CHAPTER 1

INTRODUCTION

1 GENERAL

Diabetes mellitus is a chronic metabolic disorder that affects human body in terms of physical, psychological and social health. It is defined as a group of disorders characterized by hyperglycaemia, altered metabolism of carbohydrates, lipids and proteins [1]. It is becoming the third killer of mankind along with cancer, cardiovascular and cerebrovascular diseases [2]. Historical accounts reveal that as early as 200 B.C, diabetes was a well organized disease in India. Diabetes mellitus is a global health crisis, which has been persistantly affecting the humanity, irrespective of the socioeconomic profile and geographical distribution of the population [3]. According to an estimate, one person is detected with diabetes every 5 seconds somewhere in the world, while someone dies of it every 10 seconds [4].

Several medicinal plants have been used as dietary adjunct and in the treatment of numerous diseases without proper knowledge of their function. Although plant based medicines continue to be used in several countries, few plants have received scientific or medical scrutiny [5]. Plants and plant derived compounds have a great potential to cure and control diabetes, additionally they are safer and cost effective. Since the antiquity diabetes has been treated with plant medicines and many plants were known for their hypoglycaemic activity across the world. It has been estimated that more than 400 plant species are known to possess Antihyperglycaemic activity [6, 7].
1.1 TYPES OF DIABETES

There are three main types of diabetes, classified as:

1.1.1 TYPE I DIABETES

It results from the body’s failure to produce insulin, and requires the person to inject insulin. It is also referred to as insulin-dependent diabetes mellitus (IDDM). The majority of type 1 diabetes is of immune-mediated nature, where beta cell loss is a T-cell mediated autoimmune attack [8].

1.1.2 TYPE II DIABETES

It results from insulin resistance, in which body cells fail to use insulin properly, often combined with absolute insulin deficiency. It is also known as non-insulin dependent diabetes mellitus (NIDDM).

1.1.3 GESTATIONAL DIABETES

This type of diabetes occurs in pregnant women, who never had diabetes before, but have a high blood glucose level during pregnancy, which may precede the development of type 2 diabetes mellitus [9].

1.1.4 OTHER FORMS OF DIABETES

Other forms of diabetes include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes. Pre-diabetes indicate a condition that occurs when a person’s blood glucose levels are higher than normal, but not high enough for a diagnosis of type II diabetes [10]. Diseases associated with excessive secretion of insulin antagonistic hormones can cause diabetes, many drugs impair insulin secretion and some toxins damage pancreatic beta cells [11].
1.1.5 DIAGNOSIS OF DIABETES

Different diagnostic tests currently used to test diabetes are,

(A) Measurement of blood glucose

The current WHO diagnostic criteria for diabetes is measurement of blood glucose level. The fasting plasma glucose greater than 7.0 mmol/L or 2 hour plasma glucose greater than 11.1 mmol/L indicates that the person may have diabetes. Glucose should be measured immediately after collection by near patient testing, or if a blood sample is collected, plasma should be immediately separated, or the sample should be collected into container with glycolytic inhibitors and placed on ice –water until separated prior to analysis [12].

(B) Oral glucose tolerance test (OGTT)

OGTT is used as a diagnostic test as fasting plasma glucose alone fails to diagnose approximately 30% of cases [12].

(C) Glycated Haemoglobin (HbA1C)

HbA1C can be used as a diagnostic test for diabetes, provided that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement. An HbA1C of 6.5% is recommended as the cut point for diagnosing diabetes. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. Currently HbA1C is not considered as a suitable diagnostic test for diabetes or intermediate hyperglycemia [13].

(D) Fasting blood glucose test

Blood glucose levels are checked after fasting for between 12 and 14 hours. Water can be taken during this time, but should strictly avoid any other beverage. Patients with diabetes may be asked to delay their diabetes medication or insulin dose until the test is completed [12].
Random blood glucose test

Blood glucose levels are checked at various times during the day, and it doesn’t matter the time of eating. Blood glucose levels tend to stay constant in a person who doesn’t have diabetes [12].

1.2 PREVALENCE OF DIABETES

The prevalence of diabetes for all age-groups worldwide was estimated to be 4.4% in 2030. The total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030. The prevalence of diabetes is higher in men than women, but there are more women with diabetes than men. The urban population in developing countries is projected to double between 2000 and 2030. The most important demographic change to diabetes prevalence across the world appears to be the increase in the proportion of people \( \geq 65 \) years of age. In India number of people with diabetes in 2000 was 31,705 million which will rise to 79,441 million in 2030, the number greater than China and other Asian countries [14].

The International diabetes federation stated that “every ten seconds, two people are diagnosed with diabetes somewhere in the world,” and given the current trend, it is estimated that more people will have diabetes by 2025 than the current populations of the United states, Canada and Australia combined [15].

