2) LITERATURE REVIEW

1. Srinivasan et al., (2005) developed a new rat model that replicates the natural history and metabolic characteristics of human type 2 diabetes and is also suitable for pharmacological screening. They used the high-fat diet and streptozotocin as diabetic inducers. They also studied the effect of two different combinations such as normal pellet diet + STZ and high fat diet + STZ and found that the HFD fed rats are more prone to be obese and produces insulin resistance as well as diabetes. Hyperinsulinemia together with reduced glucose disappearance rate (K-value) suggested that the feeding of HFD-induced insulin resistance in rats. They validated the model for further pharmaceutical testing, by pioglitazone (an insulin sensitizer) and glipizide (an insulin secretogogue).

2. Islam MS et al., (2007) showed in their comparative studies; that the animals receiving a high-fat diet plus STZ injection provide a better model of type 2 diabetes over animals receiving a low-fat diet plus streptozotocin injection. Serum lipid and liver glycogen were increased in HFD groups compared to other groups.

3. Srinivasan K, Ramarao P et al., (2007) reviewed different animal models of type 2 diabetes with reference to their origin/source, characteristic features, underlying causes/mechanism(s), advantages and disadvantages to the investigators in diabetes research. They also described the appropriate selection and usefulness of different animal models in preclinical testing of various new chemical entities for the treatment of type 2 diabetes.

4. Rees DA and Alcolado J C (2004) reviewed different animal models have been used extensively in diabetes research. Animal experimentation is contentious and subject to legal and ethical restrictions that vary throughout the world therefore according to them most experiments are carried out on rodents such as rats.

5. Shafrir et, al., (2006) studied different diet effects on metabolic parameters of spiny mice. The findings indicates that the serum triglyceride and cholesterol, glucose and
insulin levels increased excessively by sucrose when compared to animals with normal diet. This spiny mice developed hepatomegaly, hyperactive lipogenesis, and gross VLDL elevation.

6. **Sesti G (2006)** reported that Insulin resistance plays a major role in the pathogenesis of type 2 diabetes. Several defects in insulin signalling involving the IRS-1, GLUT4 cascade have been detected in subjects with insulin resistance. Inflammatory molecules and lipid metabolites inhibit insulin signalling by stimulating a number of different serine kinases which are responsible for serine phosphorylation of (IRS-1).

7. **Kadowaki T et al., (2002)** investigated the role of peroxisome proliferator-activated receptor γ (PPAR γ) in high-fat diet induced-obesity and insulin resistance. The study revealed a hitherto unpredicted role for PPAR γ in high-fat diet-induced obesity due to adipocyte hypertrophy and insulin resistance, which requires both alleles of PPAR γ. Both in mice and humans, PPAR γ is an important thrifty gene mediating insulin resistance and Type 2 diabetes.

8. **Sakoda H et al., (2000)** investigated the mechanism of glucocorticoid induced insulin resistance. Dexamethasone did not alter tyrosine phosphorylation of insulin receptors, and it significantly decreased protein expression and tyrosine phosphorylation of insulin receptor substrate (IRS)-1. They suggest that GLUT1 decrease may be involved in the dexamethasone-induced decrease in basal glucose transport activity, and the mechanism of dexamethasone-induced insulin resistance in glucose transport activity.

9. **Brindley DN et al., (1981)** examined the effects of chronic modification of dietary fat and carbohydrate on the insulin, corticosterone and metabolic responses of rats fed acutely with glucose, fructose or ethanol. The study reveals that the high dietary fat exaggerates the effects of ethanol, fructose and sorbitol in stimulating triacylglycerol synthesis in the liver.
10. **Martin-Sanz P et al., (1990)** investigated the effects of dexamethasone on VLDL, HDL. Dexamethasone increased the VLDL level and therefore its can lead to hyperlipidemia. Secretion of apolipoproteins in VLDL was increased by dexamethasone to an even greater extent than that of the triacylglycerol.

11. **Arulmozhi DK et al., (2004)** developed a new neonatal streptozotocin induced rat model. This model with alteration of dose and day of streptozotocin injection exhibited various stages of type 2 diabetes mellitus such as impaired glucose tolerance, and mild, moderate and severe glycemia. The β cells in the n-STZ rats bear a resemblance to the insulin secretory characteristics found in patients with type 2 diabetes mellitus.

12. **Czech MP and Corvera S (1999)** reviewed the role of insulin-regulated PI 3-kinase lipid products, including protein kinase C isoforms z and l, regulatory protein kinases of the Akt/protein kinase B system, tyrosine kinases Itk/Btk/Tec, the early endosome regulator EEA1, and ARF exchange factors GRP1, ARNO, and cytohesin-1. They suggested that PI 3-kinase appears to be required for glucose transport regulation by insulin.

