The incidence of diabetes mellitus has increased dramatically in recent decades, predominantly because of changes in lifestyle, an increase in the prevalence of obesity and longevity (Heydari et al., 2010). Current projections estimate that there are about 366 million diabetic people around the world and the number is expected to reach 552 million cases by the year 2030 (IDF, 2011). India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the ‘diabetes capital of the world’ (Mohan et al., 2007). According to the Diabetes Atlas (2012), published by the International Diabetes Federation (IDF), the number of people with diabetes in India currently around 63 million is expected to rise to 101 million by 2030 unless urgent preventive steps are taken (IDF, 2012). In 2011, India had 62.4 million people with type 2 diabetes, compared with 50.8 million the previous year, according to the International Diabetes Federation (IDF) and the Madras Diabetes Research Foundation (Shetty, 2012).

The term ‘diabesity’ was famously coined by Sims and colleagues in the 1970s, to highlight the close relationship between type 2 diabetes and obesity (Haslam, 2010). Increased rates of obesity due to low levels of physical activity and high-energy diets are driving the global epidemic of type 2 diabetes (Zimmet et al., 2001). Obesity is set to be the world’s major cause of morbidity and mortality in the 21st Century. According to World Health Organization (WHO), more than 1.4 billion adults were overweight in the world, and at least 200 million men and nearly 300 million women from them were obese (WHO, 2012). An INDO-US collaborative study conducted among Asian Indians by Dr Anoop Misra and his team, recorded that the prevalence of obesity in urban areas was 65.41% and 31.8% in rural areas, respectively (NDOC, 2013). Further, it has been observed that Indians exhibit unique features of obesity viz. excess body fat, abdominal adiposity, increased subcutaneous and intra-abdominal fat, and deposition of fat in ectopic sites. In addition, improvement in the economic situation of the India, the prevalence of obesity is showing an marked upward trend in adults (NDOC, 2013).

Obesity (defined as a body mass index [BMI] of greater than 30 kg/m²) results, when energy intake exceeds energy output with the excess being stored as fat in adipose tissue and ectopically in other tissues (Yao and MacKenzie, 2010). The most frequent pathologic
condition associated with excess body fat and particularly with visceral obesity is known as the ‘Metabolic Syndrome’, a group of symptoms, signs and pathophysiological conditions which include visceral obesity, insulin resistance, impaired glucose metabolism, type 2 diabetes, dyslipidemia, elevated blood pressure, and other comorbidities including a prothrombotic and proinflammatory state and nonalcoholic fatty liver disease (Capurso and Capurso, 2012). Most of the individuals diagnosed with type 2 diabetes are found to be obese (Ramarao and Kaul, 1999).

The increased body weight found in obese individuals might be due to the consumption of a diet rich in energy in the form of saturated fats and its deposition in various body fat pads and decreased energy expenditure. The presence of high level of triglycerides due to excess fat intake could constitute a source of increased fatty acid availability and oxidation. The preferential use of increased fatty acids for oxidation blunts the insulin-mediated reduction of hepatic glucose output and reduces the glucose uptake or utilization in skeletal muscle leading to compensatory hyperinsulinemia, a common feature of insulin resistance (Belfiore and Iannello, 1998).

Type 2 diabetes mellitus is a heterogeneous disorder characterized by a progressive decline in insulin action (insulin resistance), followed by the inability of β-cells to compensate for insulin resistance (pancreatic β-cell dysfunction). Most adverse diabetes outcomes are a result of vascular complications, both at a macrovascular level i.e. coronary artery disease, cerebrovascular disease, or peripheral vascular disease) and a microvascular level i.e. retinopathy, nephropathy, or neuropathy (UKPDS, 1998). The medical and socioeconomic burden of the disease is caused by the associated complications, which impose enormous strains on health-care systems. ‘Asian Indian Phenotype’ refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels, makes Asian Indians more prone to diabetes and premature coronary artery disease (Deepa et al., 2006; Enas et al., 2007).
Adipokines particularly leptin, adiponectin and free fatty acid (FFA) play an important role in the pathogenesis of obesity, pancreatic β-cell dysfunction and type 2 diabetes. Adipocytes secrete a variety of products known as ‘adipokines’, which play an important role in energy and glucose metabolism (Yaturu, 2011). Leptin has been implicated in the regulation of food intake, energy expenditure, and whole-body energy balance in rodents and humans (Wang et al., 2011). Adiponectin is recognized as a key determinant of insulin sensitivity and of protection against obesity-associated metabolic syndrome (Vasseur et al., 2006). Obesity, insulin resistance and diabetes are associated with reduction in serum adiponectin levels (Wang et al., 2011). However, serum leptin levels have been reported to be increased in obesity and decreased in diabetes (Wang et al., 2011).

