CHAPTER-2

Chapter 2

Aims and Objectives

2.1 Aim and Rational for the study:

Lifestyle, modernization, dietary components, rural-urbanization shift, genetic makeup and geographic location are the major contributory factors into a multifactorial, and a complex metabolic disease. TIIDM is one of the silent resultant of the above changes, which has been the pivotal axis of metabolic disorder that has covered massive masses throughout the globe.

Increasing prevalence of diabetes is a burden to the economy, health and social life of people and is associated with hypertension, CVD and obesity. The incidence of diabetes is due to alterations in the metabolism of carbohydrate, fat and protein caused by absolute deficiency of insulin secretion or its action. The pathogenesis of this disease is very well known and studied since its discovery in 1889; however, there is a large void space between mechanistic pathways and treatment of disease. Since, chronic diabetes affects the peripheral metabolism, the pharmaceutical world is in the rein of innovating lucrative and efficacious drugs for ameliorating these manifestations. Many drugs like Metformin, Thiazolidinediones, GLP-1, DPP-4 etc. are available for the treatment but with plausible side-effects. Hence, it has become mandatory to extend our search for a novel therapeutic alternative that will supersede our current diabetes treatment.

The shortcoming and unwanted side effects of the synthetic drugs has reinforced the value of herbal treatments. Ayurveda, the most dignified Indian heritage veda, is the boon for the treatment of varied ailments. Many herbal plants like Momordica charantia, Artemisia dracunculus, Gymnema sylvestre, etc. have been explored to a large extent in amelioration of obesity and diabetes. As per WHO guidelines, many research groups are actively involved in unraveling the potentials of the herbal plants in treatment of this deadly disease. Many active principal ingredients have been reported for antidiabetic, anti-inflammatory and anti-lipidemic activity and have been proved better alternative and complementary medicine for the treatment of diabetes. *Enicostemma littorale (*EL), a perennial herb known for best anti-diabetic effect, has been explored in various horizons for beneficiary effects with its potential active compounds like

swertiamarin, swertisin, genistein etc. For more than a decade, our lab has focused on EL's hypoglycemic, anti-oxidant, hypolipidemic and diabetic complications related diseases. and in various diabetic animal models, and human patients. Previous lab studies also demonstrated that Swertsin posses islet neogenic potential from stem progenitors.

Pharmacokinetic study of swertiamarin, one of the principal compound of EL, and best known bitter glycoside, has shown its rapid absorption into circulation reaching most of the peripheral tissues. In some of the earlier reports swertiamarin has been found very effective in hypolipidemic and hypocholesterolemic condition by controlling HMG-CoA reductase activity in animal models of obesity, which makes it a potential drug target for treatment of obesity and other diabetic complications. However, mechanistic role of swertiamarin is hidden with respect to its action on various candidate metabolic genes, transcriptional factors and insulin signaling cascade involved in peripheral tissue metabolism like liver, muscle and adipose tissue. In this regard, this study was designed to elucidate the mechanism of principal active compound of EL involved in amelioration of insulin resistance, anti-adipogenesis and integrated metabolic pathway of the peripheral tissues.

Recently, the role of PARP-1 has emerged in regulating various metabolic and cellular differentiation pathways by its interaction with the chromatin and associated proteins. Also, there are very few reports on PARP-1 having a regulatory role in the process of adipogenesis. Therefore, this study elucidate the regulatory mechanism; of PARP-1 in adipogenesis by modulating the action of the master transcriptional regulator, PPAR-γ, through TGF-β signaling pathway and also relationship between swertiamarin and PARP-1. Thus, the major aim of the study is to elucidate molecular mechanism of swertiamarin in insulin sensitive peripheral tissue and understand its interaction with PARP-1. Following are the objective to achieve the aim.

2.2. Objectives:

2.2.1 Objective-1:

To assess the effect of *Enicostemma littorale* Blume bioactive ingredient in regulation of candidate metabolic gene expression in insulin sensitive peripheral tissue of experimental NIDDM rat model.

2.2.2 Objective-2:

To study the mechanism of action of swertiamarin: An active lead from *Enicostemma littorale* in insulin resistant peripheral tissue: *in vitro.*

(a) Oleic acid induced model of Hepatic steatosis HepG2.

(b) TNF-α induced insulin resistance L6 myocytes.

(c) Dexamethasone **/** TNF-α induced insulin resistance in adipocyte.

2.2.3 Objective-3:

Assessment of molecular mechanism of swertiamarin by elucidating its anti-adiopogenic potentials.

2.2.4 Objective-4:

Role of swertiamarin and Poly (ADP) Ribose Polymerase-1 in Adipocyte differentiation.