Chapter I

Introduction

1. Introduction:

Diabetes mellitus (DM) is a clinically and genetically heterogeneous group of disorders characterized by abnormally high levels of glucose in the blood. The hyperglycemia is due to deficiency of insulin secretion or to resistance of the body's cells to the action of insulin, or to a combination of these. Often there are also disturbances of carbohydrate, fat, and protein metabolism (Himsworth HP. 1936). Chronic hyperglycemia and other metabolic disturbances of DM lead to long term tissue and organ damage as well as dysfunction involving the eyes, kidneys, and nervous and vascular systems (ADA 1998; ECDCDM 2009; ADA accessed 10 Feb 2009). It has been centuries since this syndrome was first recognized, credit for the initial observation that diabetes is not a single disorder rests with two Indian physicians Chakrata and Susruta (600 B.C.), who differentiated two forms of the disease (Himsworth HP et al 1936).

In the mid 1930s, Himsworth (Himsworth HP et al 1936) proposed that there were at least two clinical types of DM, insulin sensitive and insulin insensitive, the former being due to insulin deficiency. Confirmation of his clinical observations came with Bornstein and Lawrence's (Bornstein J et al 1951) development of a bioassay for insulin, and when radioimmunoassay for insulin became available a decade later (Berson SA et al 1963). Bornstein and Lawrence's observations were confirmed. The widespread acceptance of the terms juvenile-onset and maturity-onset DM at this time affirmed the concept that there were at least two major forms of the disease.

During the last decades of the 20th century, research has led to the recognition that DM is a syndrome and comprises a heterogeneous collection of disorders, and that the different types of DM have different etiologies, although their pathologic effects after onset of disease may be similar. The widespread acceptance of the terms juvenile-onset and maturity-onset DM at this time affirmed the concept that there were at least two major forms of the disease. During the last decades of the 20th century, research has led to the recognition that DM is a syndrome and comprises a heterogeneous collection of disorders, and that the different types of DM have different etiologies, although their pathologic effects after onset of disease may be similar (WHO Fact sheet 2009; IDF 2009).

There are mainly two types of diabetes; Type 1 diabetes is immune mediated and requires daily administration of insulin. The other common type is type 2 diabetes and characterized by insulin resistance or relative insulin deficiency (WHO Fact sheet 2009; IDF 2009). Type 2 diabetes is the most common form and comprises of 90% of people with diabetes around the world (WHO Fact sheet 2009).

According to the latest IDF estimates, 50.8 million people in India diagnosed with diabetes in 2010 and the figure will increase to approximately 75 million in 2025 and almost 80 million by 2030 (Anand Moses 2011). Phase one results of the Indian Council of Medical Research India Diabetes (ICMR-INDIAB) study have provided data from three States and one Union Territory, representing nearly 18.1 per cent of the nation's population. When extrapolated from these four units, the conclusion is 62.4 million people live with diabetes in India, and 77.2 million people are on the threshold, with pre-diabetes (Anjana M. et al 2011). In diabetes, the postprandial phase is characterized by a rapid and large increase in blood glucose levels, which is called postprandial hyperglycemia or "hyperglycemic spikes" (Bonora E. et al 2001; Aryangat AV et al 2010; Ceriello A. et al 2005).

Accumulating evidence shows that excessive fluctuations in post meal blood glucose levels (postprandial hyperglycemia) have adverse consequences for diabetes related morbidity and mortality. It is now apparent that postprandial hyperglycemia plays a central role in the decline from impaired glucose tolerance (IGT) to overt diabetes and in the development and progression of diabetes complications, particularly cardiovascular disease (CVD), good glycemic control reduces the risk of vascular complications (DCCTR Group, 1995; UKPDS Group, 1998), and prevention of postprandial hyperglycemia decreases the risk for both type 2 diabetes and CVD in individuals with IGT (Chiasson JL et al, 2002). Consequently, postprandial glucose control in conjunction with normalization of hemoglobin HbA1c and fasting plasma glucose levels in those with manifest diabetes should be a primary goal in the prevention and management of type 2 diabetes.

Chronic hyperglycemia induced by diabetes is associated with higher risks of strokes, coronary heart disease, and peripheral vascular disease, dyslipidemia, hypertension, and obesity. This chronic hyperglycemia is also associated with damage to

and failure of the eyes, kidneys, nerves, heart, and blood vessels (ADA 2002). These abnormalities occur due to the accumulation of glucose metabolites and the glycosylation of certain proteins, including hemoglobin (Raff, H et al 2004). Elevated glycosylated hemoglobin (HbA1c) levels > 7% are associated with a glucose response of = 228 mg/dl during an OGTT (Santiago, JV et al 1978). Effective management of postprandial hyperglycemia therefore involves not only the maintenance of normal blood glucose levels after meal but also the prevention of many other diabetic complications. In this realm, the α-glucosidase inhibitors attract most interest (M. Koyasu et al, 2010; S. Frantz, et al 2005; M. Shimabukuro, et al, 2006). The α-glucosidase inhibitors reduce postprandial hyperglycemia by delaying the absorption of carbohydrate from the small intestine. an α-glucosidase at the small intestinal brush border enzyme, responsible for breakdown of complex polysaccharides (Starches) and sucrose into glucose (Chiarson JC et al, 1994.).

