordica cymbalaria (250 mg/kg for 15 days) caused significant reduction in fasting blood glucose in normal rats, possibly by increasing hepatic glycogen (Kameswara Rao et al., 1999). Experiments in rats showed that two important constituents of Momordica charantia, i.e., oleanolic acid 3-0-glucuronide and momordin Ic, exert anti-hyperglycemic effect by inhibiting glucose transport at the brush border of the small intestine (Matsuda et al., 1998).
Chronic subcutaneous administration of the extract of the leaves of *Morus alba* to rabbits led to degranulation of β-cells of the islets of Langerhans (Gulubova and Boiadzhiev, 1975). Intragastric administration of fresh flower decoction (4 ml/kg) of *Musa sapientum* to hyperglycemic rabbits significantly decreased the hyperglycemic peak and/or the area under the glucose tolerance curve (Alarcon-Aguilara et al., 1998). The hypoglycemic principles of *Mucuna pruriens* seeds may be both organic and mineral, which seem to act indirectly by stimulating the release of insulin and/or by a direct insulin-like action (Akhtar et al., 1990). Oral feeding of *Murraya koeingii* leaf diet (10% w/w) for 60 days to normal rats produced hypoglycemic effect associated with increased hepatic glycogen content due to increased glycogenesis and decreased glycogenolysis and gluconeogenesis (Khan et al., 1995).

Oral administration of ethanolic extract of *Nelumbo nucifera* rhizome (400 mg/kg) significantly reduced the blood sugar level of normal, glucose-fed hyperglycemic and streptozotocin–induced diabetic rats after 1 h. The extract also improved glucose tolerance and potentiated the action of exogenously injected insulin (Mukherjee et al., 1997). Ethanol extract (70%) of leaves of *Ocimum sanctum* has been shown to cause significant reduction of blood glucose level in normal, glucose-fed hyperglycemic and streptozotocin-induced diabetic rats. This effect was 91.55 and 70.43% of that of tolbutamide in normal and diabetic rats, respectively (Chattopadhyay, 1993). Alcoholic extract of *Picrorrhiza kurroa* showed anti-hyperglycemic effect in alloxanized diabetic rats. The serum glucose decreased by 43 and 60% with 75 and 50 mg/kg of the extracts, respectively (Joy and Kuttan, 1999). In a
clinical observation, oral administration of a preparation of the whole plant of *Phyllanthus amarus* (5 g/day in divided doses) for 10 days to 9 mild hypertensives subjects (4 with diabetes mellitus) reduced blood glucose in diabetic as well as non-diabetic subjects along with significant reduction in systolic blood pressure. No harmful side effects were noted in this study (Srividya and Periwal, 1995).

Numerous studies conducted by various author have shown hypoglycemic activity of the wood extract of *Pterocarpus marsupium* in different animal models (Saifi *et al*., 1971). Epicatechin, a pure flavonoid isolated from the ethanol extract of *Pterocarpus marsupium*, has been shown to possess significant anti-diabetic effect (Chakaravarthy *et al*., 1982; Sheehan *et al*., 1983). Phenolic constituents of *Pterocarpus marsupium*, such as marsupin and pterostilbene, significantly lowered blood glucose level in streptozotocin diabetic rats and the effect was comparable to that of metformin (Manickam *et al*., 1997).

Oral administration of aqueous or ethanolic extract (50% v/v) of *Punica granatum* flowers showed significant blood glucose lowering effect in glucose-fed hyperglycemic and alloxanized diabetic rats with the maximum effect at the dose of 400 mg/kg body weight (Jafri *et al*., 2000). Oral administration of aqueous decoction (1ml/rat/day) of *Salacia reticulata* root bark to overnight-fasted rats caused 30% reduction in glucose levels at 3 h (Karunanayake *et al*., 1984). Two biologically active fractions from the petroleum ether extract of the root bark of *Salacia oblonga* has been shown to exert
hypoglycemic effect with about 60 and 76% potency of an equal dose of tobutamide (250 mg/kg) in albino rats (Augusti et al., 1995).

