Obesity increases the risk of medical illness and premature death and thus, imposes a massive economic burden on the health care system indicating the great importance of obesity treatment (Mauro et al., 2008). Obesity prevalence rates are steadily rising in the majority of the modern Western societies, as well as in the developing world (Chiara et al., 2012; Shen et al., 2012). Obesity has reached epidemic proportions in India in the 21st century, with morbid obesity affecting 5% of the country's population (NFHS, 2010).

Obesity, along with excess weight, is now the most prevalent cardiovascular risk factor in individuals with established coronary heart disease (Lo‘pez-Jime´nez and Corte´s-Bergoderi, 2011). Obesity increases the risk of diabetes, coronary artery disease, fatty liver, gall stones, sleep apnea, arthritis, and cancer and may shorten the lifespan (Ogden et al., 2007). Obesity and its associated conditions such as insulin resistance, type 2 diabetes, dyslipidemia, and steatosis hepatitis termed as the ‘metabolic syndrome’, represent major challenges for basic science and clinical research (Buettner et al., 2006).

The selected problem for the present study was entitled “To investigate the modulatory role of statin treatment on various cardiovascular biomarkers in murine model of high fat diet-induced obesity”. Effects of statin namely rosuvastatin and pitavastatin were explored in obese rat models and compared with standard antiobesity drug, orlistat which is the only approved drug for long term treatment of obesity.

In plan I (HFD obese model), the obesity was induced by standardized high fat diet (HFD) in female Wistar rats. Obesity is a disorder of energy balance and primarily considered as a disorder of lipid metabolism (Birari et al., 2011). Obesity results from an imbalance between food intake and energy expenditure, culminating in excessive accumulation of fat in adipose tissue, liver, muscle, pancreatic islets, and other organs involved in metabolism.

It is obvious that appropriate animals models are crucial for studies on the pathogenesis and therapy of this complex metabolic disorder (Buettner et al., 2006). Dietary fat is one of the most important environmental factors associated with the incidence of cardiovascular diseases (CVD) (Hsu and Yen, 2007). Fat-enriched diets have been used for decades as a model of obesity, dyslipidemia and insulin intolerance in rodents (Almind and Kahn 2004; Buettner et al., 2006). It has been observed that the disorders achieved by high-fat feeding resemble the human metabolic syndrome as was characterized by the increased body weight (obesity), mild hyperglycemia,
hypertriglyceridemia, hypercholesterolemia and compensatory hyperinsulinemia together with reduced glucose disappearance rate, and this also may extend to the cardiovascular complications (Woods et al., 2003; Srinivasan et al., 2005). A rodent model of obesity based on the intake of HFD is advantageous in studying obesity-related cardiovascular abnormalities (Carroll et al., 2006). The feeding of HFD for 2-4 weeks produced a significant increase in body weight, total fat pads’ weight, basal/fasting plasma glucose, insulin, basal triglyceride (TG) and total cholesterol (TC) levels in male rats (Srinivasan et al., 2004). Epidemiologic studies have demonstrated that the prevalence of obesity is greater in women compared to men (Ogden et al., 2003). Studies in rats have also exposed that females gain more weight and have a different metabolic response from males under HFD feeding (Priego et al., 2008).

The introduction of the rosuvastatin and pitavastatin were the major advances in the prevention and treatment of cardiovascular disease. Several clinical trials have demonstrated the benefit of lipid lowering with rosuvastatin as well as pitavastatin for the primary prevention of coronary heart disease (Igel et al., 2002). Although it is widely accepted that the majority of benefit obtained with rosuvastatin and pitavastatin are a direct result of their lipid-lowering properties, pitavastatin appears to display additional cholesterol-independent or pleiotropic effects, such as improving endothelial function, the insulin sensitivity, and antiinflammatory effects (Kawai et al., 2011; Ishihara et al., 2010).

Effect of HFD on baseline characteristics of obesity in female Wistar rats was assessed by feeding of HFD for a period of 1 week. Suitably designed and HFD by National Centre for Laboratory Animal Sciences (NCLAS), National Institute of Nutrition (NIN), Hyderabad, India was used in the present study. The HFD was formulated such that it causes insulin resistance, obesity in rats over a short period of time. Obesity induced by HFD was characterized by the increased body weight, insulin resistance, mild hyperglycemia, hypertriglyceridemia and hypercholesterolemia (Table 12). The amplified body weight found in HFD rats 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 as compared to normal pellet diet (NPD) control rats (Storlien et al., 1986 Srinivasan et al., 2004).

The study has investigated the effect of rosuvastatin and pitavastatin on a number of parameters and compared with a standard antiobesity drug orlistat.
High fat diet not only induces obesity in humans but also make animals obese (Buettner et al., 2007). In animal models as in humans, obesity can be assessed by criteria based on (1) gain of body weight or the Lee obesity index and (2) increase of body fat content (Ghibaudi et al., 2002). In most studies, the degree of obesity has been evaluated by comparing body weight (or fat) of the experimental group fed high-fat diet with control animals that show normal growth (Woods et al., 2003; Buettner et al., 2007).

The body mass index (BMI), calculated as weight (kg) divided by height squared (m²), is used as a diagnostic tool for measurement of obesity clinically (WHO, 1995). However, it does not distinguish between weight associated with muscle and weight associated with fat, BMI provides only a crude measure of body fatness (WHO, 2000).

The Lee index [body weight (g)\(^{1/3}\) divided by the naso-anal length (cm) × 1000] for assessing obesity in rats is similar to BMI in humans (Li et al., 2006). Lee index indicates the degree of obesity characterized by extraordinary adiposity in monosodium glutamate (MSG) obese rats which resembles human visceral obesity (Iwase et al., 2000).

Eating and drinking are compelled and controlled by positive and negative drives of hunger, thirst, and satiety. Obesity results when energy intake exceeds energy expenditure. Epidemiological studies have identified a significant positive correlation between average dietary fat intake and the incidence of obesity (Kuller, 1997).

Obesity is defined as increased mass of adipose tissue and confers a higher risk of arterial blood pressure (BP) elevation or hypertension (Mark et al., 1999). On the other hand, weight reduction lowers BP in obese hypertensive subjects, suggesting an important association between energy homeostasis and BP (Zhang and Reisin, 2000).

The measurement of fat distribution has become an important issue in obesity research (Sobol et al., 1991). In fact, the accumulation of intra-abdominal visceral fat in the mesentery and omentum is a better predictor of coronary heart disease than the body mass index (Nakamura et al., 1994).