1.3 DIABETES AND PHYTOMEDICINE

Alternative medicines particularly herbal medicines are available for the treatment of diabetes. Common advantages of herbal medicines are effectiveness, safety, affordability and acceptability [16]. Medicinal plants and their products have been used in the Indian traditional system of medicine and have shown experimental or clinical anti-diabetic activity [17, 18]. World health organization has also recommended the evaluation of traditional plant extracts treatment for diabetes [19].

Many ethno botanical surveys on medicinal plants used by the local population have been performed in different parts of the world including Morocco, Saudi Arabia, Taiwan and Trinidad and Tobogo. Several plant species have been described as hypoglycaemic, which include *Opuntia streptacantha* Lem, *Trigonella foenum graecum* L, *
Momordica charantia L, Gymnema sylvestre R, etc. [20]. The ethno botanical information reports that about 800 plants possess antidiabetic potential [21]. Many Indigenous Indian medicinal plants have been found to be useful in the management of diabetes, which are easily available and have least side effects [22].

1.4 OXIDATIVE STRESS AND DIABETES

Chronic elevation of blood glucose leads to generation of reactive oxygen species (ROS), resulting in increased oxidative stress in β-cells [23]. As a result, β-cells become worsened with respect to both insulin secretion and action, due to their ability to directly damage and oxidize DNA, protein and lipids [24]. In order to neutralize ROS, cells are equipped with antioxidant defense mechanisms capable of combating oxidative stress. Intriguingly, compared to other tissues, β-cells have a lower abundance of antioxidant defense enzymes [25, 26]. Thus due to low antioxidant defense status of islets, excessive ROS lead to oxidative stress during β-cell dysfunction.

Healthy pancreatic β-cells exhibit a dramatic response to nutrients and obesity associated insulin resistance through hyper secretion of insulin in order to maintain energy homeostasis; however, through a complex process that occurs over an extended period of time, β-cells can become unable to sustain a compensatory response, leading to β-cell dysfunction and death [27].

Under diabetic conditions, an increased influx of glucose through hexosamine biosynthesis pathway (HBP) leads to the formation of uridine diphosphate N-acetylglucosamine (UDP-GlcNAc), an end- product of HBP. Using UDP-GlcNAc as a substrate, O-linked N-acetylglucosamine transferase catalyzes the transfer of GlcNAc via O-linkages to specific serine or threonine residues of various target proteins [23]. Hyperglycemia mediated increase in both UDP-GlcNAc and O-GlcNAcylation which leads to both oxidative and endoplasmic reticulum stress, which have been shown to cause chronic inflammation and insulin resistance in other cell types [28].

1.5 ROLE OF ANTIOXIDANTS AGAINST OXIDATIVE STRESS

Antioxidant has been defined as “any substance exogenous or endogenous in nature that delays or inhibits oxidative damage to a target molecule and protects
biologically important molecules, DNA, proteins and lipids from oxidative damage [29]. Natural antioxidants have gained a great interest, as they reduce the risk of chronic diseases and promote human health [30]. Oxidants are counteracted by antioxidant enzyme systems such as Catalase, superoxide dismutase (SOD) and glutathione (GSH), the efficiency of this defense mechanism is altered in diabetes [31].

Oxygen free radicals have been suggested to contribute to the development of complications of diabetes leading to β-cell cytotoxicity. The production of free radicals increases the peroxidation of lipid molecules. The decrease in SOD activity during the progression of diabetes could be due to enzyme glycosylation that occurs in the diabetic state. Decreased SOD activity could also be due to accumulation of hydrogen peroxide in the affected tissues [32]. Reduced glutathione is a main factor in detoxification and antioxidant systems, providing a defense against free radicals and cytotoxins.

ROS can be detoxified by an elaborated battery of enzymatic defense system, comprising SOD, CAT, and GPX or nonenzymatic systems by the scavenging actions of GSH, while organic peroxides can be detoxified by the activity of GST [33]. Modulation of these enzymes and GSH levels play a major role in the balance of redox status through the reduction in ROS and peroxides produced in the organism as well as in the detoxification of xenobiotics [34].

Vitamin E, well known lipid soluble antioxidant plays a major protective role against oxidative stress and prevents the production of lipid peroxides by scavenging free radicals, particularly strong scavengers of hydroxyl radicals in biological membranes [35, 36].

1.6 DIABETES AND LIVER DAMAGE

Liver is a vital organ, supports almost every organ in the body and it is vital for survival. Because of its multidimensional function the liver is also prone to many diseases. However, the liver has great capacity to regenerate and has a large reserve capacity, in most cases liver produced symptoms only after extensive damage [37]. Liver plays a central and crucial role in the regulation of carbohydrate metabolism. Its normal functioning is essential for the maintenance of blood glucose levels and of a continued supply to organs that require a glucose energy source [38].
Liver has a great capacity to detoxify toxic substances and synthesize useful ones; therefore, the damage caused by hepatotoxic agents is of grave consequence to the body as it deprives the liver of its principal functions [39]. Significant amount of liver damage is induced by lipid peroxidation and other oxidative damages which are caused by the hepatotoxic chemicals [40, 41].