Insulin is the principal hormone of glucose homeostasis; it stimulates glucose influx into muscle, glycogen synthesis in the liver and muscle, and fat deposition in adipocytes. Other important actions of insulin include the enhancement of protein synthesis, cell survival and growth, prevention of protein catabolism, and anti-inflammatory effects (Saltiel and Kahn, 2001). Obesity-associated type 2 diabetes is evidenced by increased glucose levels in the blood, which result from elevated glucose production in the liver (gluconeogenesis and glycogenolysis) and decreased glucose uptake by muscle. Glycogen is the primary intracellular storable form of glucose and serves as a tissue reserve for the body's glucose needs. The conversion of glucose to glycogen in liver cells is dependent on the presence of insulin as insulin stimulates intracellular glycogen synthesis by stimulating glycogen synthase and inhibiting glycogen phosphorylase (Stalmans et al., 1991). A defect in this process is a major contributor to postprandial hyperglycemia. Indeed, the glycogen contents of the liver and skeletal muscle are reduced in individuals with type 2 diabetes (Shulman et al., 1990; Magnusson et al., 1992).

The hepatic glucose-6-phosphatase (Glc-6-Pase), an enzyme found mainly in the liver and the kidneys, plays a key role in the regulation of blood glucose homeostasis. Both gluconeogenesis and glycogenolysis result in the formation of glucose 6-phosphate (Glc-6-P), which is hydrolysed by Glc-6-Pase before being liberated as glucose into the circulation.
Activities of liver microsomal Glc-6-Pase have been reported to be up-regulated in diabetic states (Pushparaj et al., 2007).

Accompanying insulin resistance, β-cell dysfunction is another important pathophysiological change in type 2 diabetes. β-cell dysfunction occurs long before the occurrence of type 2 diabetes and progresses with the development of obesity. The role of β-cell dysfunction in the pathogenesis of type 2 diabetes has gradually been revealed in recent years (Zhao et al., 2006). The β-cells normally compensate insulin resistance by secreting more amounts of insulin to maintain the glucose homeostasis. In the course of time, however, this β-cell function gets impaired leading to deterioration in glucose homeostasis and subsequent development of impaired glucose tolerance and frank diabetes (Saltiel and Olefsky, 1996; Lebovitz and Banerji, 2004).

Blood pressure levels are strongly associated with visceral obesity and insulin resistance (Ferrannini et al., 1997). Aggressive blood pressure control may be the most important factor in preventing adverse outcomes in patients with type 2 diabetes (Vijan and Hayward, 2003).

Diabetes is often associated with blood lipid abnormalities, mainly increased levels of total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and decreased levels of high density lipoprotein cholesterol (HDL-C), which lead to high blood pressure, atherosclerosis and coronary heart disease (Haffner, 1998). Insulin resistance and the ‘relative’ insulin deficiency, observed in patients with type 2 diabetes, are likely to play a crucial role since insulin has an important function in the regulation of lipid metabolism. In addition, other factors, such as adipokines could also be involved in the pathophysiology of lipid abnormalities in type 2 diabetes (Vergès, 2005).

Lipases functions as a lipolytic enzyme that hydrolyzes TGs and phospholipids in circulating plasma lipoproteins. Among lipase, pancreatic lipase is the principal lipolytic enzyme synthesized and secreted by the pancreas. It is responsible for the hydrolysis of 50-70% of total dietary fats to monoglycerides and free fatty acids. Reduction of fat absorption
by the inhibition of pancreatic lipase is known to be beneficial for the regulation of obesity and related metabolic disorders (Birari and Bhutani, 2007).