Leptin is a circulating hormone that is expressed abundantly and specifically in adipose tissue, although it is also secreted from human placenta. Leptin induces a complex response involving control of body weight and energy expenditure (Auwerx et al., 1998).

Insulin resistance syndrome is linked with obesity, which is accompanied by high leptin levels (Considine et al., 1996). Weight loss is associated with a decrease in insulin concentration and an increase in insulin sensitivity in adults (Su et al., 1995).
Increasing upper body obesity is accompanied by a progressive increase in the glucose levels. Obesity is always accompanied by excess lipid accumulation, impaired glucose tolerance, and elevated serum triacyl glycerol concentration; thus, it is positively associated with the progression of various chronic diseases such as type 2 diabetes mellitus, cardiovascular diseases, and cancers (Chang et al., 2011).

Visceral obesity is frequently associated with high plasma triglycerides (TGs) and low plasma high density lipoprotein-cholesterol (HDL-C), and with high plasma concentrations of apolipoprotein-B (apo-B)-containing lipoproteins (Chan et al., 2004). Further, it may involve increased hepatic secretion of very-low-density lipoprotein (VLDL) and impaired catabolism of VLDL, intermediate-density lipoprotein (IDL), and low density lipoprotein (LDL)-apo-B. These abnormalities may be consequent on insulin resistance which is very much associated with obesity (Chan et al., 2010).

The sodium (Na) and potassium (K)-activated adenosine-triphosphatase (Na⁺K⁺-ATPase) is a membrane enzyme that rejuvenates the Na-pump by hydrolysing adenosine triphosphate and wasting energy as heat, so sharing a role in thermogenesis and energy balance (Iannello et al., 2006).

Obesity has been shown to be one of the conditions that decrease antioxidant capacity (Watson et al., 1999). Obesity decreases antioxidant defense by lowering the levels of antioxidant enzymes [catalase, glutathione peroxidase (GPx) and glutathione reductase (GR)] (Carmiel-Haggai et al., 2005; Asayama et al., 2001).

In human and animal models, the development of obesity leads not only to increased fat deposit in classic adipose tissue location but also to significant lipid deposit in other organs (Sobol et al., 1991).

Treatment with rosuvastatin, pitavastatin and orlistat produced significant reduction in levels of body weight, BMI, B.P., visceral fat pads’ weight (mesenteric, uterine and perirenal), organ weight (heart, liver and kidney), serum leptin, insulin, blood glucose, HOMA-IR, apo-B, TC, TGs, LDL, LVDL, atherogenic risk predictor indices, LDH, hepatic and cardiac lipid peroxides (TBARS), and elevation in serum HDL-C level, hepatic and cardiac Na⁺K⁺-ATPase contents, antioxidant enzymes’ contents (GSH, GPx, GR, GST, CAT & SOD). These results were further supported by histopathological findings. The results of rosuvastatin & pitavastatin treatment in high fat-fed rats were comparable with standard antiobesity drug, orlistat.

In the present study, high fat-fed rats (Group II & X) produced a significant increase in body weight as compared to NPD control rats (Group I). Treatment with (2.5, 5 & 10
mg/kg i.e. Groups III-V respectively, p.o.), pitavastatin (0.5, 1 & 3 mg/kg i.e. Groups XI-XIII respectively, p.o.) and orlistat (10 mg/kg i.e. Group VI, p.o.) along with HFD for a period of 21 days significantly suppressed the elevated body weight as compared to HFD control rats (Figure 4 and 12). Further, treatment with rosuvastatin per se (Group VII), pitavastatin per se (Group XV) and orlistat per se (Group XVI) for a period of 21 days produced significant reduction in body weight as compared to NPD control rats. This result is consistent with that reported in a previous study by Araki et al. (2008), in which peripheral administration of pravastatin was found to decrease body mass without inducing hypophagia. Araki et al. (2008) found that the pravastatin at100 mg/kg, p.o. for a period of 28 days significantly reduced the body weight as compared to diet induced obese mice. While Zhao and Wu (2005) found that atorvastatin at 2.5 mg/kg/day for 6 weeks produced no significant change in body weight in high cholesterol diet fed rabbits. This suppression on body weight gain in the present study did not depend on decreased food intake, as no significant differences were found in food intake among the different treatment groups (Table 13 and 20).

BMI is an easily obtainable measurement showing correlations with percentage body fat, absolute fat mass and serum leptin (Horlick et al., 2000). BMI is a simple index of weight-for-height that is commonly used to classify underweight, overweight and obesity in adults (WHO, 1995). There was significant increase in BMI in HFD control rats (Group II & X respectively) as compared to NPD control rats. Treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat along with HFD for a period of 21 days produced significant reduction in BMI as compared to HFD control rats respectively. The treatment with rosuvastatin per se (Group VII), pitavastatin per se (Group XV) and orlistat per se (Group XVI) for a period of 21 days produced significant reduction in BMI as compared to NPD control rats (Figure 5 and 13). The significant reduction in body weight and BMI of rosuvastatin, pitavastatin, rosuvastatin per se and pitavastatin per se treated rats indicate the antiobesity potential of both rosuvastatin and pitavastatin.

Activation of the sympathetic nervous system contributes to blood pressure (BP) elevation in high-fat diet-induced obesity (Iwashita et al., 2002). A high-fat diet (HFD), which frequently induces BP elevation, could derange the neurohumoral control of the kidney (Hall et al., 1993). Kaufman et al. (1991) investigated the effect of HFD on BP and sympathetic nervous activity (SNA) and reported that BP and urinary norepinephrine
(NE) excretion were higher in HFD-fed rats than in low-fat diet-fed rats. These data suggest that activation of the sympathetic nervous system has an important role in HFD-related BP elevation. The effect of a HFD on the development of hypertension is related in part to insulin resistance (Hall et al., 1993). In the present study, the BP; SBP, DBP and MAP were significantly higher in HFD control rats (Group II & X) than in the NPD control group. The raised SBP, DBP and MAP were significantly suppressed by treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII) and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats (Figure 6 and 14). Rosuvastatin has been reported to reduce BP levels in high fat-fed rats (Timothy et al., 2001).

