CHAPTER 1.0 INTRODUCTION

'Every human being is the author of his / her own health or disease' - Buddha

Diseases broadly refers to any condition that hinder or reduce the normal functioning of the system in the body or generally referred as dysfunction of the body’s homeostatic processes due to any cause. Diseases are always coupled with symptoms and signs which are caused by several factors externally like pathogens or dysfunctions such as immunodeficiency or hypersensitivity and autoimmunity, etc. internally. It is mainly classified into two types, namely communicable and non-communicable diseases. Communicable diseases (CDs) are transformed from one person to another person whereas non-communicable diseases (NCDs) does not spread from one person to another but are described as diseases of long term period, and slow in progression referred as "chronic diseases" which play major role for challenging health system worldwide. NCDs result in rapid deaths in conditions like diabetes, cardiovascular, kidney and autoimmune diseases, neurodegenerative disorder, osteoporosis, eye deformalities and others.

According to the NCDs Progress Monitor (2015) published by World Health Organization (WHO), globally about 56 million deaths in 2012 and NCDs kill around 38 million people per year accounting for 68% of all deaths worldwide (NCD Global Survey, 2015). In India it has been reported that NCDs caused almost 6 million deaths in the year 2014 (Infographics September 20, 2016). As a co-incidence with the WHO report, 1 in 4 Indians face the risk of death from NCD before they hit the age of 70 (India today, July 21, 2016). There are four major risk factors behind the most common NCDs are physical inactivity, unhealthy dietary pattern, the harmful use of alcohol and tobacco use. While some of them are beyond our control, others are modifiable because they’re linked to unhealthy lifestyle, less physical activity, stress, high consumption of calories such as fats and cholesterol containing diets, etc. (Chakma and Gupta, 2014; Critical illness insurance –
bounceback infographics, 2016). It has been reported that 80% of deaths are due to diabetes and heart diseases where could be preventable by nullifying well known lifestyle risk factors which make a huge impact on global population (Khuwaja et al. 2011). Thus far, NCDs have not become a priority for prevention, control and treatment in many developing nations though it is considered to be the major cause of mortality and morbidity.

Among most common NCDs, Diabetes Mellitus (DM) has been considered to be the fourth important cause of death in most of the economically developed countries. Similarly in many economically developing as well as newly industrialized countries, it is epidemic with substantial evidence represent huge threat to the management of health worldwide (Diabetes, NCD alliance 2014). DM is a multifactorial lifestyle disorder and a key threat to public well being in the 21st century (Chawla et al. 2013). According to recent report by International Diabetes Federation (IDF), it was estimated that about 415 million of most adults (1 in 11 adults) are affected by diabetes in 2015 and this may increase to 642 million (1 in 10 adults) by the year 2040. About three quarters of people are affected by diabetes in low and middle income countries, and 5.1 million people are died (every 6 seconds a person) (IDF diabetes atlas – 7th edition, 2015; Pontarolo et al. 2015; Global reports on diabetes, WHO, 2016).

In India, about 61.3 million people were suffered with diabetes in 2011 and this will double up to 101.2 million by the year 2030. The prevalence of diabetes in Tamil Nadu was estimated at 10.4% (ICMR-INDIAB study) (Deepa et al. 2014). The diabetic population in India may increase nearly one-fifth of the world in another twenty years (Vijayan et al. 2014; Gupta et al. 2015). Recent reports state India as the “Diabetes Capital of the World” as it leads with largest diabetic population. However, the prevalence of diabetes is consistently increasing, but still there is a lack of an effective treatment for the management of this epidemic (Baynes, 2015).
It has been demonstrated that in two different conditions diabetes will occur: 1) if the β-cells in pancreas produce less amount of insulin (the hormone regulates blood glucose level) to meet the physiological need or 2) if the body can’t able to efficiently use the insulin produced whereby the sugar levels in blood are high. On the other hand, when there is impairment in the metabolism of biomolecules due to the deficient insulin secretion may also lead to chronic hyperglycemia (Baynes, 2015). The elevation of free fatty acid, glucose in blood and targeted tissues cause reduced insulin action and decreases the insulin dependent-glucose uptake. All types of diabetes can lead to a greater complications in the body and increase the overall threat of dying at the earlier stage of life in individuals. The chronic, uncontrolled diabetes often leads to complications like cardiomyopathy, macrovascular and microvascular complications includes retinopathy, neuropathy, nephropathy, blindness, kidney failure, lower limb amputation and more specifically development of heart diseases, the primary reason of death worldwide (Cade, 2008). In pregnancy, poor control of diabetes or gestational diabetes increases the risk for foetus and leads to many other pre-and post-natal complications.

