INTRODUCTION
1. INTRODUCTION

DIABETES

*Diabetes mellitus* is a common and very prevalent disease affecting the citizens of both developed and developing countries. The incidence of *diabetes mellitus* is high all over the world and according to recent estimates, the human population world wide appears to be in the midst of an epidemic of diabetes. It is estimated that 25% of the world population is affected by the disease. Despite the great strides that have been made in the understanding and management of diabetes, the disease and disease related complications are increasing unabated.

In a person suffering from Type I diabetes there is an insufficient or no supply of insulin. In Type II diabetes insulin may be present in sufficient quantities but it is unable to unlock the doors of the cell. In the normal case, insulin fits on to specific sites called insulin receptors located on the surface of the cell (the key holes) and unlocks the doors to let glucose enter. If the insulin cannot fit in properly due to lack of insulin receptors on the cell surface, the door remain locked, causing a condition called insulin resistance. In such cases of diabetes, administrations of insulin does not help because there are few receptor sites. If the doors of the cells remain unopened due to lack of insulin or difficulty in utilizing insulin, glucose cannot enter the cells and remains in the blood. This causes increase in blood sugar level even if no food is eaten, urine sugar level increases. When some of the excess blood sugar is excreted the body begins to use alternative fuel source (eg. body fat and protein) for energy. The patient therefore loses weight, tires easily and has an increased appetite (polyphagia) (Valinathan, 1998).

*Diabetes mellitus* is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin (Maiti *et al.*, 2004). The term *diabetes mellitus* describes a metabolic disorder of multiple actiologies and is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. The causes of Type II diabetes are either insulin resistance with relative insulin deficiency or predominantly an insulin secretory defect with or without insulin resistance (WHO, 1999).
The disease is a result of the failure of the body to control blood sugar levels adequately. The normal fasting blood sugar levels are in the range 75-115 mg/dl (milligrams per deciliter of blood). After a meal, the body tightly regulates increase in blood sugar to a level not exceeding 180 mg/dl in people without diabetes. In a normal person, food which is made up of protein, carbohydrate and fat is digested by the enzymes in the digestive tract. Glucose, a simple sugar is an important end product of digestion. It is absorbed in to the blood stream and transported to the various life activities. Insulin is a hormone which acts as a key that opens the doors of the cells to allow glucose to enter. Insulin is produced in the body by beta cells, specialized cells located in the islets of langerhans of the pancreas. The islets of langerhans contain three types of cells that help in glucose metabolism: alpha cells make glucagon, beta cells which produce insulin and delta cells which secrete somatostatin, a hormone which regulates the production of insulin and glucagons. Normally, insulin and glucagons regulate blood glucose levels, causing almost all carbohydrate and about 50 to 60 percent of protein to be converted in to glucose. Glucose is consumed as fuel by almost every type of body cell.

Chronic hyperglycaemia during diabetes causes glycation of body protein that in turn leads to secondary complications affecting kidneys, nerves and arteries. These may be delayed, decreased or prevented by maintaining blood glucose values close to normal. The increasing number of aging population, consumption of calories rich diet, obesity and sedentary life style have lead to tremendous increase in the number of diabetics world wide (Sharma, 1993).

Different types of oral hypoglycaemic agents such as biguanides and sulphonylurea are available alongside insulin for the treatment of diabetes mellitus (Holman and Turner, 1991). Their uses are however associated with side effects (Kameswara et al., 1997; Valinathan, 1998). Diabetes is becoming something of a pandemic and despite the recent surge in new drugs to treat and prevent the condition its prevalence continues to soar. Perhaps the most worrying aspect of all is that the rise is even reflected in children. Although several drugs targeted for carbohydrate hydrolysing enzymes, release of insulin from pancreatic β-cells (sulphonyl urea), glucose utilization (biguanides), insulin sensitizers, PPAR (peroxisome proliferator activated receptors) agonists (glitazones) are in clinical practice. The glitazones are meant to target the problem of insulin resistance and enhance insulin action at the cellular level, however some of these drugs are linked to liver toxicity.
(triglitazone), including a number of deaths from hepatic failure and raising the symptoms and risk factors of heart disease leading to heart failure (rosiglitazone) (Defronzo et al., 1992).