The important factor related to obesity is body-fat distribution, particularly visceral adipose tissue. Visceral adipose tissue has a higher rate of lipolysis, resulting in enhanced portal non-esterified fatty acids that increase hepatic VLDL production, increase hepatic glucose production, and impair peripheral insulin sensitivity (Klein, 2004). Administration of HFD produced significant increase in mesenteric, uterine and perirenal fat accumulation as compared to NPD control rats, respectively. The fat accumulation was significantly reduced by treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII) and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats (Figure 7, 8, 15 and 16). Further, the mesenteric, uterine and perirenal fat accumulation were significantly reduced by treatment with rosuvastatin per se (10 mg/kg i.e. Group VII, p.o.), pitavastatin per se (Group XV) and orlistat per se (Group XVI) for a period of 21 days as compared to NPD control rats (Group I) (Figure 7, 8, 15 and 16). Araki et al. (2008) found that the pravastatin treatment at100 mg/kg, p.o. for a period of 28 days significantly decreased the adipocyte size/volume in the white adipose tissue (WAT) and brown adipose tissue (BAT) and decreased mass of epididymal fat tissue as well in diet induced obese mice.

Consequently, the results of the present study are of worth in terms of the fact that visceral adipose tissues were suppressed with the rosuvastatin and pitavastatin treatment. Taken together, the data suggest that the rosuvastatin as well as pitavastatin may be helpful in humans in preventing diet-induced obesity.

The high fat-fed rats produced significant increase in weight of heart, liver and kidney as compared to NPD control rats (Group I) which corroborates the reports of Jayasooriya et al. (2000) ($P < 0.01$). The weight of heart, liver and kidney were significantly reduced by
treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII) and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats which corroborates the earlier reports by Kaur and Kulkarni, (2000) on organs’ weight reduction in high fat-fed rats (Kaur and Kulkarni, 2000) (Table 14 and 21).

Leptin was originally discovered as an adipocyte-derived hormone involved in the central control of body weight and energy homeostasis (Zhao and Wu, 2005). Plasma leptin concentrations are strongly correlated with adiposity (Ren, 2004). Body fat amount is a main determinant of leptin gene expression and release. Fried et al. (2000) indicated that basal levels of leptin are known to be strongly positively correlated with body fat on a HFD (Uygun et al., 2000). Obesity is often associated with high circulating leptin concentrations and leptin resistance (Kamoda et al., 1998). In the present study, rats under HFD control group present significant elevation in serum leptin levels than their NPD control group (Group I) indicating the leptin resistance and explained as a satiety signal (Mars et al., 2005). Treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat (Group VI) along with HFD for a period of 21 days produced significant reduction in serum leptin levels as compared to HFD control rats, respectively. Zhao and Wu (2005) reported that the baseline concentrations of circulating leptin were not significantly different among the groups. High-cholesterol diet for 8 weeks induced significantly increased serum leptin levels, while no change was observed in control group. After 6 weeks of treatment with atorvastatin, the leptin level was significantly decreased. Similarly the in vitro study of Zhao and Wu (2005) reported that incubation of adipocyte with atorvastatin induced a significant reduction of leptin secretion measured by ELISA in dose-dependent manner in high cholesterol diet fed rabbits. Stejskal et al. (1998) reported that pravastatin significantly lowered serum leptin levels in patients with accelerated atherosclerosis (Stejskal et al., 1998). In the present study, it has been found that HFD produced obesity with elevated serum leptin levels and the changes of leptin levels were nearly identical to the changes of serum cholesterol concentrations throughout the study. Thus, it would appear that rosuvastatin as well as pitavastatin improves leptin sensitivity (Table 15 and 22). The obese rats are both hyperleptinemic and hyperinsulinemic, and as occurs in humans, both insulin and leptin concentrations were directly correlated with the degree of adiposity (Woods et al., 2003). The numerous evidences state that statin administration can improve whole-body insulin sensitivity in resistant individuals and in animal models.
of insulin-resistance too (Wong et al., 2006). In the present study, the high fat fed rats (Group II & X) produced a significant increase in the levels of serum insulin as compared to NPD control group (Group I & IX). There were significant reduction serum insulin levels by treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII) and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats which corroborate previous studies of statin. Araki et al. (2008) reported that pravastatin at 100 mg/kg, p.o. for 28 days significantly reduce the insulin level (Table 15 and 22) as compared to diet induced obese mice.

Obese subjects are often hyperglycemic and glucose intolerant, and this could be due to increased insulin resistance and/or defects in insulin secretion. Diet-induced obesity dysregulated glucose homeostasis and causes hyperglycemia (Chang et al., 1990). This is consistent with previous study that feeding of HFD for a period of 4 weeks produced a significant increase in plasma glucose levels (Srinivasan et al., 2004). In the present study, HFD control rats (Group II & X) results in significant increase in serum glucose as compared to NPD control rats (Group I). Treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat (Group VI) along with HFD for a period of 21 days produced significant reduction in blood glucose levels respectively, which corroborate previous studies of atorvastatin at 80 mg/kg for a period of 30 days on MSG obese mice (Zhang et al., 2010), showing normal glucose metabolism improvement in insulin functions (Table 15 and 22).

Adipose tissue is an important endocrine organ that regulates the insulin sensitivity of other peripheral insulin target tissues. Excess adipose tissue, especially in the visceral compartment, results in excess secretion of peptide hormones and cytokines, which leads to whole-body insulin resistance and predisposes to type 2 diabetes mellitus (Zhang et al., 2010). Although the precise pathogenesis of insulin resistance remains ill-defined, several factors have been proposed to have a role in this process, such as adipokines, defects in the insulin signaling pathway, mitochondrial dysfunction and inflammation (Muoio and Newgard, 2008; Kim et al., 2008). Insulin resistance is the critical pathological feature of type 2 diabetes mellitus, obesity, metabolic syndrome, and aging (Zhang et al., 2010). In the present study, the effect of rosuvastatin and pitavastatin on glucose metabolism and insulin resistance assessed in high fat fed obese rats, a model of obesity, hyperinsulinemia, insulin resistance, hyperlipidemia and hyperglycemia (Srinivasan et al., 2005).
HFD control rats (Group II & X) produced significant elevation in HOMA-IR index as compared to NPD control rats (Group I). HOMA-IR index confirmed the prominent insulin resistance reduction potential of rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII) and orlistat (Group VI) treatment along with HFD for a period of 21 days which corroborate previous studies of statin on MSG obese mice (Zhang et al., 2010).

Similar to this study, clinical trials have been conducted to investigate whether statins can improve insulin resistance and adipocytokine levels (Araki et al., 2008). The effects of statins on insulin sensitivity had been reported in the past years, simvastatin and atorvastatin may improve insulin sensitivity in diabetic patients (Paolisso et al., 2000); however, others have reported that simvastatin either did not change or worsened insulin sensitivity in diabetic patients (Farrer et al., 1994; Ohrvall et al., 1995). These findings suggest that rosuvastatin and pitavastatin may improve insulin resistance in high fat fed obese rats. Thus, it would appear that rosuvastatin and pitavastatin improve insulin sensitivity which is comparable with orlistat (Table 15 and 22).