Changes in the behavior of human beings, their lifestyle and diet pattern have resulted in a remarkable raise in the occurrence of diabetes throughout the globe over the last century (Soumya and Srilatha, 2011). In modern society of life, people use to commonly consume food or beverages contain rich calories (energy), fat and/or sugar content. The large consumption of processed / prepared food and beverages such as soft drinks with added sugars, and low calories nutrient has began to increase day by day. Fructose, commonly known as sweetner (corn syrup) added in desserts, condiments, soft drinks and processed food items. Ultimately, consumption of these food and beverages with high amounts of refined carbohydrates elevates the risk of dyslipidemia, obesity, insulin resistance, and heart disease.
Table 1.1 Comparative projection of top countries with numbers of people (20-79 years) affected with diabetes in 2011 and 2030*

<table>
<thead>
<tr>
<th>Country</th>
<th>2011 (Millions)</th>
<th>Country</th>
<th>2030 (Millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>90.0</td>
<td>China</td>
<td>129.7</td>
</tr>
<tr>
<td>India</td>
<td>61.3</td>
<td>India</td>
<td>101.2</td>
</tr>
<tr>
<td>USA</td>
<td>23.7</td>
<td>USA</td>
<td>29.6</td>
</tr>
<tr>
<td>Russia</td>
<td>12.6</td>
<td>Brazil</td>
<td>19.6</td>
</tr>
<tr>
<td>Brazil</td>
<td>12.4</td>
<td>Bangladesh</td>
<td>16.8</td>
</tr>
<tr>
<td>Japan</td>
<td>10.7</td>
<td>Mexico</td>
<td>16.4</td>
</tr>
<tr>
<td>Mexico</td>
<td>10.3</td>
<td>Russia</td>
<td>14.1</td>
</tr>
<tr>
<td>Bangladesh</td>
<td>8.4</td>
<td>Egypt</td>
<td>12.4</td>
</tr>
<tr>
<td>Egypt</td>
<td>7.3</td>
<td>Indonesia</td>
<td>11.8</td>
</tr>
<tr>
<td>Indonesia</td>
<td>7.3</td>
<td>Pakistan</td>
<td>11.4</td>
</tr>
</tbody>
</table>

(*Whiting et al. 2011)

According to the latest report by American Diabetes Association (2016) on understanding the advances in the etiology and pathogenesis of diabetes, it has recommended the revised classification for DM based on the pathogenetic process which progress to hyperglycemia rather on the basis of age of onset or type of therapy. It is always a tricky situation for the clinician to assign an individual with the type of diabetes as it may depend upon the diagnosis with the onset of diabetes do not fell into a particular class. Thus, the preference should be given for the understanding of the pathogenesis rather to label the particular type of hyperglycemia which is less important in order to treat effectively.
1.1 Classification of Diabetes

The modified classification is based on the new intention in considering the etiological views as the previous terminology proposed by world health organization (WHO) namely insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM) in 20th century are vanished. The new system of classification gives four different terms of diabetes mellitus namely type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), other specific type of diabetes and gestational diabetes American Diabetes Association (ADA), 2014; Baynes, 2015; ADA, 2016).

1.1.1 Type 1 diabetes mellitus (β-cell destruction leads to insulin deficiency)

The autoimmune damage to the pancreatic β cells which are known to be insulin-producing leads to the formation of T1DM. Those individuals who are affected needs to be on complete administration of insulin and the condition is known as "Insulin-Dependent Diabetes Mellitus" or "Juvenile Diabetes".