13. **Delaunay F et al., (1997)** investigated whether glucocorticoids play a significant role in β cell function independent of their effects in other tissues. For this they have generated transgenic mice with increased β cell glucocorticoid sensitivity by over expressing the rat GR in β cells. These results showed that glucocorticoids directly inhibit insulin release in vivo. Glucocorticoids mediate their effects through a specific intracellular receptor present in almost all cell types, including pancreatic β cells.

14. **Szkudelski T (2000)** explained details of alloxan and STZ actions. Alloxan-induced insulin release is, however, of short duration and is followed by complete suppression of the islet response to glucose. Alloxan reacts with two -SH groups in the sugarbinding side of glucokinase resulting in the formation of the disulfide bond.
and inactivation of the enzyme. NIDDM can easily be induced in rats by intravenous or intraperitoneal treatment with 100 mg/kg b.w. STZ on the day of birth. STZ is taken up by pancreatic B cells via glucose transporter GLUT2. STZ itself restricts GLUT2 expression \textit{in vivo} and \textit{in vitro} when administered in multiple doses.

15. \textbf{Shalam M et al., (2006)} investigated the preventive effect of SH-01D, a herbomineral preparation, on the development of insulin resistance. They used two different models of insulin resistance; dexamethasone and fructose induced. Results showed that fructose feeding increased serum biochemical parameters and decreased liver and skeletal muscle glycogen levels. The rats fed with high fructose diet induced a nonobese model of hyperlipidemia, insulin resistance, hyperinsulinemia and mild hypertension. Dexamethasone for 10 days in rats caused an imbalance in lipid metabolism leading to hyperlipidemia and an increase in glucose levels leading to hyperglycemia.

16. \textbf{Saad Mario MJ et al., (1993)} studied molecular mechanism of insulin resistance produced by glucocorticoid. In the present study they have examined the levels and phosphorylation state of the insulin receptor and IRS-1, as well as the association/activation between IRS-1 and PI 3-kinase in the liver and muscle of rats treated with dexamethasone. Dexamethasone treatment induced a state of insulin resistance characterized by three- to fourfold increase in blood glucose and a sixfold increase in plasma insulin levels also reduction in insulin-stimulated IRS-1-associated PI 3-kinase, which might have played a role in the pathogenesis of insulin resistance at the cellular level in these animals.

17. \textbf{Ogawa A et al., (1992)} studied roles of insulin resistance and β-Cell dysfunction in dexamethasone-induced diabetes in Wistar and Zucker (fa/fa) rats. Wistar rats treated with 5 mg/kg per d of dexamethasone for 24 d exhibited increased β-cell mass and basal and arginine-stimulated insulin secretion, indicating insulin resistance, which concluded that dexamethasone induces insulin resistance, whether or not it induces hyperglycemia. Whenever hyperglycemia is present, GLUT-2-
positive β cells are reduced, high K. glucose transport into cells is attenuated and the insulin response to glucose is absent.

18. Shirwaikar A et al., (2000) examined antidiabetic potential of the alcoholic stem extract of *Coscinium fenestratum* Colebr STZ-nicotinamide induced type 2 diabetic model. NIDDM was induced in overnight fasted animals by a single intraperitoneal injection of 60 mg/kg STZ, 15 min after the i.p. administration of 120 mg/kg nicotinamide. The diabetic syndrome in rats administered STZ and partially protected with suitable dosages of nicotinamide was characterized by stable moderate hyperglycemia, glucose intolerance and significant glucose stimulated insulin secretion. Serum triglycerides and cholesterol levels were also increased by this model of NIDDM.

19. Zhang F et al., (2003) developed rat model of type 2 diabetes mellitus with the help of low dose (15mg/kg) STZ after high fat diet (30% of calories as fat). High fat diet increased the triglyceride and cholesterol levels significantly. This rat model was showed hyperglycemia and light impaired insulin function plus insulin resistance, which resembles the clinical manifestation of type 2 diabetes mellitus.

20. Tang Li-Qin et al., (2006) induced diabetes in fasted rats by injecting them with alloxan in a dose of 55 mg/kg body weights through tail vein; to investigate the effect of berberine on diabetes. For induction of diabetic dyslipidemia, diabetic rats were allowed free access to a high-cholesterol diet. Alloxan administration elicited severe injury of pancreas diminishing of the diameter of pancreatic island. The islets were shrunken in diabetic rat when compared with normal rat.

