Introduction
Diabetes mellitus is a metabolic disease as old as mankind and its incidence is considered to be high (4-5%) all over the world (Pickup and Williams, 1997; Prince et al., 2003; Koyuturk et al., 2005). It is also a major cause of disability and hospitalization and it results in significant financial burden (Foster, 1994; Nagappa et al., 2003). It is a syndrome characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism associated with absolute or relative deficiency in insulin secretion or insulin action (ADA, 1997; Siyem et al., 2002; Jayakar and Suresh, 2003). When fully expressed, diabetes is characterized by fasting hyperglycemia (Annapurna et al., 2001; Maroo et al., 2002). The disease can be recognized, in less overt stages and before fasting hyperglycemia appears, by the onset of glucose intolerance. Diabetes mellitus may be suspected or recognized clinically by the onset of one or more of the characteristic symptoms such as polyuria, polydipsia, polyphagia and otherwise unexplained weight loss (Sharma, 1986; Kameswara Rao et al., 2001b; Sachdewa and Khemani, 2003). When the insulin deficiency is extreme, it leads to the development of ketoacidosis. Development of ketoacidosis is the major cause of death in men with diabetes (Zia et al., 2001).

Diabetes is also associated with a set of degenerative late complications involving various organs, which progress over many years (Lacy and Davie, 1984; Andallu and Vardacharyulu, 2002). It is now the leading cause of adult blindness, a major cause of renal failure, gangrene, myocardial infarction and stroke, and early development of atherosclerosis, which are responsible for severe morbidity and mortality associated with diabetes in men (Jaiprakash et al., 1995; Grover et al., 2002b). It is well

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established that excessive level of sugar leads to lens opacification. Aldose reductase, has also been implicated in the etiology of cataracts in diabetic animals (Srivastava and Afaq, 1988; Srivastava et al., 1988; Siddiqui et al., 2003).

Clinical diabetic nephropathy is characterized by polyuria, albuminuria, renal enlargement, and an increase in serum creatinine value (Rasch and Mogensen, 1980; Sassy-Prigent et al., 1995). Poor control of diabetes is associated with enlargement of the kidneys and a high glomerular filtration rate (Rasch, 1979a; Yotsumoto et al., 1997). Coronary artery disease, as a result of premature atherosclerosis, is a major cause of death both in type I and type II diabetes (ADA, 1989; ADA, 1997). Although the exact cause of premature atherosclerosis in diabetes is not well understood, several independent risk factors such as hypertriglyceridemia and hypertension may contribute to coronary artery disease (Kimura et al., 1984; Ferrannini et al., 1987; Zavaroni et al., 1987; Schwartz et al., 1993). It has been suggested that abnormalities in circulating lipids and blood pressure may relate to the insensitivity of peripheral tissue to insulin, not only in patients with diabetes, but also in a large subset of population with glucose intolerance, who have a strong tendency to develop diabetes (Zavaroni et al., 1989).

Diabetic nerve damage may affect visceral, somatic and cranial nerves, as well as spinal nerve roots, but signs of damage are generally present in more than one branch of the peripheral nervous system (Boulton and Ward, 1986; Anjaneyulu and Chopra, 2004). Currently available scientific evidence strongly suggests that the secondary complications arise as a consequence of
the metabolic derangements that characterize the diabetic state (Unger, 1992; Jaiprakash et al., 1993). Experimental and clinical evidences suggest that strict control of carbohydrate metabolism can prevent or, to some extent reduce, the progression of the secondary complications (Sutherland, 1981). The secondary complications are due to the ineffectiveness of the present forms of therapy to maintain the blood glucose levels within normal limits at all times (Lacy and Davie, 1984; Palumbo, 2001).

In the WHO classification, two major types of diabetes viz., type-I (insulin-dependent diabetes mellitus-IDDM) and type-II (non-insulin-dependent diabetes mellitus-NIDDM), which reflect the treatment mode as the basis of the classification have been identified (Dash, 1999; Chakrabarti et al., 2003). In insulin-dependent diabetes mellitus, beta (β) cells of islets of Langerhans are destroyed or altered. Insulin resistance is common in non-insulin dependent diabetes mellitus, and is enhanced by obesity, which in itself may be a cause of insulin resistance (Yajnik, 2001).