20% of people newly diagnosed with Type II diabetes fail to respond to sulphonylurea drugs and in a further five percent of people, these drugs stop working altogether after a time. Not only they are after ineffective, but sulfonyl urea drugs are also a major cause of drug induced hypoglycaemia, require admittance to hospital. Other side effects include a skin rash and digestive problems, dizziness and headache. Metformin has many side effects including loss of appetite, nausea, vomiting and diarrhoea. Acarbose is a competitive inhibitor of intestinal alpha glucosidases and acts by delaying carbohydrate digestion and slowing down carbohydrate absorption. However, the side effects include digestive disturbances due to impaired absorption of carbohydrates (Campbell, 1997).

**OBESITY**

Obesity is a metabolic disorder resulting from an imbalance between the intake and expenditure of metabolisable energy. It is known to be a strong risk factor for life style related diseases, including diabetes, hypertension and atherosclerosis (Willett et al., 1999). The prevalence of obesity is increasing globally and high fat diet induced caloric hyperphagia is considered to be one of the important environmental factors contributing to the obesity epidemic (Bray et al., 2004).

_Diabetes mellitus_ is caused either by a lack of the hormone insulin (Type I diabetes) or the body’s inability to use insulin (Type II diabetes also known as maturity onset diabetes). Type II diabetes is often triggered by obesity, stress and a sedentary life style. Individuals who are abdominally obese tend to have diminished capacity to utilize glucose. They also have high levels of circulating free fatty acids (which impair glucose metabolism) and a low number of insulin receptor sites (Kissebah, 1995).

Type II diabetes has developed into a world wide epidemic (Zimmet et al., 2001). The dramatic increase in the prevalence of Type II diabetes can be attributed to the rapid economic development and correlated to changes in life style within the last 50 years. Type II diabetes is closely associated with obesity. It seems likely that the readily available high caloric food and a sedentary life style are major cause for obesity. Obesity contributes to insulin resistance and Type II diabetes. Type II diabetes is caused by insulin resistance,
which is defined as defective insulin signaling and a decreased insulin efficiency to induce glucose transport from the blood into key target cells such as muscle and fat (adipocyte) cells (Kahn and Flier, 2000). In general, obesity leads to hyperglycaemia, which intum leads to and exacerbates insulin resistance.

Insulin resistance, if not treated, results in hyperinsulinemia and eventually leads to full blown Type II diabetes (Saltiel and Khan, 2001). Obesity (or) excessive adiposity, particularly visceral adiposity, contributes to and worsens insulin resistance (Kopelman, 2001). Most antidiabetic drugs are hypoglycaemic (or) anti-hyperglycaemic (blood glucose level reducing). However, most of these drugs are to different extents, weight gain promoting (adipogenic) (Zhang and Moller, 2000; Moller, 2001). Thus these drugs treat one of the key symptoms of Type II diabetes, hyperglycaemia, but exacerbate the condition of being over weight or obese, one of the leading causes of Type II diabetes. The most desirable situation would be the development of new types of antidiabetic drugs that are either hypoglycemic (or) anti-hyperglycaemic without the side effect of promoting weight gain (adiposity). Herbal medicines are known to be useful in diabetes treatment with combination of ideal therapeutic properties (Samane et al., 2006).

If excess glucose remains in circulation, high insulin levels will stimulate lipogenesis (fat production and storage). To compound the problem, high insulin levels trigger the hypothalamus to send out hunger signals. Insulin regulates carbohydrate metabolism by controlling blood sugar levels. During a meal the insulin level is a determining factor in signaling the brain that the body is full. Over consumption of carbohydrates leads to insulin imbalance. Once the imbalance becomes constant, low insulin level will elevate glucose and cause one to eat more and consequently gain weight. Over weight people burn sugar less efficiently than those with normal weight do (Dymock et al., 1981).

As the insulin travels through the circulatory system it converts some glucose into glycogen, a sugar polymer that is stored in the liver and muscle tissues. Glycogen acts as a storage fuel like a spare gallon of gasoline for a car and can be converted back into glucose quickly and easily on an as needed basis. The remaining glucose circulates in the blood stream to be used for energy. But if too much glycogen gets stored, it accumulates as body fat and organ fat, resulting in obesity. If the pancreas secretes an excess of insulin inorder to deal with all the extra glucose from eating too many carbohydrates, the body will become overwhelmed by the amount of insulin, sluggish in response to it and develop insulin
resistance and this results in excessive abdominal fat, elevated blood pressure (130/85 or higher), the production of more LDL [(low density lipoprotein) (bad cholesterol)] by the liver due to insulin stimulation, Low HDL [(high density lipoprotein) (good cholesterol)] and elevated triglycerides (Matsurra et al., 2004).