HFD-induced obesity leads to cardiac abnormalities such as cardiac oxidative stress assessed by lactate dehydrogenase (LDH) enzyme (Diniz et al., 2008). The measurement of cytoplasmic LDH activity is a well-accepted assay to quantify viable cell numbers and monitor cell proliferation (Mosmann, 1983). On the other hand, the leakage of cytoplasmic LDH caused by the damage of cell membrane integrity is also a good indicator of cell death and is used to estimate cytotoxicity (Arechabala et al., 1999). Increased serum LDH levels in HFD control rats as compared to NPD rats were reported earlier (Amin and Nagy, 2009). In the present study, significant increased serum LDH levels were observed in HFD control rats (Group II & X). Treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat (Group VI) along with HFD for a period of 21 days produced significant reduction in serum LDH levels as compared to HFD control rats, respectively (Table 15 and 22).

In the present study, there was a significant increase in the levels of serum apo-B in HFD control rats (Group II & X) as compared to NPD control rats (Group I). Treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat (Group VI) along with HFD for a period of 21 days produced significant reduction in serum apo-B levels as compared to HFD control rats (Table 15 and 22). Apolipoprotein B (apo-B) is associated with LDL, intermediate density lipoprotein (IDL), VLDL and chylomicrons (D’Souza et al., 2007). Apo-B secretion by the liver is regulated by factors such as rate
of cholesterol biosynthesis, availability of triglycerides and cholesterol esters (Dixon et al., 1991). It has been shown that rosuvastatin treatment can induce considerable amelioration of metabolic dyslipidemia in the insulin resistant/fructose-fed hamster model and normalize cardiac apo-B secretion. Thus, it would appear that rosuvastatin normalizes the apo-B levels in obesity as do earlier (Korotvicka et al., 2009).

Data of the present study clearly showed that feeding of the HFD significantly increases the levels of TC, TGs, LDL, VLDL, coronary risk index (CRI; TC/HDL-C), atherogenic risk predictor (ARP; LDL-C/HDL-C) and decrease in HDL as compared to NPD control rats (Group I) respectively \((P < 0.01)\). Treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat (Group VI) along with HFD for a period of 21 days produced significant reduction in TC, TGs, LDL, VLDL, coronary risk index (CRI; TC/HDL) and atherogenic risk predictor (ARP; LDL-C/HDL-C) levels as compared to HFD control rats and significant elevation in serum HDL-C as compared to the HFD control rats (Figure 9 and 17; Table 16 and 23) which corroborate previous studies of by Araki et al., (2008), Zhao and Wu (2005), Lavie and Milani (2003) and Blanco-Rivero et al. (2011). Araki et al., (2008) reported that pravastatin at100 mg/kg, p.o. for a period of 28 days significantly decreased the liver and muscle TG contents as compared with diet induced obese mice. While Zhao and Wu (2005) found that atorvastatin at 2.5 mg/kg/day for 6 weeks treatment reduced plasma levels of TC and LDL-C as compared with high-cholesterol group. Lavie and Milani (2003) indicated that obesity adversely affects plasma lipids, especially by increasing TC, LDL- C, VLDL-C, TGs and decreasing the level of HDL-cholesterol. Further, Blanco-Rivero et al. (2011) reported significant reduction in TGs, TC and elevation in HDL by rosuvastatin (15 mg/kg/day, p.o. for 7 weeks on HFD fed rats). Various studies demonstrate the efficacy of rosuvastatin in improving the atherogenic lipid profile and dyslipidemia in patients with the metabolic syndrome (Ballantyne et al., 2003). Insulin resistance causes various dyslipidemic states such as increase of small dense LDL particles, remnant lipoprotein, and decrease of HDL cholesterol. In diabetes mellitus, reduced activity of lipoprotein lipase leads to low HDL cholesterol because of impaired catabolism of VLDL (Rosenson, 2009). Increase in TGs content leads to increase in accumulation of fat tissues (Araki et al., 2008). Present study showed a significant increase in both TGs content and fat pads’ weight in high fat fed rats. The increase in TGs levels were significantly reduced by rosuvastatin as well as pitavastatin in high fat fed rats.
Na\(^+\)K\(^+\)-ATPase is a membrane enzyme that energizes the Na pump, hydrolyzing ATP and wasting energy as heat so playing a role in thermogenesis, energy balance, and obesity development. Obesity is associated with reduction of tissue Na\(^+\)K\(^+\)-ATPase, linked to hyperinsulinemia, which may repress or inactivate the enzyme, influencing thermogenesis and energy balance (Iannello et al., 2006). In the present study, hepatic and cardiac Na\(^+\)K\(^+\)-ATPase contents were significantly decreased in HFD control rats (Group II & X) as compared to NPD control rats (Group I). The hepatic and cardiac Na\(^+\)K\(^+\)-ATPase contents were significantly enhanced by treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII) and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats (Table 17 and 24). Obesity is connected with tissue Na\(^+\)K\(^+\)-ATPase reduction, apparently linked to hyperinsulinemia (Iannello et al., 1998). Takeuchi et al. (1995) who reported the activity of Na\(^+\)K\(^+\)-ATPase in the liver and skeletal muscle was lower in rats fed with the lard diet. The decrease of ATPases could be due to enhanced lipid peroxidation by free radicals. Since this membrane bound enzymes are ‘SH’ group containing enzymes, so are lipid dependant.

Oxidative stress is an imbalance between tissue free radicals, reactive oxygen species (ROS) and antioxidants, and might be chief mechanism underlying obesity related co-morbidities. Obesity has been shown to be one of the conditions that reduce antioxidant capacity (Watson et al., 1999).

The increased lipid peroxidation in obesity has been repeatedly observed in different human studies (Yesilbursa et al. 2005). Free radicals are known to be involved in a variety of human pathologies, including atherosclerosis (Steinberg, 1997), and obesity (Van Gaal et al., 1995). The levels of hepatic and cardiac TBARS were found to be increased in HFD control rats (Group II & X) as compared to NPD control rats (Group I). The hepatic and cardiac TBARS contents were significantly reduced by treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII) and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats (Table 18, 19, 25 and 26). A potential mechanism for the generation of free radicals may be the activation of β-adrenergic receptors reported for obesity prone rats (Levin et al., 1983). This could increase lipolysis to yield free fatty acids that are able to uncouple the mitochondrial phosphorylation and further, generate free radicals (Turrens, 1997).
Fardet et al. (2008) suggested that the diet-induced obesity in rat models produced an increase in the levels of oxidative stress in their liver and that oxidative stress can result from the excessive production of reactive oxygen species and/or deficient anti-oxidant capacity (Fardet et al., 2008).