Various crude extracts and their isolated fractions of *Swertia chirayita* have shown hypoglycemic activity in various animal models (Grover et al., 2002b). Isolated fibers, saponins and other proteins from fenugreek seeds given with meals for 21 days to alloxan–diabetic dogs showed significant antihyperglycemic and anti-glycosuric effects, along with reduction in high plasma glucagon and somatostatin (Ribes et al., 1984). Oral administration of the water extract of *Tinospora cordifolia* root (2.5, 5 and 7.5 mg/kg) caused a significant reduction in body weight, blood glucose, brain lipid, hepatic glucose–6–phosphatase, serum levels of acid phosphatase, alkaline phosphatase and lactate dehydrogenase, total hemoglobin and hepatic hexokinase in alloxanized diabetic rats (Prince and Menon, 2000). Oral administration of water soluble fraction of ethanolic extract of *Vinca rosea* leaves (100, 250, 500 and 1000 mg/kg) resulted in significant dose-dependent decrease in blood sugar at 4 h by 26.22, 31.39, 35.57 and 33.37%, respectively in normal rats (Chattopadhyay et al., 1991).
Elephantopus scaber (Fam : Asteraceae)

Genus Elephantopus of family Asteraceae is found in Tropical countries and contains 32 species (Willis, 1966). Elephantopus scaber L. is found throughout the dry or semi arid regions including central India where it is an important part of ground cover in forests and open places. The plant has been extensively used in different systems of medicine, for the treatment of various types of diseases (Singh et al., 1983; Aggarwal and Ghosh, 1985; Ambasta, 1986; Jain, 1991, 1999; Jain et al., 1991; Saklane and Jain, 1994; Varghese 1996; Pal and Jain, 1998; Varma et al., 1999; Kapoor, 2001; Sharma and Singh, 2001). The infusion and decoction of the whole plant, roots and leaves are used in folk medicine for the treatment of fever and to eliminate bladder stones (Jain, 1999). The plant extract is bitter, acrid, astringent, antipyretic, antidiabetic, diuretic and tonic. A decoction of the roots and leaves are given in dysuria, intermittent fevers,
diarrhoea, and bronchitis and especially for haemorrhoids and various other disease conditions (Warrier et al., 1995). The plant extract shows anticancer (Lee et al., 1980; Haruna et al., 1985; Hayashi et al., 1987; Poli et al., 1992; Kumar and Rao, 2002; Geetha et al., 2003) and antibiotic activity (Kapoor, 2001).

**Eugenia jambolana (Fam : Myrtaceae)**

It is widely distributed throughout India. Literature on Indian folk medicines mentions its use for the treatment of diabetes mellitus (Chopra et al., 1958; Nadkami, 1992). Preliminary scientific studies on *Eugenia jambolana* seeds have shown hypoglycemic effect (Mahaptra et al., 1985). Decoction of dry leaves of *Eugenia jambolana* has been shown to produce hypoglycemic effect (Coimbra et al., 1992). Oral feeding of this plant (170, 240 and 510 mg/rat for 15 days) caused 50% reduction in blood glucose of normal fasted rats while chlorpropamide showed 52% reduction. In addition, there was a 2.4–6.8-fold and 9.2-fold increase in cathepsin B activity (which brings about proteolytic conversion of proinsulin to insulin) by the plant extract and chlorpropramidine, respectively (Bansal et al., 1981). Oral administration of pulp extract of the fruit to normoglycemic and streptozotocin–induced diabetic rats brought about hypoglycemic activity in 30 min, possibly mediated by insulin secretion. In addition, the extract inhibited insulinase activity in the liver and kidney (Achrekar et al., 1991). Oral administration of dried alcoholic extracts of the seeds caused hypoglycemia and reduced glycosuria (Indira and Mohan Ram, 1992). The aqueous extract of seeds (2.5 and 5 g/kg for 6 weeks) showed hypoglycemic (> glibenclamide) and anti-oxidant activities. The hypoglycemic effect was most prominent at a dose of 5 g/kg, while no
significant effect was observed at 7.5 g/kg (Prince et al., 1998). Daily administration of lyophilized powder (200 mg/kg) brought about maximum reduction of 73.51, 55.62 and 48.8% as compared to their basal values in mild (plasma sugar > 180 mg/dl, duration 21 days), moderate (plasma sugar > 280 mg/dl) and severe (plasma sugar > 400 mg/dl, duration 60 days) diabetic rats. In addition, the treatment also partially restored altered hepatic and skeletal muscle glycogen content and hepatic glucokinase, glucose–6–phosphatase and phosphofructokinase activities (Grover et al., 2000). Fruits are used as astringent, stomachic, diuretic and anti-diabetic (Timbola et al., 2002). Hypoglycemic effect of this plant was also reported in fructose-fed rats (Vikrant et al., 2001). Pandhey and Khan (2002) reported that the hypoglycemic effect of this plant is due to water soluble gummy fibre, whereas the water insoluble neutral detergent fibre (NDE) and other constituents of the seeds have no significant hypoglycemic effects.