1.1.1.1 Pathogenesis of Type 1 diabetes mellitus

As mentioned, the end stage of β-cell destruction is caused by the action of macrophage infiltrating the islets and T cells. The pathogenic features of T1DM are given in figure 1.1 (Baynes, 2015). In T1DM, circulating islet cell antibodies are present in almost 85% of patients and within pancreatic β cells they are directed against glutamic acid decarboxylase (GAD). The anti-insulin antibodies are detectable in patients before diagnosing and receiving insulin therapy. The β-cells destruction in the pancreas causes a deficiency or loss secretion of insulin in T1DM individuals result in abnormal functioning of pancreatic α-cells through metabolic derangements with an increased secretion of glucagon compared to hyperglycemic condition. In conditions such as insulin deficiency, there is a suppression of glucose metabolism in peripheral tissues through an uncontrolled hydrolysis lipids and increased free fatty acid levels in the plasma
which in turn impairs the utilization of glucose. This is the major cause for insulin resistance as the above mentioned process down regulates the expression of various genes required to respond normally to insulin and suppresses glucose metabolism in liver and the glucose transporters type-4 in adipose tissue.

**Figure 1.1 Pathogenetic pathway leading to type 1 Diabetes Mellitus**

*(Sen et al. 2016)*

### 1.1.2 Type 2 diabetes mellitus *(Meier et al. 2013)*

T2DM is the most prevalent form of diabetes considered to be expensive and chronic fatal conditions. Currently, there are over 382 million individuals suffer from T2DM with 175 million cases undiagnosed worldwide (Chen et al. 2011; Mattei et al. 2015) where the cells failed to consume insulin properly or deficient insulin production. This form is known as Non Insulin-Dependent Diabetes Mellitus or "Adult-Onset Diabetes".

T2DM happen due to a multiple combinations like genetic susceptibility, environmental factors, behavior (calorie intake and physical activity), and also due to some unexplained risk factors. The insulin insensitivity is due to repeated
exposure to high level glucose which causes insulin resistance, reduced production of insulin and ultimate failure of pancreatic beta cell. These conditions affect the transport of glucose and causes rapid breakdown of fat with hyperglycemia in individuals especially obese (Baynes, 2015). The primary pathophysiological defects of T2DM are increased production of glucose by liver, inadequate secretion of insulin, glucose uptake and increased β-cell apoptosis (Skyler et al. 2017). The symptoms of this condition include tiredness, changes in food and water intake, frequent urination, reduction in weight, unclear vision, and problem in healing of wounds or sores.

T2DM can be diagnosed clinically by fasting glucose, glucose tolerance, and HbA1c which can provide more information about risk factors such as physical activity, unhealthy food pattern and genetic susceptibility of individuals. It is important that the combination of life style pattern and hypoglycemic agents together may contribute to achieve a reasonable improvement in the management of T2DM.

1.1.2.1 Pathogenesis of Type 2 diabetes mellitus

The cause of type 2 diabetes mellitus is always determined mainly by the two pathological defects, 1) impaired insulin secretion due to malfunction in β-cell of pancreas, and 2) impaired action of insulin with insulin resistance. When the insulin resistance overshoots, the transformation of β-cells leads to increased supply of insulin and compensates for the abnormal requirement. The concentration of both fasting and postprandial plasma insulin level increased in diabetic condition but in case of insulin resistance, the level of insulin is inadequate to meet the physiological need. The T2DM is associated with increasing urbanization, aging populations, dietary changes, reduced physical activity, changes in lifestyle, recent economic development and other cultural patterns. In evidence, global prevalence of T2DM was recently increased with current trend of life and consumption of high quantity of fructose (Zimmet et al. 2001). Excess intake of fructose causes oxidative stress (Pasko et al. 2010)
through changes in the fat metabolism (Gaby, 2005) thus leads to the insulin resistance and its complications. With these observations, both types of diabetes mellitus are a multifactorial autoimmune disorder with genetic, lifestyle and ecological factors in recent days.