Insulin is a hormone secreted by β-cells of islets of Langerhans of pancreas (Hellerstrom, 1984; Rorsman, 1997; Niki, 1999). The discovery of insulin by Banting and Best and its extraction in 1922 are hailed as great milestones in diabetes research (Zia et al., 2001). The successful isolation of insulin marked the dawn of a new horizon in the treatment of diabetes. Treatment of diabetes mellitus consists fundamentally of diet management and/or pharmacological therapies, which attempt to normalize metabolic activities with special reference to glucose levels. Pharmacotherapy is based on two types of drugs viz., insulin injection and oral hypoglycemic agents
(Lebovitz and Pasmantier, 1990; Bailey, 1992; White, 1996; Ghosh and Suryawanshi, 2001). Insulin therapy offers effective glycemic control; yet, its shortcomings such as ineffectiveness on oral administration, short shelf life, and requirement of constant refrigeration and, in the event of excess dosage fatal hypoglycemia limit its usage (Rang and Dale, 1991; Anuradha et al., 2004). Due to the ineffectiveness of insulin through oral route in the treatment of diabetes, search was made for compounds, which would prove effective if taken orally. The oral hypoglycemic agents that are capable of reducing blood sugar level belong to two chemical classes, sulfonylureas and biguanides (Trejo-Gonzalez et al., 1996; Chatwal, 1999).

Biguanides lower blood glucose levels in pancreatectomized animals and, thus, do not act by stimulating the release of insulin from pancreas. They may act by virtue of inhibiting intestinal transport and absorption of sugars and at the level of liver by inhibiting gluconeogenesis by enhancing glucose uptake or inhibiting oxidative phosphorylation (Goth, 1985; Amalraj and Ignacimuthu, 1998). On the other hand, sulfonylureas, which are potent blood sugar lowering agents, act, mainly, by stimulating the release of endogenous reserves of insulin from pancreas (Jafri et al., 2000). The use of oral drugs is limited due to adverse side effects including hematological, cutaneous and gastrointestinal reactions, hypoglycemic coma and disturbances of liver and kidney functions. In addition, they are not suitable for use during pregnancy (Gerich, 1985; Larner, 1985; Alarcon-Aguillara et al., 2000).
Experimental diabetes was first induced by total pancreatectomy. In later years, production of experimental diabetes by the administration of certain chemicals was found to be an easier method than pancreatectomy. The substances most used to induce diabetes in the rat are alloxan and streptozotocin (Takasu et al., 1991; Garg et al., 1996). The diabetogenic property of streptozotocin, a nitrosoderivative of glucosamine was first reported in 1963 (Rakieten et al., 1963). It is an antibiotic extracted from Streptomyces achromogenes (Ganda et al., 1976; Mc Letchie, 2002). Dunn and Mc Letchie made a remarkable discovery in 1943 that a single injection of alloxan can produce diabetes mellitus in experimental animals. Alloxan (2,4,5,6-tetraoxypyrimidine; 5,6-dioxyuracil), a simple nitrogenous organic compound, was originally obtained by the action of dilute nitric acid on uric acid (Lenzen et al., 1988; Szkudelski, 2001). Alloxan exerts its diabetogenic action when it is administered intravenously, intraperitoneally or subcutaneously. The dose of alloxan required for inducing diabetes depends on the animal species, route of administration and nutritional status. Fasted animals are more susceptible to alloxan (Katsumata et al., 1992; Szkudelski et al., 1998).

Alloxan is a hydrophilic and unstable substance. Its half-life at neutral pH and 37°C is about 1.5 min and is longer at lower temperatures (Lenzen and Munday, 1991). Alloxan, because of its diabetogenic properties, is used to induce experimental diabetes in animals. Its diabetogenic action results from its selective cytotoxicity in relation to insulin secreting pancreatic cells (Dunn et al., 1943; Weaver et al., 1978; Gorus et al., 1982; Tiedge et al., 1997). The compound inhibits the activity of glucokinase in the β-cells of the
islets of Langerhans of pancreas (Lenzen et al., 1987; Lenzen and Mirzaie-Petri, 1991) and contributes to the formation of a radical, which causes damage and death of the cells (Grankvist, 1981; Jorns et al., 1997).

Because of the limitations of the currently practised therapies for diabetes mellitus, there remains an interest in alternative treatments (Katin and Schechter, 1991; Roman-Ramos et al., 1992, 1995; Trejo-Gonzalez et al., 1996). Alternative strategies to the currently practised pharmacotherapies of diabetes mellitus are urgently needed because of the ineptness of the existing modern therapies to control all the pathological aspects of the disorder, as well as the enormous cost and poor availability of the modern therapies for much of the rural population in the developing countries (Gerich, 1985; Groop et al., 1985; Trejo–Gonzalez et al., 1996). During the last two decades, traditional systems of medicine and medicinal plant research have become topics of global interest and importance (Platel and Srinivasan, 1997; Ojewole, 2002).