HFD control rats (Group II & X) produced a significant decrease in contents of hepatic and cardiac antioxidant enzymes as compared to NPD control rats (Group I). The suppressed hepatic enzymes contents were significantly enhanced by treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats. Further, suppressed cardiac enzymes contents were significantly enhanced by treatment with rosuvastatin (Groups III-V), pitavastatin (Groups XI-XIII); and orlistat (Group VI) along with HFD for a period of 21 days as compared to HFD control rats.

In animal and human studies, obesity is associated with a decrease in tissue or plasma antioxidant capacity (Ozata et al., 2002). GSH constitutes the first line of defense against free radicals and is also responsible for the maintenance of protein thiols and acts as a substrate for GPx and GST (Prakash et al., 2001). The present data indicate that GSH content was depleted in the rats with obesity induced by a HFD. Enzymatic antioxidants, such as superoxide dismutase, catalase or GPx, GR and GST can scavenge reactive oxygen species and free radicals or prevent their formation (Husain et al., 2005). Thus, it is clear that rosuvastatin as well as pitavastatin enhanced antioxidant defense mechanism in the hepatic and cardiac tissues of high fat-fed obese rats.

In the histopathological studies, photomicrograph of haematoxylin–eosin stained hepatic tissues showed necrotic focus containing fibrotic areas and mononuclear cells (B), connective tissue enlargement at perivascular areas (P), vacuolation in the hepatocytes (V) (Figure 10B and 18B) in HFD control rats (Group II & X) as compared to NPD control rats (Group I) which showed normal architecture with regular morphology of hepatic cells. The impaired architecture with morphology of hepatic cells were improved and normalised by treatment with rosuvastatin and pitavastatin; rosuvastatin (Group III) and pitavastatin (Group XI) showed mild microvesicular fatty changes, mild improvement in the vacuolated hepatocytes (Figure 10C and 18C); rosuvastatin (Group IV) and pitavastatin (Group XII) showed lesser microvesicular fatty changes, improvement in the vacuolated hepatocytes, while some hepatic cells still suffered from some degenerative changes especially the vacuolation, (Figure 10D and 18D):
rosuvastatin (Group V) and pitavastatin (Group XIII) showed better microvesicular fatty changes, preserved normal appearance of the vacuolated hepatocytes, (Figure 10E and 18E): orlistat (Group VI) showed reduced changes and preserved normal hepatic architecture indicating reduced steatosis and degenerative changes (Figure 10F and 18F).

Further, photomicrograph of haematoxylin–eosin stained cardiac tissue of HFD control rats (Group II & X) showed moderate inflammatory cell infiltration (I), loss of myocardial fibers with small and large cytoplasmic vacuoles and intramuscular hemorrhage as compared to NPD control rats (Group I) which showed normal architecture with regular morphology of myocardial cells (Figure 11B & 19B). The impaired architecture with morphology of cardiac cells were improved and normalised by treatment with rosuvastatin and pitavastatin; rosuvastatin (Group III) and pitavastatin (Group XI) showed moderate myofibrillar disintegration and focal cytoplasmic vacuolization, (Figure 11C and 19C); rosuvastatin (Group IV) and pitavastatin (Group XII) showed mild myofibrillar disintegration and focal cytoplasmic vacuolization (Figure 11D and 19D); rosuvastatin (Group V) and pitavastatin (Group XIII) showed regular myofibril arrangement and better-preserved appearance of cardiac muscle fibers with very few infiltrative cells (Figure 11E and 19E); orlistat (Group VI) showed better preserved appearance of cardiac muscle fibers. Ultra structural changes in were almost indistinguishable from the NPD control, with regular myofibril arrangement (Figure 11F and 19F).

In the present study, a well controlled and standardized experimental animal models i.e. high fat died-induced obesity in normal female Wistar rats was selected as obesity model (Plan I). There was a significant reduction in body weight and fat pads’ weight (mesenteric, uterine & perirenal) by both test drugs (rosuvastatin and pitavastatin) in HFD obese model. To confirm whether the weight reduction in HFD model is due to decrease in fat pad’s weight (mesenteric, uterine & perirenal); a visceral obesity model i.e. monosodium glutamate (MSG) obese model was also used (Plan II).

In plan II (MSG obese model), the obesity was induced by monosodium glutamate (MSG) in male neonatal Wistar rat pups. Model of obesity induced by MSG has demonstrated some of the clinical features observed in individuals with metabolic syndrome (MS). The MSG injected subcutaneously in neonatal period causes hypothalamic damage, and as a consequence, these animals present several neuroendocrine and metabolic alterations, which leads to higher levels of adipose tissue.
accumulation and insulin resistance. So the use of this model may add new information concerning the effects of possible treatments for both obesity and risk factor for CVD commonly observed in MS (Yamazaki et al., 2011). MSG obese model shows extraordinary increase in fat accumulation with reduced weight and stunted growth as compared to lean control rats (Li et al., 2006; Kaur and Kulkarni, 2001). The important factor related to obesity is body-fat distribution, particularly visceral adipose tissue. Visceral adipose tissue has a higher rate of lipolysis, resulting in enhanced portal non-esterified fatty acids that increase hepatic VLDL production, increase hepatic glucose production, and impair peripheral insulin sensitivity (Klein, 2004).

Generally male neonatal Wistar rats have been used in MSG obese model. Richard et al. (1986) reported that female MSG-treated rats, unlike male MSG-treated rats, exhibited consistent systolic hypotension at 6, 9 and 12 weeks of age. While human obesity is associated with increase in blood pressure (hypertension), consequently male neonatal Wistar rats mimics the human obesity characteristics in MSG obese model.

HFD obese model exhibits increase in body weight, BMI, fat pads’ weight (Srinivasan et al., 2005; Woods et al., 2003) whereas MSG obese model shows extraordinary increase in fat accumulation with reduced weight and stunted growth as compared to lean control rats (Li et al., 2006; Kaur and Kulkarni, 2001).

