ABSTRACT

Diabetes is a major public health challenge that is approaching global epidemic propagation and is emerging as one of the leading causes of death worldwide. It is a group of metabolic diseases characterized by high blood glucose levels (hyperglycemia) resulting from either defects in insulin secretion from the pancreatic β cells or insulin action in peripheral insulin target cells.

The prevalence of diabetes has increased rapidly all over the world. The International Diabetes Federation (IDF) estimated that diabetes affected 415 million people worldwide in the year 2015, and this number is projected to reach upto to 642 million by the year 2040. In India, 69.1 million people are reported to suffer from diabetes in 2015 which is expected to increase upto 123.5 million by the year 2040.

Depending upon the insulin responsiveness, diabetes mellitus can be classified into two types. Type 1 diabetes mellitus (T1DM) or insulin dependent diabetes mellitus (IDDM) is basically due to autoimmune mediated destruction of the pancreatic β cells resulting in insulin deficiency. Type 2 diabetes mellitus (T2DM) or noninsulin dependent diabetes mellitus (NIDDM) is characterized by insulin unresponsiveness or resistance in the insulin target cells.

According to the World Health Organization (WHO), Type 2 diabetes (T2DM) has turned into an epidemic afflliting more than 90-95% of people diagnosed with diabetes world wide. Type 1 diabetes (T1DM) comprises about 3-5% of the global population suffering from the disease.

It is generally believed that obesity induced insulin resistance is the major risk factor contributing to development of T2DM because insulin resistance is a common pathologic state in which the target cells fail to respond to normal levels of circulating insulin.

Free fatty acid (FFA) is found to be one of the major players in obesity induced insulin resistance and T2DM. Several reports demonstrate that the elevation of circulatory FFA due to the oversupply of lipid induces the

development of T2DM. The excess of lipid leads to the generation of hyperlipidemia resulting in acute insulin resistance. The signs of abnormal lipid metabolism, increased circulatory lipid concentration and elevated deposition of lipid in the skeletal muscle are seen in the patients suffering from insulin resistance.

Although diabetes is the most widespread non-communicable disease in the world, the primary cause still remains unclear. Insulin resistance is one of the common features of T2DM patients. Insulin resistance in the muscle cells has been reported to be prompted by increase in plasma free fatty acid (FFA). Lowering of glucose transport by FFA has been shown to be linked to reduce insulin stimulated IRS-1 tyrosine phosphorylation and IRS-1 associated PI3 kinase activity which in turn affects downstream effectors like AKT/PKB and GLUT4. There are several commercially available antidiabetic drugs in the market but none of these drugs address the pathogenesis of insulin resistance and T2DM. These drugs address only the problem with increased insulin release or direct administration of insulin. Although dearth of insulin is not the actual problem of this disease but loss of insulin activity is the key event of insulin resistance. However, excess of insulin provides a relief, though whether this has a long term adverse effects is still not clear. Since, it is also responsible for other functions beside glucose regulation, an imbalance is expected, leading to certain unwanted effects. Only the TZD class of drugs increases the insulin sensitivity and that exactly address the T2DM. This class of drugs is responsible for the activation PPARγ to stimulate adipogenic differentiation. This class of drugs increases the level of lipid uptake and decrease circulating FFA level and thus improves insulin signalling pathway. It also reduces the level of proinflammatory cytokines such as TNFα and IL6. But the use of these drugs for long period shows some adverse effects.

Therefore, there is a great need to develop suitable therapeutic alternative for treating T2DM. Ethnobotanical approach and the traditional herbal medicines provide the much required platform for discovery of new drugs. For thousands of years, natural products have been the basis of treating and preventing human diseases. Many of the clinically used therapeutic agents are used in their naturally occurring forms or as derivatives or analogues after structural optimization. The

influence of natural products upon drug discovery has been well recognized and documented and continues to play an important role in humankind. Twenty-five percent of the drugs used worldwide have their origins in plants and 121 such active compounds are still in use. Eleven percent of the 252 basic and essential drugs, as claimed by the World Health Organisation, originate from plants and other natural sources.

Chapter 1 covers in detail the Introduction of the problem of diabetic complications with special focus on free fatty acid (FFA) induced insulin resistance and type 2 diabetes mellitus (T2DM). The chapter also explains the requirement of new drugs addressing the problem of FFA induced insulin resistance. The importance of exploring plant metabolites on the basis of traditional knowledge is also highlighted in the special context of the rich plant biodiversity of North East India.

Chapter 2 comprises of the Review of Literature, and presents comprehensive review on the problem of FFA induced insulin resistance and T2DM. The chapter also explains the roles of different molecules involved in insulin signaling and the molecular mechanism of impairment of their activity in insulin sensitivity by the action of FFA. Available drugs present in the market for the treatment of diabetes and their limitations also discussed in this chapter. This chapter covers the new drugs in the pipeline for the treatment of T2DM. The chapter reviews the *in silico* based network pharmacology approach in the field of drug discovery.

Chapter 3 comprises of the screening of the traditionally used medicinal plants along with the brief description of the plants and their medicinal use. This chapter also contains the isolation of the bioactive fraction(s) from the plant (*L. aspera*) showing best glucose uptake activity followed by isolation of the active compounds and their characterization and structure elucidation.

Chapter 4 explains the probable molecular mechanisms through which the active fraction of *L. aspera* inhibited the FFA induced insulin resistance and improvement of glucose uptake.

Chapter 5 contains the molecular mechanisms of ferulic acid isolated from *Hibiscus mutabilis* in ameliorating the FFA induced insulin resistance.

Chapter 6 comprises of the role of free fatty acid in the gene regulation as well as enzymatic activity of cellular antioxidants. It also presents the protective role of the active fraction of *L. aspera* and ferulic acid in reducing the FFA induced alteration of cellular antioxidants.

Chapter 7 comprises of a computational study using network pharmacology approach for the development of new potential antidiabetic molecules. This chapter explains the investigation of some active natural compounds from traditionally used antidiabetic plants by various ethnic groups of Assam targeting multiple proteins associated with insulin resistance and type 2 diabetes mellitus. The objective is to see if the concoction of these compounds has any beneficial effect in the treatment of insulin resistance and T2DM.

Chapter 8 presents the conclusion of the present work and proposes future works in line with the presented work.

The last part of the thesis contains the appendices.