Figure 1.2 Pathogenetic pathway leading to Type 2 Diabetes Mellitus (Sen et al. 2016)

1.1.3 Other specific types
According to the report of WHO, these types of causes can be identified specifically with the following processes:
A. Abnormalities in the genes related to β-cell function and insulin action
B. Dysfunctional behaviour of the exocrine pancreas and endocrinopathies
1.2 Criteria for the diagnosis of diabetes

These recommendations are some diagnostics tests for the confirmation of diabetes mellitus by WHO (Tangvarasittichai et al. 2015; Diabetes Care 2017).

1. A1C assay ≥ 6.5% (48.0 mmol/mol) or
2. Fasting Plasma Glucose ≥ 126 mg/dl (7.0 mmol/mol) or
3. Post-prandial (2-h) plasma glucose ≥ 200 mg/dl (11.1 mmol/mol) or
4. Random plasma glucose ≥ 200 mg/dl (11.1 mmol/mol).
5. BMI ≤ 25 kg/m²

1.3 Complications of diabetes mellitus

The uncontrolled hyperglycemia leads to the pathology of various complications that affect microvascular and macrovascular, or in combination in many instances. This will lead to chronic damage of various organs like eyes, kidneys, nerves, and the heart. The vascular complication leads to form advanced glycation end products, superoxide radicals and activation of protein kinase C causes hypertension, dyslipidemia along with hyperglycemia and cellular immunity dysfunction (Evans et al. 2002; Holt 2004; Chawla et al. 2013; Chowla et al. 2016).

1.3.1 Microvascular disease

Microvascular disease may lead to impairment in healing of wound when the integrity of the skin get disturbed. Intensive care and management of DM may prevent or delay many of these microvascular complications like diabetic retinopathy, nephropathy and neuropathy (Giacco and brownlee, 2010).

1.3.2 Macrovascular disease

Large-vessel atherosclerosis and diabetic cardiomyopathy are the characteristic manifestation of DM. The routine diagnosis include screening tests are made by
physical examination and other parameters such as coronary artery Ca$^{2+}$ score. Treatment is multifactorial approach to reduce the intense of cardiovascular events with rigorous control on the level of lipids, blood pressure, glucose, avoidance of atherosclerotic risk factors like smoking and management with aspirin and angiotensin converting enzyme inhibitors.

![Figure 1.3 Schematic diagram of Mechanism of hyperglycemia-induced cellular damage (Giacco and Brownlee, 2010)](image)

1.3.3 Infection

Patients with poor control on diabetes are subjected to infections as a result of the compromised immune system. Most common are bacterial foot infections (including osteomyelitis) and mucocutaneous fungal infections (eg, oral and vaginal candidiasis).

1.3.4 Other diabetic complications

Diabetic patients have an increased risk of developing ophthalmological, rheumatological, hepatobiliary diseases and dermatologic diseases apart from depression and dementia are also common.
1.4 Fructose and its mechanism (Altas et al. 2010)

Fructose is a common natural sugar used as a sweetener instead of glucose and sucrose which is found commonly in many fruits and honey. Fructose was also known with a common old name levulose, upon its levorotatory property on polarized light (in contrast to glucose which is dextrorotatory).

![Fructose structure](image)

Figure 1.4 Structure of fructose

1.4.1 Source

- Fruits: Most of the fruits include bananas, apple, citrus fruits, grapes, pears, berries such as raspberries, blueberries, blackberries and huckleberries and melons like cantaloupe, watermelons as well as the honeydews are also rich in fructose.
- Vegetables: Vegetables such as cabbage, onion, tomato, asparagus, beans, broccoli, artichoke, leek, peanuts and zucchini contain high levels of fructose.
- Dried fruits: Dried fruits include dates, figs, raisins, apples and pineapples are rich in concentrated fructose.
- Toppings and sauces, jams and fruits jellies contain high levels of fructose.
- Beverages: Most processed drinks such as decaffeinated and caffeinated carbonated drinks, deserts wines, port, sherry and muscatel, soft drinks and other beverages, agave, pear, and fruit drinks contain high levels of fructose.
- Processed food: Some commercially available products such as ketchup, sweet pickles, canned foods, crackers, breads and chocolates contain rich fructose.
1.4.2 Signs of Insulin resistance syndrome

