INTRODUCTION

1.0 INTRODUCTION

Diabetes is a most common serious disease and it remains a crippling global health problem today. It is characterized by derangements in carbohydrate, lipid and protein metabolism. The basis of the abnormalities in diabetes mellitus is the deficient action of insulin on target tissues. Deficient insulin action results from inadequate insulin secretion and/or diminished tissue responses to insulin at one or more points in the complex pathways of hormone action. It is the most common metabolic disorder worldwide and is a major public health problem (American Diabetes Association, 2008a; Dieye *et al.*, 2008).

India is one of the leading countries for the number of people with diabetes mellitus. India has the dubious distinction of having the highest prevalence of diabetes worldwide (Ramachandran *et al.*, 2004). Further, the number of individuals with diabetes will reach many more million by 2030 with earlier age manifestations (Balagopal *et al.*, 2008). Approximately 70 per cent of India's population lives in rural areas in resource-poor settings where the increasing prevalence and chronic nature of type 2 diabetes have become added burdens. Lack of awareness and poor access to quality care increase diabetes related complications. Lifestyle intervention is the most cost-effective strategy to prevent type 2 diabetes (Wild *et al.*, 2004).

Because of its chronic nature, the severity of its complications and the means required to control the disease, diabetes is a costly disorder, not only for affected individuals and their families, but also for the health systems. Studies in India estimate that, for a low-income Indian family with an adult with diabetes, as much as 25 per cent of family income may be devoted to diabetes care (WHO, 2008).

Type 1 diabetes was previously called insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes. Type 1 diabetes develops when the body's immune system destroys pancreatic beta cells, the only cells in the body that make the hormone insulin which in turn regulates blood glucose. To survive, people with type 1 diabetes must have insulin delivered by injection or a pump. This form of diabetes usually strikes children and young adults, although disease onset can occur at any age. Type 1 diabetes accounts for 5 to 10 per cent of all diagnosed cases of diabetes. Risk factors for type 1 diabetes may be autoimmune, genetic, or environmental. There is no known way to prevent type 1 diabetes. Several clinical trials of methods for the prevention of type 1 diabetes are currently in progress or are being planned (WHO, 2008).

Type 2 diabetes was previously called non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes. Type 2 diabetes accounts for about 90 to 95 per cent of all diagnosed cases of diabetes. It is characterized by deficiency of insulin or reduced responsiveness of target cells due to some change in insulin receptors, shortly known as insulin resistance. Some consequences are decreased glucose uptake by muscle and storage by liver. It is hereditary, but excess body weight and lack of exercise increase the risk. Type 2 diabetes is often seen in people over 40 years of age and people who are overweight (American Diabetes Association, 2008b).

Type 2 diabetes is associated with older age, obesity, a family history of diabetes, a history of gestational diabetes, impaired glucose metabolism, physical inactivity, and race/ethnicity. Clinically-based reports and regional studies suggest that type 2 diabetes in children and adolescents, although still rare, is being diagnosed more frequently, particularly in American

Indians, African Americans and Hispanic/Latino Americans (CDC Division of Media Relations, 2008).

Other types of diabetes result from specific genetic conditions (such as maturity-onset diabetes of youth), surgery, drugs, malnutrition, infections and other illnesses. Such types of diabetes may account for 1 to 5 per cent of all diagnosed cases of diabetes (Radha *et al.*, 2003).

Over 90 per cent of diabetic patients have type 2 disorder. The rest have type 1 diabetes. Although the two types of diabetes have distinct pathogenesis, hyperglycemia and various life threatening complications resulting from long term hyperglycemia are the most common features. Epidemiological studies and clinical studies strongly support the notion that hyperglycemia is the principal cause of complication. The most serious complication of diabetes is diabetic nephropathy, which is characterized pathologically by glomerulosclerosis, glomerular nephropathy, deposition of IgG and albuminuria (Osinubi *et al.*, 2006).

Free radicals may play an important role in the causation and complications of diabetes mellitus. The increased oxidative stress and accompanying decrease in antioxidants may be related to the causation of diabetes (Punitha *et al.*, 2005). In diabetes mellitus, alterations occur in the endogenous free radical scavenging of reactive oxygen species, resulting in oxidative and tissue injury. Oxidative stress has been shown to produce glycation of proteins, inactivation of enzymes and alteration in structural function of collagen in basement membrane (Parham *et al.*, 2008).

Oxidative stress may have significant effect on the glucose transport protein or insulin receptor. Scavengers of oxidative stress may have an effect in reducing the increased serum glucose level in diabetes and may alleviate

diabetes as well as reduce its secondary complications (Sabu and Kuttan, 2000).

The emotional and the social impact of diabetes and the demands of therapy may cause significant psychological dysfunction in patients and their families. In modern medicine, the beneficial effect on glycemic levels are well documented, the preventing activity of these drugs against progressive nature of diabetes and its macro and microvascular complication was modest and was not always effective. Currently available therapy for diabetes includes insulin and various oral antidiabetic agents such as sulfonylurea, metformin, α-glucosidase inhibitors and troglitazone. These drugs are used as monotherapy or in combination to achieve better glycemic control. Each of the above oral agents suffers from a number of serious adverse effects (Kameswararao *et al.*, 2003).