Liver injuries caused by the variety of deleterious agents induce inflammation, necrosis, fibrosis, cirrhosis and functional deteriorations [42]. Diabetes is associated with several structural and functional liver abnormalities that affect glycogen and lipid metabolism [43]. Excess glycogen deposition, fibrosis, cirrhosis, steatohepatitis and biliary disease in the liver have been reported in 55-80% of diabetic patients [44].

Liver damage is associated with necrosis of hepatocytes, lipid peroxidation and depletion of tissue GSH levels. In addition to it serum levels of many biochemical parameters like SGOT, SGPT, ALP, TAG, and bilirubin levels are also elevated [45]. High levels of SGOT indicate liver damage such as that due to viral hepatitis as well as cardiac infarction and muscle injury. SGPT catalyses the conversion of alanine to pyruvate and glutamate, and is released in a similar manner, therefore SGPT is more specific to liver, and is thus a better parameter for detecting liver damage [46].

Serum ALP and bilirubin levels are related to hepatic cell damage, increase in the levels of serum ALP is due to increased synthesis in presence of increasing biliary pressure, effective control of bilirubin, ALP levels point towards an early improvement in the secretory mechanism of hepatocytes [47]. Increase in malondialdehyde (MDA) levels in the liver suggests enhanced lipid peroxidation leading to tissue damage and failure of antioxidants defense mechanisms to prevent formation of excessive free radicals.

Glutathione (GSH), a tripeptide present in all the cells is an important antioxidant [48]. Decreased GSH levels in diabetes have been considered to be an indicator of increased oxidative stress [49]. GSH also functions as free radical scavenger in the repair of radical caused biological damage [50].
1.7 HEPATOPROTECTIVE ROLE OF HERBAL MEDICINES IN DIABETES

Plants used in traditional medicine for the treatment of liver disorders are of great interest, as they may serve as potential sources for new therapeutic agents that could be applied in the management and prevention of hepatic injuries. Plants rich in different photochemical derivates such as triterpenes, flavonoids or polyphenols, have been reported to exhibit antihepatotoxic effects in experimental liver injury models induced by different types of hepatotoxicants, such as carbon tetrachloride, cadmium, acetaminophen etc [51, 52].

Phenolic compounds in the plants, found to have strong and significant positive correlation with free radical scavenging potential and inhibition of lipid peroxidation [53]. The hepatoprotective effects of herbal medicines in diabetes, is mainly due to the presence of the great amount of phenolic and flavonoid compounds and their antioxidant effects, besides the free radical scavenging property [54].

Flavonoids are a group of naturally occurring compounds widely distributed as secondary metabolite in the plant kingdom. They have been recognized for having interesting clinical properties, such as anti-inflammatory, antiallergic, antiviral, antibacterial and antitumoral activities [55].

1.8 DIABETES AND HYPERLIPIDAEMIA

The most common lipid abnormalities in diabetes are hypertriglyceridemia and hypercholesterolemia [56]. Hyperlipidaemia is one of the major cardiovascular risk factors. Insulin deficiency in diabetes mellitus leads to a variety of derangements in metabolic and regulatory processes, which in turn leads to accumulation of lipids especially Triglycerides and Total cholesterol in diabetic patients [57]. In diabetic state, there is inactivation of lipoprotein lipase by which free fatty acids are converted into phospholipids and cholesterol, which are finally discharged into blood causing marked elevation of serum phospholipids level [58].

A significant change in lipid metabolism occurs in diabetes, associated with the development of vascular disease, increased lipid peroxidation also associated with
hyperlipidaemia [59]. Liver, an insulin dependent tissue that plays a pivotal role in glucose and lipid homeostasis, is severely affected during diabetes. Liver participates in the uptake, oxidation, and metabolic conversion of free fatty acids, synthesis of cholesterol, phospholipids, and triglycerides. In diabetes, a profound alteration in the concentration and composition of lipid occurs. Decreased glycolysis, impeded glycogenesis, and increased glyconeogenesis are some of the changes of glucose metabolism in the diabetic liver [60].

Hyperlipidaemia is a metabolic complication of both clinical and experimental diabetes. In diabetes, excess free fatty acids in serum, lower the insulin-mediated glucose disposal and promote conversion of excess fatty acids into phospholipids and cholesterol in liver. These two substances along with excess triglycerides formed at the same time in the liver may be discharged into the blood in the form of lipoprotein [61]. High cholesterol concentration in human serum is one of the primary factors in the development of atherosclerosis [62]. The marked hyperlipidaemia that characterizes the diabetic state may be therefore regarded as a consequence of the uninhibited actions of lipolytic hormones on the fat depot [63].

Diabetes is associated with coronary complications, which is the major cause of morbidity and deaths in diabetic subjects, due to high levels of total cholesterol and LDL cholesterol [64, 65]. Recent reports suggest that Triglyceride levels are independently related to coronary heart disease [66, 67].