**Type 2 diabetes:** Most common presentation and a progressive disease indicated by deficient insulin sensitivity, insulin secretion, decline in β-cell function. This accounts for almost 90% of diabetic cases worldwide mainly due to the improper functioning of the pancreas when it is unable to produce sufficient insulin.

**High blood pressure:** Studies suggest that the insulin resistance caused hypertension as impaired the blood pressure, the worse the insulin resistance though the mechanism is unclear.

**Abnormal cholesterol levels:** Westernized diets contribute to insulin resistance with an increased cholesterol intake in many countries. The mechanism of occurrence of insulin resistance as a characteristic of elevated cholesterol, triglycerides and reduced HDL level.

**Heart disease:** As discussed earlier, the insulin resistance results in formation of atherosclerosis with the disturbances in lipid metabolism and also with an increased risk of blood clots in the vessels promoting various types of cardiovascular diseases.

**Obesity:** It is associated with an increase threat of metabolic diseases and major factor in the development of insulin resistance which has a negative impact on insulin responsiveness in an individual. Weight loss can be achieved by promoting the ability of body to use insulin which is a challenging task to manage diabetes through therapeutics in extremely obese patient.

**Kidney damage:** Insulin resistance plays a key role in kidney damage which can be measured by the detection of protein in the urine but the underlying mechanism is not clear.
Polycystic ovarian syndrome: Insulin resistance is a main factor in promoting diabetes in women and a common disorder of the female endocrine system especially in younger ages at present. The disturbances in endocrine system causes increase in glucose level in which polycystic ovary syndrome is always observed.

Figure 1.5 Mechanism of fructose induced insulin resistance
(Tappy and Le 2010)

1.5 Management of diabetes mellitus

Life style management leads the top of list in the management of diabetes and cardiovascular diseases as it demonstrated encouraging improvement with risk factors. Meta-analysis demonstrated that lifestyle interventions (diet and physical activity) make a huge reduction (63%) in the occurrence of diabetes in individuals at high risk. The dietary management is a complement of lifestyle management in case of diabetes mellitus and has a positive effect on the long term health. It also aims at establishing a balance between food intake, physical
activity in order to optimize the metabolic control and medication to avoid complications (Piero et al. 2015).

Figure 1.6 The relationship between fructose metabolism and insulin resistance

1.6 Oral therapeutics for Diabetes Mellitus

There are several therapeutic strategies available for the management of diabetes mellitus that target several major site of action (Thule, 2012; Olokoba et al. 2012; Evans et al. 2016).

1.6.1 Biguanides

Biguanides are first line of anti-hyperglycemic drugs in practice which lower blood sugar in two ways. Primarily they decrease the amount of sugar
synthesized by liver and also increase the absorption of sugar by muscles thereby reduces insulin resistance. Metformin is the most widely used drug in practice which suppress glucose production in liver, increases insulin sensitivity and oxidation of fatty acids. It has the ability to reduce fasting glucose mainly through its action on hepatic glucose output mechanistically with the enzyme (AMP-activated protein kinase) involved in the expression of hepatic gluconeogenic genes. Commonly reported side effects include lactic acidosis, diarrhea, nausea, and vomiting with a low incidence of hypoglycemia.

1.6.2 Sulfonylureas

They are organic compounds used in medicine and agriculture which act through increasing release of insulin from the β-cells which may lead to hypoglycemia. Glyburide may lead to hypoglycemia compared to glipizide with a risk of age-related impaired renal function (greater than 60 years). Hence, instead of using of long acting sulfonylurea, short-acting glipizide can be used in elderly patients with DM.