Insulin therapy affords effective glycemic control, yet its shortcomings such as ineffectiveness on oral administration, shelf life and requirement of constant refrigeration and in event in excess dosage fatal hypoglycemia limit its usage (Satyanarayana *et al.*, 2006).

Synthetic hypoglycemic agents can produce serious side effects including hematological effects, coma and disturbances of the liver and the kidney. In addition, they are not suitable for use during pregnancy (Xia and Wang, 2006). Alternative strategies to the current modern pharmacotherapy of diabetes mellitus are urgently needed because of the inability of existing modern therapies to control all the pathological aspects of the disorder as well as the enormous cost and poor availability of the modern therapies in developing countries. As a consequence, there continues to be a high demand for new oral antidiabetic drugs (Djomeni *et al.*, 2006).

Before the discovery of insulin in 1922, the only treatment options for diabetes were those based on traditional practices. Ethno-botanical knowledge played a particularly important role in historical diabetic therapies with over 1200 species and medicinal plants recognized throughout the world for their ability to treat diabetic indications (Ribnicky *et al.,* 2006).

Plants are indispensable sources of medicinal importance used both in Western type pharmaceutical use of plant material for treatment of human ailments dating back to prehistoric times. According to the World Health Organizations, 80 per cent of the world's population relies on traditional medicines to meet their daily health requirements. However, from the estimated 2,50,000 species of higher plants described to date, only 5-15 per cent have been studied for their potential therapeutic value (Nalamolu *et al*., 2004).

Herbal medicine is also called as botanical medicine or phytomedicine and is defined as use of whole plants to prevent or treat illness. Herbalists generally use unpurified whole plant extracts containing several different compounds. They claim that toxicity is reduced when whole herbs are used together instead of active ingredients and they are relatively safe. But there is limited human research or prospective data concerning adverse effects and herbal drug interactions. They are less potent than their pure drug relatives because they contain a mixture of many chemical in small quantities. Generally fresh and dry parts of the plants are used for the preparation of medicine (Greenblatt *et al*., 2006).

Fabricant and Farnsworth (2001) discussed several approaches to select higher plants as candidates for drug development with the role of information derived from various systems of ethno medicine and its utility for drug discovery purposes. They have identified the structure of

122 compounds, obtained from only 94 species of plants that are used globally as drugs and demonstrated that 80 per cent of these have had an ethno medical use of identical or related to the current use of the active element of the plant. Prajapati *et al.* (2003) aimed at isolating bioactive compounds for direct use as drugs eg: digoxin, digitoxin and morphine and producing bioactive compounds of novel or known structures as lead compounds for semisynthesis to produce patentable entities of higher activity and lower toxicity.

Kumar *et al.* (2007a) studied on identification and isolation of new therapeutic compounds of medicinal importance from higher plants for specific diseases. The most important bioactive constituents of these plants were found to be alkaloids, tannins, flavonoids and phenolic compounds.

Many studies have confirmed the benefits of medicinal plants with hypoglycemic effects in the management of diabetes mellitus. The effects of these plants might delay the development of diabetic complications and correct the metabolic abnormalities. Moreover, during the past few years some of the new bioactive drugs isolated from hypoglycemic plants showed antidiabetic activity with more efficacy than oral hypoglycemic agents used in clinical therapy (Bnouham *et al.*, 2006).

Helicteres isora, which is commonly known as Valampuri or Thirugupalai in Tamil is a large arborescent shrub of the family *Sterculiaceae,* which grows in Central and Western India, Southeast Asia and Southern part of China. It is one of the Jamu raw materials used in traditional folk medicine in Indonesia; it is called "Buah Kayu Ules or Ulet – Ulet" in Jawa Island and is used for treating gastrospasm and as an antihelmintic for tapeworm in Indonesia and as an antispasmodic,

antipyretic, antidirrahoic and antidysentric in Saudi Arabia and as a tonic compound after child birth in Malay Islands (Satake *et al.*, 1999).

In tradition the root juice is claimed to be useful in diabetes, emphysema, and a favorite cure for snakebite. From the roots, compounds like betulic acid, daucosterol, sitosterol, and isorin were isolated. Cucurbitacin B and isocucurbitacin B were isolated and reported to possess cytotoxic activity (Bean *et al.,* 1985). The fruit and the bark of the *Helicteres isora* are being used as popular remedy for the treatment of diabetes mellitus. However, no scientific data with regard to the effectiveness of this herb are available.

Helicteres isora has thus been chosen for the study with the following objectives:

1. To quantify the nutrients, the antioxidants, free radical scavenging activity and antimutagenic activity of the fruit and the bark of *Helicteres isora.*

2. To investigate the antidiabetic activity of streptozotocin-induced diabetes in rats by assessing relevant biochemical parameters and through histopathological examination of the tissues of the experimental rats.

3. To identify and elucidate the active constituents if any, responsible for the antidiabetic activity.