Nephropathy is one of the major complications of both type 1 and type 2 diabetes mellitus, and the morbidity and mortality due to diabetic nephropathy continues to increase in industrialized nations (Balakumar et al., 2009). Nephropathy associated with type 2 diabetes is much more widespread and account for about one third of all patients requiring kidney replacement therapy in western countries (Ruggenenti and Remuzzi, 2000). Diabetic nephropathy is characterized by a progressive increase in albuminuria, proteinuria, reduction in glomerular filtration rate (GFR), hypertension, and a high risk of cardiovascular morbidity and mortality (Balakumar et al., 2009). Insulin plays a homeostatic role in normal kidney function. However, insulin-resistance has been associated with alterations in glomerular hemodynamics and renal damage (Knight and Imig, 2007). Currently, measuring urine albumin excretion and creatinine (for estimation of GFR) remains the most effective screening method for the early detection of diabetic nephropathy (Kramer, 2004). Increased levels of lactate dehydrogenase (LDH) are found in renal, hepatic, pulmonary and cardiovascular diseases. Alkaline phosphatase (ALP) levels are significantly increased in human patients suffering from renal insufficiency (Sanchez Navarro et al., 2002). Further, it has been shown that ALP-enzyme-regulating gene is expressed not only in the liver but also at high level in the kidneys too (Lindblom et al., 2007).

Oxidative stress is believed to play an important role in the development of vascular complications in obesity and type 2 diabetes. Oxidative stress has been linked to high plasma glucose concentrations as well as with high reactivity of the polyol pathway, glucose autooxidation and protein glucosylation. These mechanisms enhance the production of oxidative molecules and reduce the antioxidant defense (Halliwell and Gutteridge, 1999; Ahmed, 2005). Hyperglycemia can inactivate enzymatic antioxidants such as superoxide dismutase (SOD) and catalase (CAT) by glycating these proteins, thus, promotes free radical generation, which results in lipid peroxidation (Kennedy and Lyons, 1997). Malondialdehyde (MDA) is a by-product of lipid peroxidation and reflects the degree of
oxidation in the body (Ohkawa et al., 1979). Glutathione (GSH) is one of the most prominent non-enzymatic antioxidant in the liver and its level in liver reflects the detoxification potential of the liver. GSH concentration is found to be decreased in the liver, kidney, pancreas, and kidneys of chemically induced diabetic animals (Maritim et al., 2003).

The rising concern over obesity as a global health hazard is relatively recent and it has outpaced the pharmaceutical industry’s ability to develop new and safe drugs. Current therapeutic strategy for treating obesity and related metabolic disorders includes diet control, physical exercise, surgery, and medications (Hamilton, 2002), but their side effects remain a major clinical problem. Diet and exercise are the most obvious remedies for obesity but have proved ineffective for most individuals (Wu et al., 2009). Despite the increasing need for new anti-obesity therapeutics, the food and drug administration (FDA) has not approved a new anti-obesity drug since orlistat in 1999. In 2008, reports of increased depression and suicide led an FDA panel to recommend that Rimonabant, a potent, selective endocannabinoid (CB1 receptor) inverse agonist, be denied approval despite promising results in clinical trials. The European Medicines Agency also suspended its approval in 2008. Sibutramine, a centrally-acting serotonin–norepinephrine reuptake inhibitor structurally related to amphetamines, was introduced in the US market in 1997. It was, however, removed from both the UK and US markets in 2010 due to increased cardiovascular risks. Currently, orlistat is the only drug FDA-approved for long-term obesity management. It is sold with prescription under the name of Xenical (Roche Pharmaceuticals) and over-the-counter as Alli (GlaxoSmithKline). Orlistat is a lipase inhibitor that reduces intestinal fat absorption and has undesirable gastrointestinal side effects such as steatorrhea. In addition, reports of severe liver injuries prompted the FDA to issue a warning on May 2010 (Colon-Gonzalez et al., 2013). This history of obesity pharmacotherapy highlights the need for new, safer, and more effective approaches to treat and prevent obesity.