Herbal preparations attracted attention of various workers in the management of metabolic syndrome. Since time immemorial medicinal plants have been used virtually all culture as a source of medical evaluation. There is a growing interest in herbal remedies because of their effectiveness, minimal side effects in clinical experience and relatively low costs. Herbal durgs or their extracts are prescribed widely, even when their biologically active compounds are unknown. Even the WHO approves the use of plant durgs for different diseases, including diabetes mellitus. Therefore, studies with plant extracts are useful in order to establish their efficacy, mechanism of action and safety (Shukla et al., 2000; Grover et al., 2002).

Recently there has been a resurgent interest in the herbal treatments of diabetes. The growing public interest and awareness of natural medicines have led the pharmaceutical industry and academic researchers to pay more attention to medicinal plants (Day, 1998). The natural products are safe because they are more harmonious with biological systems (Erasto, 2003). As the disease is progressing unabated there is an urgent need of identifying indigenous natural resources in order to procure them and study in detail their potential on different newly identified targets in order to, develop them as new therapeutics (Ashok and Rao, 2002).

On the other hand traditional medicinal plants with various active principles and properties have been used since ancient times by physicians and laymen to treat a great variety of human disease such as diabetes, coronary heart disease and cancer (Middleton et al., 2000). The beneficial multiple activities like manipulating carbohydrate metabolism by various mechanisms, preventing and restoring integrity and function of β-cells, insulin releasing activity, improving glucose uptake and utilization. Such properties present in medicinal plants offer exciting opportunity to develop them into novel therapeutics (Shukla et al., 2000; Ashok and Rao, 2002).
In the present study *Salacia chinensis* L. has been selected to find its antidiabetic and antiobesity potential (Plate 1). It is an important medicinal plant belonging to the family Hippocrateaceae. It is a woody climbing shrub. The plant and its extracts have been evaluated for number of activities like anti-inflammatory, cardio tonic, sedative and neuro muscular. The roots are used in indigenous system of medicine and treated for astringent, dysmenorrhea, amenorrhea, veneral disease, rheumatism, itch and asthma (Muruganandan et al., 2000). The stem extracts have been extensively used for carminative, blood tonic and in the treatment of rheumatism and stimulated lochial excretion. The stem and leaves are commercially used as a gutt-a-linear isomer of natural rubber (Yoshikawa et al., 1998; Matsuda et al., 1999). Traditional people used to drink water stored over night in a mug carved of *Salacia* wood to control their blood sugar level. To validate the traditional belief an attempt has been made to study the medicinal properties of this plant.

**Collection and authentication of plant material**

The plant material was collected from Kolli Hills, Thuraiyur Talluk, Triuchirapalli District, Tamil Nadu, India. Found nearly 900 feet above the sea level. Correct botanical identity of plant material is imperative for a good start hence the material was submitted to Botanical Survey of India, Southern circle, Coimbatore, India and identified as *Salacia chinensis* L. (Syn.: *Salacia prionoides* D.C.) belonging to the family Hippocrateaceae.

**Systematic position (Bentham and Hooker) (Mathew, 1983)**

- **Class** - Dicotyledons
- **Sub class** - Polypetalae
- **Series** - Disciflorae
- **Order** - Celastrales
- **Family** - Hippocrateaceae
- **Genus** - *Salacia*
- **Species** - *chinensis*

In Tamil this plant is known as Perumkattukkodi and in Hindi Saptarangi. Because of the increased awareness on the medicinal plants they are subjected to over exploitation and many of them are at the brink of extinction. Most of the pharmaceutical industries are highly dependent on wild populations for the supply of raw materials for extraction of medicinally important compounds. Due to the lack of proper cultivation practices, destruction of plant habitats, the illegal and indiscriminate collection of plants, many medicinal plants are
Salacia chinensis L.

Plate I A. Habit; B. Flower; C. Twig with Inflorescence D. Twig with fruit
severely threatened. Advanced biotechnological methods of culturing plant cells and tissues would provide new means of conserving and rapidly propagating the rare and endangered medicinal plants (Nalawade et al., 2001).

**Objectives of the present study**

1. To develop a standard protocol for propagation via direct and indirect regeneration, since *S. chinensis* is an endangered plant.
2. To study the morphological and anatomical features of the selected plant including phytochemical analysis.
3. To evaluate antidiabetic and antiobesity potential of the leaf, stem and root extracts of *S. chinensis* through *in vitro* and *in vivo* pharmacological studies.
4. The structural elucidation of the enzymes involved in the management of diabetes and obesity for *in silico* drug discovery.