1 Introduction

Diabetes mellitus characterized by hyperglycemia, is a clinically heterogeneous disorder of glucose intolerance. It is associated with disturbance in carbohydrate, fat and protein metabolisms which may be attributed to the absolute or relative deficiency of insulin secretion and/or action.

Diabetes mellitus is described as insulin resistance, a condition in which insulin dependent cells fail to use insulin properly, or an absolute insulin deficiency when the β cells cannot meet this demand. It may present itself in characteristic symptoms such as polyuria, polydipsia, polyphagia, blurring of vision, and weight loss. The persistent chronic elevation of plasma glucose causes many of the major complications of diabetes, including nephropathy, retinopathy, neuropathy and macrovascular complications that lead to death.

Despite multiple etiologies, it is classified as Type I and Type II diabetes mellitus. Type I diabetes (T1DM) ("insulin-dependent diabetes mellitus" or "juvenile diabetes") often arises in children below the age of 20 years. It is an autoimmune disease in which the patient’s own immune system reacts against islet antigens and results in partial or complete loss of pancreatic β cell function (WHO, 2014). Type II diabetes mellitus (T2DM) ("non-insulin-dependent diabetes mellitus" or "adult-onset diabetes") is more common in above 40 years of age and accounts for 90% of all diabetes (ADA, 2013). Other form of diabetes mellitus (DM) includes gestational diabetes that occurs when pregnant women develop a high blood glucose level without previous history of diabetes. It may precede development of T2DM which is due to defects of insulin secretion.

Diabetes may be or may not be a part of metabolic syndrome. The metabolic syndrome (MetS) is defined as a clustering of abnormalities including abdominal obesity, dyslipidemia, hyperglycemia and hypertension in an individual (Alberti et al., 2009). The MetS afflicts 40% of people in their 60s and 70s and the number is expected to rise along with aging population (Stone et al., 2013). An estimated 50-75% of patients with T2DM or impaired glucose tolerance (IGT) have MetS. The presence of MetS in diabetic populations is associated with a higher prevalence of cardio vascular disease (CVD) as compared to the diabetics without the MetS (Yadav et al., 2013). The pathophysiology is
very complex and has been only partially elucidated. Though the exact mechanism of the complex pathways of MetS are not yet completely known, it is thought that sedentary lifestyle makes people more prone to MetS. The most important factors for MetS are obesity, genetics, endocrine disorders, aging and stress (Alberti et al., 2009).

The epidemic of diabetes has reached every nook and corner of the world regardless of region, race, religion, sex, age and other socio-demographic criteria. According to recent global estimates by International Diabetes Federation (IDF), approximately 415 million people, in the 20–79 years age group, have been reported to be afflicted with diabetes in 2015, and by 2040 the number is likely to reach 642 million (IDF, 2015). In Southeast Asia, the prevalence was 1.6 billion in 2015 and is expected to be 1.8 billion in 2040. However, surveys in India, reported 65.1 million (9.1%) cases in 2014 likely to reach 109 million by 2035 (IDF, 2015). The global increase in the prevalence of diabetes has been attributed to urbanization, obesity and physical inactivity.

Epidemiological evidences suggest that lack of effective intervention may further increase the incidence of diabetes worldwide. Thus, prevention of diabetes and its consequences are not merely the major challenges for future but essential goals to be achieved, if ‘health for all’ is to be an attainable target. Randomized clinical trials in several countries have provided evidence that, in high-risk individuals with IGT, progression of T2DM can be reduced by intensive changes in diet, increased physical activity and/ or with drug therapy using glucose lowering agents (Gillies et al., 2007).

Oral anti-hyperglycemic drugs play an important role in the treatment of T2DM. There are mainly two groups of oral anti-hyperglycemic agents available for clinical use, i.e. sulfonylureas, the insulin secretors and biguanides, the insulin sensitizers. Sulfonylureas bind to ATP-sensitive potassium channel, activating a sequence of events within the cells that lead to an increase in the amount of insulin release from pancreatic β-cells. The mode of action of biguanides is not clear, but is likely to increase glucose uptake by the cell by several mechanisms. Other medicines are α-glucosidase inhibitors and DPP IV inhibitor (Stein et al., 2013). Currently available medicines have undesirable side effects. According to the World health organization (WHO), traditional herbals may provide valuable leads for the development of alternative drugs and strategies for T2DM
and its related complications (WHO, 2014). Herbal medicines prove good anti-diabetic agents as they not only improve glucose and lipid metabolism by stimulating insulin release, attenuating the absorption of carbohydrates from the gut but also improve the antioxidant status (Singh et al., 2015). Many studies on oral anti-hyperglycemic agents of plant origin (used in traditional medicine) have been conducted.

*Gymnema sylvestre* (*G. sylvestre*) is a woody, climbing plant, native to India that belongs to the *Chyloanpyase* family. Sushruta describes *G. sylvestre*, as a destroyer of madhumeha (glycosuria) and other urinary disorders. On account of its property of abolishing the taste of sugar, it has been given the name of gur-mar meaning sugar destroyer and it is believed, therefore, that it might neutralize excess sugar in diabetics (Khanna et al., 2009).

The leaves of *G. sylvestre* are reported to lower blood sugar, to stimulate the heart, uterus, and circulatory systems, and to exhibit antisweet & hepatoprotective activities (Rana and Avadhoot, 1992). *G. sylvestre* leaf extract also demonstrated a lipid lowering and antioxidant potential in animal models (Kang et al., 2012). These effects are also seen in human subjects (Baskaran et al., 1990). It is one of the medicinal plants widely used as an anti-diabetic drug, alone or in combination with other herbs.

**In silico** docking or molecular docking is used for screening the drug likeness of the natural or synthetic compound. Drug target identification in **in silico** method includes many distinct algorithms for finding the target proteins (Liu et al., 2010). Besides, studies on cell lines represent an animal-free opportunity to investigate the physiology or biochemistry of cells, to test the effects of various chemical compounds or drugs on specific cell types (Skelin et al., 2010) and can help to find the mechanism of action of the drug.

The present work focuses on the selection of type II diabetics with MetS from the Gwalior population by conducting epidemiological study and evaluation of anti-diabetic function of *G. sylvestre* in subjects with T2DM and MetS: Elucidation of molecular mechanism in insulin signalling pathway and Glucose transporter 4 (GLUT 4) translocation by using both **in silico** and cell line studies.

~ 3 ~
1.1 Objectives

1. Screening of human subjects for type II diabetes mellitus and metabolic syndrome from Gwalior-Chambal region.

2. Comparative evaluation of aqueous and ethanolic extracts of *G. sylvestre* for
   a. anti-hyperglycemic activity
   b. anti-hyperlipidemic activity
   c. anti-oxidant function.

3. Exploration of molecular targets of *G. sylvestre* by *in silico* approach.

4. Studies on the effect of *G. sylvestre* on GLUT-4 translocation and other molecular targets in cell lines *in vitro*. 