Importantly, these agents reduce blood glucose without increasing insulin secretion and do not cause hypoglycemia or weight gain. The inhibition of α-glucosidase activity reliably reduces HbA1c and postprandial insulin levels in individuals with type 2 diabetes. In addition, treatment with an α-glucosidase inhibitor can improve lipid metabolism, reduce fasting plasma glucose levels, and improve insulin sensitivity. Currently, three α-glucosidase inhibitors exist: acarbose, miglitol and voglibose (A desktop guide to Type 2 diabetes mellitus. 1999; Rutten GEHM et al 2000).

In the early 1990s, acarbose as the first α-glucosidase inhibitor to be introduced into the market (Krentz et al 2005) Later on, two other inhibitors were introduced in some countries: voglibose in Japan (1994) and miglitol in the United States (1996) (Asano N et al 2003). According to a survey of World Health Organization (1993) (WHO), the practitioners of traditional system of medicine treat about 80% of patients in India (Vijayan K. et al 2012).

In traditional systems of medicine the Indian medicinal plants have been used in successful management of various disease conditions like bronchial asthma, chronic fever, cold, cough, malaria, dysentery, convulsions, diabetes, diarrhea, arthritis, emetic syndrome, skin diseases, insect bite etc. and in treatment of gastric, hepatic, cardiovascular & immunological disorders (Soumaya K.Vijayan et al 2012; Atal CK et al

1989; Sen P 1993; Chopra RN et al 1993; Chopra RN et al 1956; Satyavati GV et al 1976; Nadkararni AK et al 1976).

Diabetes has been managed by ayurvedic practitioners for millennia. However, like most traditional and folk remedies these methods of treatment have not been subjected to rigorous scientific analysis. Ayurveda is derived from religious texts the vedas. Hence, it has been accepted on faith (Hardy et al 2001). Herbal medicines have been in use for millennia. In recent years, there has been increasing interest in herbal medicines as they have increased in popularity in the developed world (M.H.S. Jayawardena et al 2005). Several plants have been considered for use as antidiabetic agents in the Indian material medica many of have been the subject of human and animal trails (Nadkarni AK. et al 1954.).

Salacia oblonga and *S. reticulate* (Flammang AM et al 2006) (Family: Celastraceae or Hipppocrateaeceae) have been used for thousand years in the Ayurvedic system of Indian traditional medicine for the oral treatment of diabetes and having α-glucosidase inhibitory activity. Salacia also has potent antioxidant properties, and triglyceride and LDL cholesterol lowering effects that aid in weight loss (Soumaya K. Vijayan et al 2012). *Salacia reticulata* a plant distributed in India and Shrilankan forest and having hepato protective and antioxidant activity (Yoshikawa M. et al 2002) has been used as a supplementary food in Japan to prevent obesity and diabetes (Yoshikawa M et al 2002.). Extracts from the roots and stems of *Salacia oblonga*, a woody climbing plant that grows in parts of India and Sri Lanka, have been shown to have α-glucosidase inhibitory activity in vitro and may be useful in the prevention and/or treatment of diabetes (Augusti KT et al 1995; Yoshikawa M et al 1998; Yoshikawa M et al 2002; Shimoda H et al 1998; Jennifer A. et al 2007) and also reduces fat (Is diabetes troubling you? 2005).

It is found that in a medical food containing *Salacia oblonga* or *Salacia reticulata* consumed for two weeks did not result in clinical, chemistry or histopathological indication of toxic effects in male Spraugue – Dawely rats (Wolf BW et al 2007). It is also proved that *Salacia Oblonga* was well tolerated and it does not produce any general

organ or systemic toxicity when fed to male and female rats at dietary concentration as high as 2500 mg/kg/day for a period of at least 90 days (Flammang AM. et al 2007).

Two thiosugars isolated from *S. oblonga* extract, salacinol and kotalanol, have inhibitory effects, in vitro, against maltase, isomaltase, and sucrase, with the inhibitory effect against sucrose being more potent than the prescription α-glucosidase inhibitors acarbose and voglibiose that are used in the treatment of diabetes (Matsuda H et al 2005). M.H.S. Jayawardena et al conducted a randomized single centre double blind cross over clinical trial to investigate the effects of a herbal tea containing *Salacia reticulata* (Kothala Himbutu tea) in patients with type II diabetes mellitus all patients completed both arms of the trial. The HbA1c at the end of drug treatment was significantly lowered (Jayawardena M.H.S. et al 2005).

Two potent α-glucosidase inhibitor salacinol, kotalanol and another thiosugar analogs, ponkolanol and salaprinol isolated from *Salacia reticulata* (Muraoka O et al 2008). So this study was undertaken so as to assess the comparative safety and efficacy of the Acarbose, Miglitol alone and in combination with salacia species in the patients of type 2 diabetes mellitus. Currently available synthetic antidiabetic agents like sulfonylureas, biguanides, miglitinides, thiazolidinediones and glucosidase inhibitors etc besides being expensive produce serious side effects. Further their use is not safe during pregnancy. Apart from currently available therapy, herbal medicines recommended for treatment of diabetes throughout the world. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost (Venkatesh S et al 2003).