Effect of MSG on baseline characteristics of obesity induced in neonatal Wistar rat pups was assessed 42nd day (6 weeks) of life. Neonatal MSG treatment leads to obesity in adult animals, usually characterized by a significant increase in epididymal and retroperitoneal fat pads’ weight and higher Lee index without hyperphagia (Yoshioka et al., 1989). In the present study, MSG (4 g/kg, s.c.) treated rats became obese as characterized by significantly increased epididymal and retroperitoneal fat pads’ weight, higher Lee index with normophagia, increased insulinemia with elevation of glycemia on day 42 of life (Table 27). These results confirm the obesity induction by MSG and corroborate previous studies (Yamazaki et al. 2005; Macho et al., 2000). The obesity of MSG-treated rodents appears to be metabolic in nature because food intake is not enhanced by MSG treatment (Dawson et al., 1989).

In the present study, the body weight and Lee index of MSG treated rats increased significantly compared with normal control rats, but food intake was not changed significantly. As a result, the main cause of obesity was not thought to be a interruption of appetite, suggesting that obesity is caused by a decrease in energy metabolism,
secondary to brown adipose tissue (BAT; a major site for energy expenditure and thermogenesis (Tsukahara et al., 1998) and autonomic nerve dysfunction (Yasuda et al., 2004).

Several metabolic changes of MSG obese rat model arise due to hypothalamic lesions, mainly on the arcuate nucleus (Yamazaki et al., 2011; de Andrade et al., 2006). These lesions bring about impaired insulin signaling and reduction of GHRH (Growth Hormone Releasing Hormone), which is associated with body length reduction and body weight reduction as well (Table 27). The MSG obese rat model also shows reduction of sympathetic activity and low HSL (Hormone Sensitive Lipase) activity which is an enzyme with a role in the triacylglycerol hydrolysis (Yamazaki et al., 2011; Dolnikoff et al., 2001). These modifications in adipose tissue metabolism may explain the high quantities found in epididymal and retroperitoneal adipose tissues. Hence, the MSG control rats (Group XVIII) have been used for studies of obesity because they usually present insulin resistance and high depots of fat.

Treatment with rosuvastatin as well as pitavastatin produced a significant ($P < 0.01$) reduction in fat tissues (epididymal and retroperitoneal), Lee index, body weight, serum leptin, insulin, blood glucose, HOMA-IR, TC, TGs, LDL-C, LVDL-C and, atherogenic risk predictor indices and elevation in serum HDL-C levels in MSG obese Wistar rats. The results of rosuvastatin treatment in MSG control rats (Group XVIII) were comparable with standard antiobesity drug, orlistat.

The body weight of adult Wistar rats treated with MSG during the neonatal period was significantly decreased as compared to normal control rats (Group XVII) as reported earlier in various research studies in MSG treated rats (Macho et al., 2000; Yoshioka et al., 1989). Rosuvastatin (10 mg/kg i.e. Group XIX, p.o.), pitavastatin (3 mg/kg i.e. Group XXV, p.o.) and orlistat (10 mg/kg i.e. Group XXI, p.o.) treatment in MSG obese rats produced decrease in body weight as compared to MSG control rats (Group XVIII) from week 2 to week 4 treatment periods (Figure 20 and 25) that corroborates earlier report by Kaur & Kulkarni (2001) and Zhang et al. (2010). Zhang et al. (2010) reported that atorvastatin at 80 mg/kg for a period of 30 days on MSG obese mice significantly reduced the body weight in MSG control rats.

Various studies reported stunted growth in MSG treated neonatal rats. MSG-treated rats had significantly shorter both naso-anal and tail length than normal control rats (Miskowiak et al. 1993; Waxman et al., 1990). In the present study, the naso-anal length
of adult Wistar rats treated with MSG during the neonatal period was significantly decreased in MSG control rats (Group XVIII) as compared to normal control rats (Group XVII). However, no significant difference was found in naso-anal length among rosuvastatin (2.5 & 10 mg/kg i.e. Groups XIX & XX respectively), pitavastatin (0.5 & 3 mg/kg i.e. Groups XXIV & XXV respectively) and orlistat (10 mg/kg i.e. Group XXI) treatment in MSG obese rats for a period of 28 days when compared with MSG control rats (Group XVIII) respectively ($P > 0.05$) (Figure 21 and 26).

Lee index in MSG control rats (Group XVIII) indicates the degree of obesity (Iwase et al., 2000). MSG control rats (Group XVIII) produced a significant increase in Lee index as compared to normal control rats (Group XVII) ($P < 0.01$) which corroborates the previous studies (Yamazaki et al., 2011). Treatment with rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV) and orlistat (Group XXI) for a period of 28 days significantly reduced Lee index in MSG control rats (Group XVIII) as compared to MSG control rats ($P < 0.01$) indicating the antiobesity potential of rosuvastatin as well as pitavastatin (Figure 22 and 27).

Treatments with rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXV) as well as orlistat (Group XXI) in MSG obese rats for a period of 28 days produced no significant difference in daily food intake as compared to MSG control rats (Group XVIII) ($P > 0.05$) (Table 28 and 32). A number of research studies have been suggested that MSG obesity could be the result of a lower metabolic rate rather than of elevated food intake (Yoshioka et al., 1989).

The important factor related to obesity is body-fat distribution, particularly visceral adipose tissue. Visceral adipose tissue has a higher rate of lipolysis, resulting in enhanced portal non-esterified fatty acid that increases hepatic VLDL production, increase hepatic glucose production, and impair peripheral insulin sensitivity (Klein, 2004). The effects of statins on fat tissues in MSG obese animals had been reported earlier; atorvastatin reduces the increased intraperitoneal fat weight in MSG obese mice (Zhang et al., 2010). The epididymal and retroperitoneal fat pad’s weight were increased significantly in MSG control rats (Group XVIII) as compared to normal control rats (Group XVII) ($P < 0.01$). The extraordinary increased fat pad’s weight were significantly suppressed by administration of rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV) as well as orlistat (Group XXI) in MSG obese rats for a period of 28 days as compared to MSG control rats (Group XVIII) (Figure 23 and 28). This result is
consistent with that reported in a previous study by Zhang et al. (2010), in which administration of atorvastatin at 10 mg/kg, p.o. for a period of 30 days was found to decrease retroperitoneal fat weight. The significant reduction of visceral fat pad’s weight (epididymal and retroperitoneal) by rosuvastatin & pitavastatin in MSG obese model confirms that significant reduction in body weight and BMI in HFD obese model by rosuvastatin & pitavastatin is due to decrease in visceral fat pad’s weight.

