Diabetes mellitus describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism. Several pathogenic processes are involved in the development of diabetes. These range from autoimmune destruction of the β-cells of the pancreas with consequent insulin deficiency to abnormalities that result in resistance to insulin action. The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. Over the past thirty years, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle-aged people.

Despite significant advances in understanding the molecular mechanism involved in the pathogenesis of hyperglycemia, the real cure of diabetes is still beyond horizon. The major aim of treatment of diabetes is to control hyperglycemia and its mediated complications. Currently available oral hypoglycemic drugs currently used for the treatment of diabetes such as sulphonylureas, biguanides, α-glycosidase inhibitors and thiazolidinediones are often associated with undesirable side effects or diminution in response after prolonged use. Hence, the search continues for novel drugs with effective antidiabetic activity at low concentration without side effects.

In recent years, there has been a growing interest in trace element concentrations in the environment and they are considered a factor indispensable for its proper functioning. Insulin action was reported to be potentiated by some trace elements like Chromium, Magnesium, Vanadium,
Zinc, Manganese, Molybdenum and Selenium. Among the various trace metals which are known to exert beneficial actions in the human system, Zinc is an essential trace element succeeding iron in the human system. Zinc is a structural part of key anti-oxidant enzymes such as superoxide dismutase, and Zinc deficiency impairs their synthesis, leading to increased oxidative stress. Insulin, is stored as a hexamer containing two Zinc ions in β-cells of the pancreas and released into the portal venous system at the time of β-cells degranulation.

For the development of a clinically useful metallopharmaceuticals, the research of zinc complexes on the long-term toxicity including side effects, clear-cut evidence of target molecule for the in vivo pharmacological action and good pharmacokinetic properties are essential in the current and future studies. Flavonoids are plant derived secondary metabolites found rich in fruits and vegetables. Flavanoids are classified as flavone, flavonol, flavanone, isoflavone, anthocyanidin and proanthocyanidins. Among these classes, flavonol is known to chelate metal ions with the presence of multiple hydroxyl groups and α-hydroxycarbonyl group. Morin, a natural bioflavonolexhibit several pharmacological properties including antioxidant, anti-inflammatory, nephroprotective, chemoprotective as well as insulin mimetic activity. In the view of the above, we have designed and synthesized a novel zinc complex with morin, a polyphenol categorized as flavonolto increase its potency and reduce toxicity is formulated and its therapeutic
efficacy in high fat diet low dose streptozotocin induced experimental diabetes in rats was studied.

**The objectives of the present study includes,**

I. Synthesis of zinc flavonol complex (Zinc-morin complex) and characterization of the complex by spectral studies.

II. Evaluation of toxicity and dosage fixation studies of zinc-morin complex to fix the optimum dosage of zinc-morin complex to alleviate HFD-STZ induced hyperglycemia in experimental rats.

III. Evaluation of anti-diabetic properties of zinc-morin complex by

2. Performing oral glucose tolerance test (OGTT).
3. Insulin tolerance test was performed (ITT).
4. Determining the levels of fasting blood glucose, plasma insulin, glycosylated hemoglobin, urine sugar to reveal the glycemic index upon Zinc-morin complex treatment.
5. Determining liver and muscle glycogen content.
6. Estimating the plasma levels of urea, uric acid and creatinine.
7. Assaying the activities of AST, ALT and ALP.

IV. Assessing of the insulin sensitising potency of Zinc-morin complex by homeostasis assessment model for insulin resistance (HOMA-IR).

V. Evaluation of the levels of circulating adipokines such as adiponectin and leptin, the crucial markers for the
VI. Zinc-morin complex improves glucose homeostasis in HFD-STZ-induced diabetic rats, which is evident from OGTT and ITT, liver as well as muscle glycogen content and other basic biochemical parameters. The observed improvement in the glycemic status of the diabetic rats upon treatment with zinc-morin complex may be due to

1. the protection of remnant pancreatic β-cells from hyperglycemia induced oxidative stress (or)
2. enhanced β-cell proliferation (or)
3. increased insulin secretion from the β-cells (or)
4. reduced hepatic glucose production by regulating the key enzymes involved in carbohydrate as well as glycogen metabolism (or)
5. its action on skeletal muscles in facilitating the preferential uptake of glucose into the cells for energy production.

Given this background, we have investigated the effects of zinc-morin complex on pancreatic β-cells and skeletal muscles to elucidate the possible mechanism underlying its action by conducting the following in vivo and in vitro studies using HFD-STZ induced diabetic rats and RINm5F pancreatic β-cell line and rat L6 skeletal muscle cell line.
1. investigating the role of zinc-morin complex on pancreatic β cell function in diabetic rats,

2. analyzing skeletal muscle 2-deoxyglucose uptake in HFD-STZ diabetic rats.

3. analysis of cytotoxic effect of zinc-morin complex on RINm5F pancreatic β cells

4. evaluation of the role of zinc-morin complex on RINm5F pancreatic β cell proliferation

5. elucidating the stimulatory role of zinc-morin complex on insulin secretion from RINm5F pancreatic β cells

6. evaluation of the role of zinc-morin complex on RINm5F pancreatic β cell cells under glucotoxicity by
   - RINm5F pancreatic β cell viability under high glucose condition
   - assaying antioxidant status and inflammatory markers
   - Insulin content in RINm5F pancreatic β cells

7. elucidating the role of zinc-morin complex on rat L6 skeletal muscle glucose metabolism by
   - analyzing cytotoxic effect of zinc-morin complex on rat L6 myotubes
   - determining L6 myotubes glucose uptake
   - analyzing the translocation of GLUT4
investigating the effect of LY294002 (PI-3kinase inhibitor), Cytochalasin B (GLUT4 inhibitor) and HNMPA-(AM)3 (Tyrosine kinase inhibitor) on zinc-morin complex induced glucose uptake in rat L6 myotubes

analyzing the levels of p-Akt, Akt, and nuclear PPARδ in rat L6 myotubes.

VII. Under normal physiologic conditions, insulin controls the balance between postprandial fatty acid storage as triglycerides and their release into the circulation during the fasting state. Globally around 90-95% of diabetics are of type 2 diabetes, which is due to resistance to the action of insulin in peripheral tissues especially skeletal muscle. However, persistent lipid oversupply to skeletal muscle causes insulin resistance by promoting the accumulation of lipid metabolites, which are capable of inhibiting insulin signal transduction. Hence, the role of zinc-morin complex on insulin sensitivity in skeletal muscles, could be is explored by

- evaluating the role of zinc-morin complex on glucose uptake in free fatty acid (FFA)-induced insulin resistant myotubes
- determining the role of zinc-morin complex on insulin sensitivity in FFA treated myotubes by glucose uptake assay, IRS-1 ser(307) phosphorylation and lipid accumulation in FFA treated rat L6 skeletal muscle cells.

The results from the present study paves a way for an extensive study that can lead to the formulation of new therapeutic intervention for the
treatment of diabetes and may be a valuable substitute to the currently available oral anti-hyperglycemic drugs. The antidiabetic properties of zinc-morin complex on experimental diabetes throws a positive thought that zinc-morin complex can be considered as a successful aspirant in the treatment of type 2 diabetes mellitus.