1.6.3 Meglitinides

These glinides class of drugs are non-sulfonylurea analogues binds to ATP-dependent potassium channels in the β-cells with weaker binding affinity and faster dissociation stimulates the release of insulin. Meglitinides like repaglinide or nateglinide administered before or after meals have lower risk of hypoglycemia.

1.6.4 Thiazolidinediones

A new class of drugs known as glitazones improves metabolic control in patients. Thiazolidinedione, an insulin sensitizer includes pioglitazone, never associated with hypoglycemia but due to the adverse effects like fluid retention and peripheral edema, it can be limited with diabetes mellitus.
1.6.5 Alpha-Glucosidase Inhibitors

This class of drugs used to prevent the digestion and conversion of carbohydrates into simple sugars. Acarbose, Voglibose and Miglitol are likely to be safe and effective in achieving normoglycemia but they have not been widely used in practice for T2DM individuals. These drugs are effective in controlling postprandial glucose level but their use is limited with side-effects.

1.6.6 Incretin-Based Therapies

Glucagon-like peptide 1 (GLP-1) analogues like exenatide, an incretin mimetic, and liraglutide exert their actions through potentiation of incretin receptor signaling results in improved glycemic and body weight control. These are available as monotherapy or in combination with oral hypoglycemic agents.
Table 1.2 Drugs used in the management of diabetes mellitus

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Molecular target</th>
<th>Site of action</th>
<th>Adverse reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Insulin</td>
<td>Liver, muscle, fat</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>SU receptor</td>
<td>Pancreatic β-action</td>
<td>Hypoglycemia, weight gain</td>
</tr>
<tr>
<td></td>
<td>SU receptor, K+</td>
<td>Liver, muscle</td>
<td></td>
</tr>
<tr>
<td>Biguanides</td>
<td>ATPchannel</td>
<td>Intestine</td>
<td>Gastrointestinal disturbance, lactic</td>
</tr>
<tr>
<td>Acarbose, milgitol</td>
<td>Not clear</td>
<td>Fat, muscle, liver</td>
<td>acidosis</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>α-glucosidase</td>
<td>Pancreatic α-cells, intestinal</td>
<td>Weight gain, edema, anemia</td>
</tr>
<tr>
<td>Exenatide</td>
<td>PPAR-γ</td>
<td>mucosal cells, Nucleus</td>
<td>Nausea, hypoglycemia, diarrhea</td>
</tr>
<tr>
<td>Pramlintide</td>
<td>GLP-1 receptor</td>
<td>accumbens, dorsal vagal complex</td>
<td>Nausea, hypoglycemia</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Amylin receptors</td>
<td>Intestine</td>
<td>Headache, nausea</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>DPP-4</td>
<td>Pancreatic β-cells</td>
<td>Hypoglycemia, bellyache, nausea, liver</td>
</tr>
<tr>
<td></td>
<td>K+ ATP channel</td>
<td></td>
<td>damage</td>
</tr>
</tbody>
</table>


1.6.7 Dipeptidyl-Peptidase IV Inhibitors

These are new class of relatively expensive anti-diabetogenic agents or oral hypoglycemics that inhibits dipeptidyl-peptidase-4 (DPP-4) which improves islet function and glycemic control. They are effective as monotherapy and as add-on therapy in combination with metformin and insulin.
1.6.8 Insulin

Insulin therapy or administration is most common with a larger perspective in the management of diabetes mellitus in order to keep the blood sugar level at the normal range. In most instances, insulin may be prescribed alone or along with oral anti-hyperglycemic drugs under admissible level. Injectable forms of insulin are available based on the mode of action such as rapid, short, intermediate and long acting. Based on several factors like the type of diabetes, lifestyle, blood glucose levels and its fluctuation through out the day, the physician has to decide the treatment plan and also the delivery options.

1.6.9 Others

There are a very large in number of modalities assessed for the development as new therapeutics in diabetic patients like the inhibitors of the sodium-glucose co-transporter 2, and inhibitors of 11β-hydroxysteroid dehydrogenase 1, which increase glucose elimination through kidney and decrease the effects of glucocorticoid in liver respectively. Many other management strategies also available depend on the choice of the physician and the condition of the patients.

