CHAPTER - 2

Aim and Objectives
The association between obesity and type II diabetes mellitus has been well recognized for decades and the major link is insulin resistance. The natural history of diabetes and obesity states that insulin resistance precedes abnormal glucose i.e., hyperglycemia. Insulin resistance in both these metabolic diseases is manifested by decreased insulin stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired hepatic glucose output.

Several interventional studies have demonstrated that significant weight reduction could lead to a decreased incidence of obesity and progression to type II diabetes. Thus obesity and overweight are major risk factors for chronic diseases including type II diabetes mellitus, cardiovascular diseases, hypertension, stroke and cancer.

Despite the great strides that have been made in the understanding and management of diabetes, the disease and disease-related complications are increasing unabated. Parallel to this, recent developments in technology, in drug designing and in understanding the pathophysiology of the disease process have opened up several new avenues to identify and develop novel therapies to combat the diabetic plague (Ashok and Madhusudana Rao, 2002).

The Indian subcontinent has given to the medicinal world natural remedies such as ayurveda, unani and sidda. In addition to this during the last two decades, traditional systems of medicine and medicinal plant derivatives research has become topics of global interest and importance. Based on such systems, we found not only new remedies, but also new lead molecules.

The plant has not been associated with published reports of human toxicity. Blood urea and hemoglobin levels remained in the normal range in patients is receiving gymnema supplements in addition to their usual antidiabetic medication. These reports suggested the absence of hepatotoxicity or nephrotoxicity at normal doses. In acute toxicity study in mice gross behavioural, neurological autonomic effects were absorbed. One of the alternative medicines to both diabetes and obesity could be *G. sylvestre* plant preparation or its phytochemicals.
*G. sylvestre* (Asclepediaceae) is a woody climbing plant indigenous to the tropical forests of central and southern India. Distribution is worldwide and is recognised in the traditional medicinal literature of many countries including India, Australia, Japan and Vietnam. The leaves are most commonly used; stem also appears to have some pharmacological action. Chewing leaves of this plant destroys the ability to discriminate the sweet taste giving it the common name in Hindi-Gurmar and in Sanskrit-Meshasringi which means sugar destroyer. Gymnema leaves have been used for centuries in the traditional Indian system of ayurvedic medicine. Clinical trials conducted in India have shown that an extract of *Gymnema sylvestre* is useful for controlling blood sugar. However, gymnema has also been used as a remedy for many diseases because of its highly effective properties like suppressing the perception of sweetness, digestion and weight control.

Although there are many phytoconstituents that could combat diabetes and obesity a single phytoconstituent that could be used in the treatment of both the diseases simultaneously would be a welcome addition. The multiple pharmacological actions of a unique compound is a prerequisite for classifying drugs as highly efficacious, because the multiple pharmacological actions offers the possibility of treating various symptoms of chronic diseases like diabetes mellitus and obesity.

The antidiabetic array of molecules has been identified as a group of closely related gymnemic acids (GA) after it was successfully isolated and purified from the leaves of *G. sylvestre* (Sinheimer and Subbarao, 1970; Liu et al., 1992; Kanetkar et al., 2007). The structure of GA (3β, 16β, 21β, 22α, 23, 28-hexahydroxy-olean-12-ene) was established by X-ray analysis of the 3β, 23; 21β, 22α-di-O-isopropylidene derivative. Different antisweet principles were isolated in pure states from the leaves of *G. sylvestre* (Liu et al., 1992).

GA-IV has antisweet, antihyperglycemic, glucose uptake inhibitory and gut glycosidase inhibitory effects, while GA-I and III have only antisweet activity and GA-II has antisweet and glucose uptake inhibitory activity. Most of these
pharmacological effects of GA-IV may synergistically contribute to alleviating obesity and type II diabetes-related symptoms (Kimura, 2006).

The reasons for selecting the GA as lead molecule for the study are the antisweet activity, the inhibition of intestinal sugar absorption and enhancement of insulin secretion. In order to understand the mode of action of GA with the target proteins it is studied by comparing with the known inhibitors of the target proteins and to develop a more efficient drug. However, a single pure compound by itself has multiple pharmacological actions similarly to a single crude drug. Their actions may be linked to common proteins in physiological or pathological circuits. Protein sciences, combined with bioinformatics tools, also allow us to dissect the genetic basis of multifactorial diseases and to determine the most suitable areas for intervention for future therapies, thereby increasing the number of treatment options.

Computer-aided drug designing has come into focus with the discovery of new softwares that is made available to us today in the market. In contrast to the traditional trial and error techniques the use of recently developed structural based drug design techniques promises to yield more efficacious drugs and to increase the rate at which they are developed with much less expense. The present study is aimed to develop an effective antihyperglycemic agent that can target the proteins – sweet taste receptors, glucose transporters and glycogen phosphorylase (GP).

This has prompted to take up the present research work in, *in silico* with the following objectives:

1. To build the homology model of the 3D structure of selected target proteins – general olfactory GPCR, T1R2, T1R3, GLUT2, GLUT4, GLUT5, GLUT6, GLUT7 and brain GP using OPENEYE, commercial software.
2. Identification of binding site of target proteins using CASTp server based on the template site.
3. Designing of selected sweeteners [glucose, fructose, sucrose, sucralose, saccharin, sodium cyclamate, stevioside, acesulfame potassium,
neohesperidin dihydrochalcone, D-tryptophan, glycyrrhizic acid, rebaudioside and aspartame] and inhibitors [thapsigargin, caffeine, flavopiridol, ingliforib, 1,4-dideoxy-1,4-d-arabinitol (DAB), tannic acid, chloramphenicol, urea (4-cyanophenyl), urea (methanesulfonic acid), amiloride, 2-(4-methoxyphenoxy)propionic acid (PMP), ziziphins and gymnemic acid-IV] by using Chemsketch software.

4. To dock the sweeteners and inhibitors against homology models of human GPCR, T1R2, T1R3, using OPENEYE, commercial software.

5. To find out the best inhibitor, that can effectively bind to sweet taste receptor but not to the other olfactory GPCRs (human RDC1 gene protein).

6. As the GA is found to be the lead molecule among the selected inhibitors, further work was extended to develop efficient antihyperglycemic GA derivative, using GA as a core molecule with different side chain substitutions.

7. To predict druglikeness of derivatives using molsoft, molinspiration and OSIRIS property explorer.

8. To dock the screened GA derivatives with general olfactory GPCR, T1R2 and T1R3.

9. To dock the ligands with GLUTs to find the effects of selected compound.

10. To identify the inhibitors of GP of liver, muscle and brain by docking with the ligands.

11. To identify the compound that act as effective drug for hyperglycemia.

Keeping in view of the above objectives, the present work was carried out.