Similar to Macho et al. (2000) studies, the present study showed significant decrease in liver weight with no change on heart weight in MSG obese as compared to normal control rats (Group XVII) \( (P < 0.05) \) (Table 29 and 33) (Macho et al., 2000). Liver and heart weight was not affected significantly by treatment with rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV) and orlistat (Group XXI) in MSG obese rats for a period of 28 days as compared to MSG control rats (Group XVIII).

Adipocytes store energy as triacylglycerols. Additionally to serving as an energy store site, adipocytes secrete hormones (e.g. leptin, adiponectin, resistin) that regulate energy balance, metabolism, and neuroendocrine response to altered nutrition (Arner, 2003). Leptin receptor mRNA is available in the hypothalamus, hypothesized as a potential site of action for leptin (Mercer et al., 1996). Obesity is often associated with high circulating leptin concentrations and leptin resistance (Kamoda et al., 1998). Leptin production is enhanced in animal models of obesity associated with experimentally induced hypothalamic damage, including the MSG treated model (Frederich et al., 1995). It has been showed that serum leptin level is well correlated with body fat tissues, and that leptin secretion is regulated by insulin (Iwase et al., 2000). In the present study, serum leptin level was found to be significantly increased in MSG control rats (Group XVIII) as compared to normal control rats (Group XVII). The elevated levels of serum leptin were significantly reduced by rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV); and orlistat (Group XXI) treatment in MSG obese rats for a period of 28 days as compared to MSG control rats (Table 30 and 34). In the present study, serum leptin was well correlated with Lee index, and epididymal as well as retroperitoneal fat pads’ weight. Thus, it would appear that rosuvastatin as well as pitavastatin improves leptin sensitivity which is comparable with orlistat.

Insulin is very important hormone that inhibits gluconeogenesis (Li et al., 2006). Insulin resistance has been recognized as an important risk factor for the development of cardiovascular disease. It has been previously estimated that nearly 70% of patients with
coronary artery disease have some form of glucose intolerance (Lebovitz, 2006). Hyperinsulinemia as well as moderate increase of glycemia had been reported in adult MSG treated rats (Macho et al., 2000). The numerous evidences state that statin administration can improve whole-body insulin sensitivity in resistant individuals and in animal models of insulin-resistance too (Wong et al., 2006). In the present study there was a significant increase in serum insulin levels with MSG control rats (Group XVIII). Rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV) and orlistat (Group XXI) treatment in MSG obese rats for a period of 28 days significantly suppressed elevated insulin levels (Group XVIII) which corroborated the study of Zhang et al. (2010) that reported significant reduction in serum insulin level by atorvastatin at 80 mg/kg, p.o. for 30 days in MSG obese rats ($P < 0.01$) (Table 30 and 34). These findings indicated that the rosuvastatin as well as pitavastatin enhances the insulin sensitivity after 4 weeks treatment in MSG control rats.

Obese subjects are often hyperglycemic and glucose intolerant, and this could be due to increased insulin resistance and/or defects in insulin secretion (Macho et al., 2000). In the present study, MSG control rats results in significant increase in blood glucose levels as compared to normal control rats (Group XVII) ($P < 0.01$). Rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV) and orlistat (Group XXI) treatment in MSG obese rats for a period of 28 days produced a significant decrease in blood glucose levels which corroborated the study of Zhang et al. (2010) that reported significant reduction in blood glucose level by atorvastatin at 80 mg/kg, p.o. for 30 days, showing normal glucose metabolism and improvement in insulin functions ($P < 0.01$) (Table 30 and 34).

HOMA-IR index was significantly increased in MSG control rats (Group XVIII) as compared to normal control rats (Group XVII) ($P < 0.01$). Rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV) and orlistat (10 mg/kg i.e. Group XXI, p.o.) treatment in MSG obese rats for a period of 28 days suppressed the elevated HOMA-IR index in MSG obese rats (Group XVIII) as compared to MSG control rats (Group XVII) which corroborated the study of Zhang et al. (2010) that reported significant reduction in HOMA-IR level by atorvastatin at 80 mg/kg, p.o. for 30 days in MSG obese rats ($P < 0.01$) (Table 30 and 34). Increased serum glucose concentrations and HOMA-IR levels in MSG control rats (Group XVIII) indicate the presence of insulin resistance. HOMA-IR index confirmed the prominent insulin resistance reduction potential of rosuvastatin as well as pitavastatin and corroborate previous studies on statin (Zhang et al., 2010).
MSG control rats (Group XVIII) produced significant increase in levels of serum TC and TGs and decrease in serum HDL-C levels as compare to normal control rats ($P < 0.01$). The levels of LDL-C, VLDL-C and atherogenic risk predictor indices were significantly increased in MSG control rats (Group XVIII) as compare to normal control rats respectively ($P < 0.01$). Present study showed that the rosuvastatin (Groups XIX & XX), pitavastatin (Groups XXIV & XXV respectively) and orlistat (Group XXI) treatment in MSG obese rats for a period of 28 days significantly reduce the levels of serum TC, TGs, LDL, VLDL, coronary risk index (CRI; TC/HDL-C), atherogenic risk predictor (ARP; LDL-C/HDL-C) and a significant increase in serum HDL-C as compared to the MSG control rats ($P < 0.01$) (Figure 24 and 29; Table 31 and 35). This result is consistent with that reported in a previous study by Zhang et al. (2010), in which administration of atorvastatin at 80 mg/kg, p.o. for 30 days in MSG obese rats was found significant reduction in TGs, TC and LDL levels as compared to normal control group.

To summarize, treatment with rosuvastatin and pitavastatin at different doses levels produced significant reduction in body weight, BMI, Lee index, B.P., visceral fat pads’ weight (mesenteric or retroperitoneal, uterine or epididymal and perirenal), organ weight (heart, liver and kidney), serum leptin, insulin, blood glucose, HOMA-IR, apo-B, TC, TGs, LDL, LVDL, coronary risk index (CRI), atherogenic risk predictor (ARP), LDH, hepatic and cardiac lipid peroxides (TBARS), and elevation in serum HDL-C level, hepatic and cardiac Na⁺K⁺-ATPase contents, antioxidant enzymes’ contents (GSH, GPx, GR, GST, CAT and SOD). These results were further supported by histopathological findings. The results of rosuvastatin & pitavastatin treatment in high fat-fed rats were comparable with standard antiobesity drug, orlistat.