21. Saad Mario MJ et al., (1993) studied the levels and phosphorylation state of the insulin receptor and IRS-1, as well as the association/activation between IRS-1 and PI 3-kinase in the liver and muscle of rats treated with dexamethasone. The study showed that dexamethasone has differential effects on the proteins involved in the early steps in insulin action in liver and muscle. In both tissues, dexamethasone treatment resulted in a reduction in insulin-stimulated IRS-1-associated PI 3-kinase,
which may play a role in the pathogenesis of insulin resistance at the cellular level in these animals.

22. Shimabukuro M et al., (1998) demonstrated a possible link between Fatty acid-induced β cell apoptosis, obesity and diabetes. In prediabetic and diabetic ZDF islets, apoptosis measured by DNA laddering was increased 3-and >7-fold, respectively, compared with lean ZDF controls. Ceramide, a fatty acid-containing messenger in cytokine induced apoptosis, was significantly increased ($P < 0.01$) in prediabetic and diabetic islets. They suggested that elevated levels of circulating FFA and lipoproteins transport to islets of obese ZDF rats far more FFA than can be oxidized.

23. Etuk EU and Muhammed B (2010) studied whether there is a significant difference in response by chemically (alloxan) induced hyperglycaemic and oral glucose loading induced hyperglycaemic wistar rats to antidiabetic agents. The maximum blood glucose levels reached after induction with glucose and alloxan were 338.3±61.2mg/dl and 514.7±34.7mg/dl respectively. This study suggests that alloxan administration produced a higher and sustainable form of hypergly-kaemia in comparision to oral glucose administration.

24. Toye AA et al., (2004) reported the first cloned N-ethyl-nitrosourea (ENU)-derived mouse model of diabetes. Study demonstrated that ENU mutagenesis screens can be used to generate models of complex phenotypes, such as type 2 diabetes, that are directly relevant to human disease.

25. Sakr HF (2010) induced the type 2 diabetes mellitus in rats by feeding them on high fat diet for one month, then received streptozocin (25 mg/kg) intraperitoneally as a single dose and continued feeding on high fat diet.

26. Etuk EU et al., (2004) reviewed all the reported models for type 2 diabetes mellitus and highlighted their short comings and drew the precautions required for each technique. According to him although chemical induction of diabetes mellitus
with streptozotocin was the most widely used procedure, chemical induction with alloxan appears to be the easiest, reliable and the most practicable method of inducing diabetes mellitus in rodents. Genetic and surgical models were rarely used because they required highly technical skills and the percentage of animals lost during the procedures were higher.

27. Reuter TY (2007) reviewed diet-induced models for obesity and type 2 diabetes. In case of fructose fed rats the abnormalities and the disease progression resemble the human condition of metabolic syndrome, and are important risk factors for coronary heart disease but it requires long duration for development of type 2 diabetes mellitus. High fat/STZ rodent models are commonly used but have poor standardization.

28. Winzell MS et al (2004) developed high-fat diet–fed mouse as a model for impaired glucose tolerance (IGT) and type 2 diabetes. For this they used female C57BL/6J mice which were fed with high-fat diet (58% energy by fat). Study suggests that the high-fat diet–fed C57BL/6J mouse model is a robust model for IGT and early type 2 diabetes, which may be used for studies on pathophysiology and development of new treatment.

29. Severino C et al., (2002) developed new animal model to study insulin resistance. Study reveals that chronic low-dose subcutaneous dexamethasone (2 g/day) is a useful model to study the relationships between insulin resistance and blood pressure in the rat, and dexamethasone might decrease insulin sensitivity and increase blood pressure through an endothelium-mediated mechanism.

30. Karasawa H et al., (2009) developed new animal model of type 2 diabetes mellitus in BDF1 mice, the F1 hybrids of C57BL/6 and DBA/2 normal strains, by HFD induced obesity-dependent diabetes. BDF1 mice fed a HFD gained weight rapidly and developed severe diabetes characterized by hyperglycemia, glucosuria, and elevation of hemoglobin A1C levels in 3 to 4 months. The glucose tolerance of the
diabetic mice was significantly impaired, and the elevation of plasma insulin after a glucose load was significantly reduced.

31. Lenzen S (2007) reviewed mechanisms of alloxan- and streptozotocin-induced Diabetes. He suggested that both alloxan and streptozotocin induce insulin deficiency. While the mechanisms of beta cell-selective action through uptake via the GLUT2 glucose transporter and beta cell death via necrosis are identical, ROS in the case of alloxan and DNA alkylation in the case of streptozotocin mediate the toxic action of these glucose analogues.