Since the time of Charaka and Sushruta, many herbal medicines in different oral formulations have been recommended for the treatment of diabetes mellitus (Grover and Vats, 2001; Santhakumari et al., 2003). Medicinal plants have been found to possess certain active principles useful for treating diseases (Akhtar, 1985). Herbal drugs are considered to be less toxic and more free from side effects than synthetic chemicals (Momin, 1987; Atta-Ur-Rahman and Zaman, 1989; Bailey and Day, 1989; Ivorra et al., 1989; Alarcon-Aguilera et al., 1993; Al-Khazraji et al., 1993; Roman-Ramos et al., 1995). World Ethnobotanical Information about medicinal plants reports
almost 800 plants used in the control of diabetes mellitus (Alarcon-Aguilara et al., 1998; Grover et al., 2002b). Several such plants have shown antidiabetic activity when assessed adopting the presently available experimental techniques (Saifi et al., 1971; Mukherjee et al., 1972; Ajitkar et al., 1999; Jafri et al., 2000). A wide array of active principles, representing numerous chemical compounds, has demonstrated activity consistent with their possible use in the treatment of NIDDM. Among these are alkaloids, glycosides, galactomannose, polysaccharides, peptidoglycans, hypoglycans, guanidine, steroids, carbohydrates, glycopeptides, terpenoids, amino acids and inorganic salts (Ivorra et al., 1988; Bailey and Day, 1989; Marles and Farnsworth, 1995).

The impetus to carry out this investigation came up after reading Folklore, Indian Systems of Medicine and Scientific Literature on the medicinal properties of the following five plants. *Elephantopus scaber* Linn., commonly known as Anachuvadi, belongs to the Family Asteraceae. It is a mucilaginous plant, an astringent and used as tonic (Warrier et al., 1995; Geetha et al., 2003). A decoction of the root and leaf is reported to be administered in dysuria, diarrhea, dysentery and swelling or pain of the stomach. The root of the plant is reported to arrest vomiting and, in the form of powder with pepper powder, is applied for toothache (Upadhayay and Pandey, 1984; Jain and Singh, 1997; Jain, 1999).

*Eugenia jambolana* Linn., belongs to the Family Myrtaceae and is commonly called Jamun. Various medicinal properties of *Eugenia jambolana*, including its astringent, diuretic and anti-diabetic properties, have been
described in traditional medicine (Nadkami, 1992; Prince et al., 2003). The Jamun tree is large and evergreen, and is native to India but is also found in other parts of the world especially in tropical countries (Chopra et al., 1958; Indira and Mohan Ram, 1992).

*Clitoria ternatea* Linn., belonging to the Family Fabaceae, is a perennial twining herb, found in Indo-China, Philippines and Madagascar (Devi et al., 2003). Since the flowers of the plant resemble a conch shell, it is commonly called “Shankpushpi” (Kulkami et al., 1988). *C. ternatea* is reported to be a good “Medhya” (toning the brain or mental faculty) drug mainly used in the treatment of ‘Manasika’ roga (mental illness), but it is also said to be useful in hectic fever (Nadkami and Nadkarni, 1976).

*Phyllanthus emblica* Linn. (Fam: Euphorbiaceae), also known as amla or the Indian gooseberry, has been used in Ayurveda, the ancient Indian systems of medicine (Dhir et al., 1991; Khopde et al., 2001), for treatment of several disorders such as common cold, scurvy, cancer and heart diseases (Chopra et al., 1956; Ram et al., 2002). *Phyllanthus acidus* Linn., also belongs to the Family Euphorbiaceae and is commonly called as star gooseberry (Rizk, 1987; Unander et al., 1990). *P. acidus* is less known than *P. emblica* in the indigenous systems of medicine.

*Eugenia jambolana* plant is well known in the indigenous systems of medicine for diabetes mellitus, whereas *Elephatopus scaber*, *Clitoria ternatea*, *Phyllanthus emblica*, and *Phyllanthus acidus* are less well known in this regard. Therefore, the present study was undertaken to evaluate the effectiveness of *E. scaber* (leaf/root), *E. jambolana* (bark/seed), *C. ternatea*
(flower/leaf), *P. emblica* (fruit) and *P. acidus* (fruit) in untreated and alloxan-induced diabetic rats.

**The objectives of the study are as follows:**

1. To assess the hypoglycemic effects of *Elephantopus scaber* (leaf/root), *Eugenia jambolana* (bark/seed), *Clitoria ternatea* (flower/leaf), *Phyllanthus emblica* (fruit) and *Phyllanthus acidus* (fruit) in alloxan–induced diabetic albino rats.

2. To elucidate the biochemical mechanism of action of the above mentioned plant parts as oral hypoglycemic agents.

3. To find the toxic effects, if any, of the above mentioned plant parts in tissues like liver, kidney and pancreas.

4. To identify the hypoglycemic active principle(s) in the above mentioned plant parts.