The present study demonstrated that rosuvastatin and pitavastatin reduced the body weight in high fat-fed Wistar rats; the loss of weight can be explained by the loss of visceral fat pads’ weight, improvement in impaired serum leptin, serum insulin, blood glucose and lipid levels. Reduction in the fat mass in obese rats may be by improvement in leptin and insulin sensitivity. In consistent with improvement of lipid profile and insulin sensitivity, rosuvastatin and pitavastatin attenuated the development of hypertension in obese rats. Further, rosuvastatin and pitavastatin reduced the levels of hepatic and cardiac TBARS and free radical generation. Improvement in histological appearance of liver tissues (necrotic focus containing fibrotic areas and mononuclear cells, connective tissue enlargement at perivascular areas, vacuolation in the hepatocytes)
and heart tissues (moderate inflammatory cell infiltration, loss of myocardial fibers with small and large cytoplasmic vacuoles and intramuscular hemorrhage) might be contributory to the reduced TGs accumulation as increase in TGs content leads to increase in accumulation of fat tissues (Araki et al., 2008).

The results of the present study reveal for the first time that rosuvastatin and pitavastatin treatments effectively alleviate the deleterious effects produced by HFD as well as MSG in Wistar rats such as leptin resistance, insulin resistance, hyperlipidemia, hypertension, fat pad’s accumulation (mesenteric or retroperitoneal, uterine or epididymal and perirenal), mild hyperglycemia and oxidative stress. Further, rosuvastatin and pitavastatin offers hepatic & cardiac protection by preventing hepatic and cardiac tissues damage as revealed by enhancement of Na\(^+\)K\(^+\)-ATPase activity, oxidative stress defense mechanism, and maintaining normal architecture of liver and heart tissues.

The antiobesity effect of rosuvastatin and pitavastatin are comparable to orlistat, a standard antiobesity drug. Lastly, pitavastatin (0.5, 1 & 3 mg/kg) treatment more significantly reduced body weight, BMI, Lee index, BP, fat pads’ weight (mesenteric or retroperitoneal, uterine or epididymal and perirenal), serum leptin & insulin, blood glucose, and serum lipid levels and enhanced hepatic & cardiac Na\(^+\)K\(^+\)-ATPase activity and oxidative stress defense mechanism as compared to rosuvastatin (2.5, 5 & 10 mg/kg) treatment.

In the present study, there was a significant reduction in body weight and fat pad weights by both test drugs (Rosuvastatin and Pitavastatin) in HFD obese model. The *per se* effect of RSV (10 mg/kg)/PTV (3 mg/kg)/Orlistat (10 mg/kg) also shows antagonizing effect on few parameters viz. BMI & fat pad weights (Fig 5, 7, 8, 13, 15 & 16) as compared to normal control group. However, most of the studied parameters in *per se* groups shows lesser antagonizing effects than treatment groups HFD + RSV/PTV/Orlistat. Though there are some antagonizing effect shown by RSV/PTV/Orlistat *per se* groups but the values are not significantly differ when compared to drug treatment groups (Table 13a & 20a).

To confirm whether the weight reduction in HFD model is due to decrease in fat pad weights, a visceral obesity model i.e. monosodium glutamate (MSG) obese model employed which showed the highly significant fat pad weight reduction by RSV and PTV treatment. HFD obese model exhibits increase in body weight, BMI, fat pad weights (Srinivasan et al., 2005; Woods et al., 2003) where as MSG obese model shows extraordinary increase in fat accumulation with reduced weight and stunted growth as compared to lean control rats (Li et al., 2006).

In the present study, the antiobesity activity of both test drugs (Rosuvastatin and Pitavastatin) were performed by two methods viz. high fat diet (HFD)-induced obese Wistar rat model (Plan I) and monosodium glutamate (MSG)-induced obese neonatal Wistar rat model (Plan II). In the present study, there was a significant reduction in body weight and fat pad weights by both test drugs
(Rosuvastatin and Pitavastatin) in HFD obese model. To confirm whether the weight reduction in HFD model is due to decrease in fat pad weights, a visceral obesity model i.e. monosodium glutamate (MSG) obese model employed which showed the highly significant fat pad weight reduction by RSV and PTV treatment. HFD obese model exhibits increase in body weight, BMI, fat pad weights (Srinivasan et al., 2005; Woods et al., 2003) where as MSG obese model shows extraordinary increase in fat accumulation with reduced weight and stunted growth as compared to lean control rats (Li et al., 2006).

The treatment of obese rats with RSV and PTV conversely causes a remarkable reduction of body weights compared to the untreated obese group (HFD control). The findings demonstrated that RSV and PTV are capable of preventing body weight gain, concomitantly helping in maintaining the current body weight. Present study investigated the treatment effects of RSV and PTV on obese rats and sought to determine whether the RSV and PTV are able to reverse the increased body weight gain caused by high fat diet in contrast with the preventive effects only. Further, RSV as well as PTV per se treatments showed reduction in BMI and fat pad weight in as compared to normal control rats. RSV and PTV may prevent excessive body weight gain, as well as decrease the body weight increase caused by high-fat diet intake. In addition, the oral administration of RSV and PTV significantly decreased the weights of epididymal and retroperitoneal and perirenal adipose tissues and, ultimately, the total adipose tissue weight of the HFD control rats as well as MSG obese rats. Leptin and insulin are fat-derived key regulators of appetite and energy expenditure, where their concentrations in the plasma are associated with general adiposity. The reductions of leptin and insulin levels reflect a decreased in the fat mass (Zhang et al., 2010). Hypothalamus receives direct input from hormones, specifically, leptin and insulin, which cross the blood–brain barrier and provide information on the levels of peripheral adipose mass. There were predictable changes in neural activity, in brain areas known to be involved in the regulatory, emotional, and cognitive control of food intake, where many of which were reversed by leptin and insulin. Following adipocytes loss, the leptin and insulin levels decrease in response to visual food signal to hypothalamus (Woods et al., 2003). The results from the present study suggest that RSV and PTV caused significant adipocytes loss, indicated by reduced leptin and insulin levels in both animal models (i.e. HFD obese rats & MSG obese rat). These findings suggest that RSV and PTV may improve insulin resistance in MSG-induced obese mice. I addition, the present study, sought out the effects of dietary fat content on the development of hepatic steatosis. Results of the present study indicate that the continuous consumption of high-fat diet may play a role in the development of hepatic steatosis associated with obesity. Further, it has been demonstrated that RSV and PTV administration may attenuate the development of hepatic steatosis and that both RSV as well as PTV are potentially effective in ameliorating fatty liver in diet-induced obese rats.

The present study strongly supports the potential of RSV & PTV in obesity disorder.