**Phyllanthus emblica** (Fam : Euphorbiaceae)

Fruits of *Phyllanthus emblica*, commonly known as ‘ama’ or the Indian gooseberry, are extensively used in the Ayurvedic and Sidha systems of medicine for the treatment of a wide spectrum of diseases (Dhir et al., 1991). It is the constituent of several marketed preparations such as Chyavanaprash, *Brahma Rasayan, Amalak, Haritaki, Triphala, Septilin*, etc., (Khandelwal et al., 2002). Some of the experimentally proved properties of the fruit included antifungal, antibacterial, antidiabetic (Daisy et al., 2004a,b), antipyretic, antioxidative (Bhattacharya et al., 1999), anticlastogenic, hepatoprotective (Jeena et al., 1999) adaptogenic (Rege et al., 1999) and antitumour activities (Jose et al., 2001). The fruit of *Phyllanthus emblica* is used for the treatment
of various cardiac problems (Chopra et al., 1958). Fruit extract of *Phyllanthus emblica* offered protective effect in experimental myocardial necrosis in rats (Tariq et al., 1977). It is believed that the major constituent responsible for these activities is vitamin C (ascorbic acid) (Khopde et al., 2001). *Phyllanthus emblica* is a constituent of various marketed Indian multiherb formulations for liver ailments, *viz.* Liver–52, Neoliv, Hepax, etc. It is reported to reduce serum, aortic and hepatic cholesterol in rabbits. In combination with iron, its dried fruit and fermented liquor prepared from fruit have been reported to be useful in jaundice.

Quercetin, a bioflavonoid present in *Phyllanthus emblica*, has been shown to prevent the cytotoxicity caused in isolated hepatocytes by carbon tetrachloride and terbutyl hydroperoxide (Gulati et al., 1995). Leaf extracts possess anti-inflammatory activity (Asmawi et al., 1983; Ihandolla–vormisto et al., 1997). Mishra et al. (1981) reported that *Phyllanthus emblica* has hypocholesterolemic activity. The fruit extracts inhibit clastogenicity and mutagenicity induced by various metals (Dhir et al., 1991; Aggarwal et al., 1992; Roy et al., 1992). Ghosh et al. (1992) have reported that protection offered by *amla* against CsCl–induced clastogenicity must be ascribed to vitamin C. However, Dhir et al. (1991) and Roy et al. (1992) reported that *amla* extract provides higher protection against clastogenicity and mutagenicity induced by lead and aluminium than equivalent amount of vitamin C, indicating that the combined action of different ingredients would be responsible for its biological activity. The therapeutic effect has been ascribed to its high vitamin C content and, possibly, to tannin-like compounds. The fruit extracts of *Phyllanthus emblica* have cytoprotective and
immunomodulatory properties which could fully be attributed to its anti-oxidant activity (Ram et al., 2002; Daisy et al., 2004b).

**Phyllanthus acidus (Fam : Euphorbiaceae)**

Fruits are edible, eaten raw or cooked, pickled or in jams or jelly (CSIR, 1950). Fruits are laxative, emetic, purgative (Perry and Metzger, 1980) and antidiabetic (Daisy et al., 2004a). Fruits are good source of Vitamins A and C and potassium (Nunez-Melendez, 1982; Unander et al., 1990). Seeds are used as an astringent, cathartic and sudorific (Martinez, 1959). Leaves and roots are used as an antidote to viper venom (Nadkarni and Nadkami, 1954). Aqueous extract of the wood is used as an antipyretic (Mokkhasmit et al., 1971). Decoction of the leaves showed antibacterial activity against *Bacillus subtilis* (Haicour, 1974).

**Clitoria ternatea (Family : Fabaceae)**

Clitoria ternatea or 'Shankhapushpi', a slender twiner, is a common garden flowering plant. The root has a sharp bitter taste and cooling, laxative, diuretic, antihelminthic and anti-inflammatory properties. The root is useful in severe bronchitis, asthma and hectic fever (Devi et al., 2003). The root is used by tribals to induce abortion while its paste is applied for curing abdominal swellings, sore throat, mucus disorders and fever (Asolkar et al., 1992). The root juice is given in cold milk to remove phlegm in chronic bronchitis. A preliminary study using fresh flowers of *Clitoria ternatea* showed hypoglycemic and hypolipidemic effects (Rajathi and Daisy, 2000). This plant is said to be a useful remedy for snake bite and scorpion sting (Chopra et al., 1982).