The current treatment for type 2 diabetes includes insulin and oral hypoglycemic drugs like biguanides, sulfonylurea derivatives, thiazolidinediones and α-glucosidase inhibitors. These
medications have plenty of side effects, such as thiazolidinediones induce obesity, osteoporosis and sodium retention; incidences of severe hypoglycemia due to sulfonylurea derivatives, and biguanide (metformin) put patients at risk of developing lactic acidosis (Hamza et al., 2010). Further, the oral monotherapy with lifestyle changes is not sufficient for most diabetic patients and requires various oral combinations or addition of insulin (Stumvoll et al., 2005). Thus, there is an increasing need to search for more effective antidiabetic agents with fewer side effects.

Natural products/dietary photochemicals have aroused considerable interest in recent years as potential therapeutic agents to counteract obesity and type 2 diabetes (González-Castejón and Rodriguez-Casado, 2011). India has a long history of using herbs/natural products for the treatment of human diseases and several medicinal plants are used for the treatment of diabetes (Modak et al., 2007). *Embelia ribes* Burm.f. is one such plant belongs to the family Myrsinaceae. In the traditional Indian System of Medicine ‘Ayurveda’, it has been used to treat fever, inflammatory diseases, and a variety of gastrointestinal ailments for thousands of year (Gupta et al., 1977). In a preliminary study, Tripathi et al., (1979) reported the anti-hyperglycemic activity of the decoction of *E. ribes* in glucose-fed albino rabbits. Bhandari et al., (2002) reported the potential of *E. ribes* ethanolic extract in diabetic dyslipidemia and protection from lipid peroxidation in tissues in streptozotocin (STZ)-induced diabetic rats. Further, therapeutic usefulness of ethanolic extract of *E. ribes* on the tissue antioxidants, blood pressure and glycosylated haemoglobin was investigated in streptozotocin-induced oxidative damage in rats (Bhandari et al., 2007, 2008).

*E. ribes* fruits contain a quinone derivative embelin, an alkaloid christembine and a volatile oil vilangin (Rao and Venkateswarlu, 1961). Among them, embelin is considered one of the major bioactive constituents and marker compounds in *E. ribes* fruits (Chauhan et al., 1999; Chitra et al., 2003; Latha., 2006). Embelin (3-undecyl 2,5-dihydroxy,1,4-benzoquinone) has a wide spectrum of biological activities, including antitumor, antibacterial, antioxidant, analgesic, antifertility, wound healing, anticonvulsant, and antidiabetic activities (Mahendran et al., 2011).
However, *E. ribes* has not been investigated so far for its potential in obesity and type 2 diabetes mellitus. As the development of obesity and type-2 diabetes is progressing at an increasing percentage in the populations of western societies and developing countries there is a great need for relevant models of obesity, type-2 diabetes and related metabolic syndrome. Therefore, in the present study, a rat model of diet-induced obesity and type 2 diabetes was selected on the basis of numerous experimental studies which indicated that diets high in fat are known to increasing body weight and fat mass, induce alterations in carbohydrate and lipid metabolism, leading to insulin resistance, and increased production and release of leptin in humans, rodents, and other animals (Mooradian *et al.*, 2000; Brown *et al.*, 2002; Reuter, 2007).

Reed *et al.* (2000) and Srinivasan *et al.* (2005) reported that a low-dose STZ injection leads to the partial destruction of pancreatic β-cells and a high-fat diet (HFD) induces insulin resistance in rodents. The degree of β-cell destruction and insulin resistance can be adjusted by dosage, duration and condition of STZ injection and HFD feeding (Shertzer *et al.*, 2008). Further, the effects of various glucose-lowering drugs have been examined in rats treated with low dose STZ and HFD as a model of type 2 diabetes (Srinivasan *et al.*, 2005).

The present study was planned to investigate the ethanolic extract of *Embelia ribes* Burm.f. for its antiobesity potential in HFD-induced obesity and antidiabetic potential in HFD plus low dose STZ-induced type 2 diabetes in Wistar rats.