1.7 Cost of diabetes management

Though there is a significant advantage over cost effective therapeutics, a huge economic burden has been imposed on the patients, their families and substantial economic loss in terms of expenditure in diabetes and its complications. Diabetes has been considered as a disease of costly affair at the societal and personal level as the cost of diabetic care and management is always very high. The cost of diabetic health care increases many folds when complications are associated with or when admitted in hospital or insulin treatment is needed. The annual median expenditure on diabetes care by an individual patients is estimated to be a minimum of Rs 10,000 in urban and Rs 6,300 in rural areas (Venkataraman et al. 2009). The people use to spend nearly 35–45% of their
annual income on diabetic care if they take proper care of their health. Because of these reasons, they tend to neglect care for diabetes which causes severe morbidities and early mortality. India has no comprehensive diabetes health care program and patients use to seek medical care from different health care providers, many of whom lack any yardsticks for quality (Olokoba et al. 2012).

1.8 Alternative therapy

The primary objective of any kind of therapeutic management is to save life, alleviate pain or symptoms and secondarily to prevent complications including various risk factors. The conventional drugs synthesized are often expensive with limited efficacy and possess the risk of adverse effects especially in the developing world. The prevalence of diabetes mellitus in rural populations is on the rise. The inabilities of available therapeutics in controlling the pathological consequences lead to the search of alternative strategies for the management of diabetes. The mechanism of action of herbal antidiabetics could be mediated through the following facts includes the stimulation of insulin secreting β-cells, reduction in insulin resistance, stimulation of glycogenesis and hepatic glycolysis, activation of PPARγ, inhibition of β-galactocidase and α–glucocidase and inhibition of glucose absorption from small intestine (Hui et al. 2009; Abdel-Moneim and Fayez, 2015).

1.9 Antioxidants

Antioxidants are man-made or natural substances which protect or delay the cells from being damaged by unstable molecules like free radicals and other toxic substances or agents. Antioxidants and other related substances interact or neutralize with and stabilize free radicals thereby prevent the cells from injury (Rahman, 2007). Although oxidation reactions are vital for life, they can also be detrimental in some extent in many cases.
Naturally plants and animals maintain a complex system of multiple types of antioxidants in order to combat the oxygen free radicals. The presence of low level of antioxidants, or inhibition or hinderance in the action of antioxidant enzymes can cause oxidative stress. Since oxidative stress might be an important player of causing or the consequence of many human diseases, the use of antioxidants for protection and treatment for various diseases has been intensively studied and demonstrated for many decades. At present, antioxidants are being widely used as dietary supplements in medical practice as they are believed to maintain normal well being and prevent various kinds of diseases (Dall et al. 2010; Zhuo et al. 2014).

1.9.1 Classification of antioxidants

They are classified into two major divisions:
(1) Primary or natural antioxidants.
(2) Secondary or synthetic antioxidants.

1.9.1.1 Primary or natural antioxidants

They are natural compounds known to have high anti-oxidant properties. These antioxidants interrupt the oxidative reactions of free radical chain which react with intermediary radicals thus forming stable products that do not initiate or propagate further oxidation of lipids. The following molecules namely phytochemicals and flavonoids, antioxidant minerals and vitamins, enzymes and melatonin are considered as antioxidants of this group (Hamid 2010; John et al. 2014; Karaaslan 2015).

1.9.1.2 Secondary or synthetic antioxidants

Secondary antioxidants are man-made, synthesized products to trap radicals and stop the chain reactions, chelate metals, regenerate primary antioxidants, or act as emulsifying agents. They are referred as decomposers of hydroperoxides into
on-reactive radicals, and thermally stable products (Hamid et al. 2010; Nimse and Pal 2015).

1.10 Herbal drugs

Many Indigenous plants, plant products have been used or investigated for their medicinal or beneficial use in Indian system of medicine including ayurveda, sidhha, etc. The activity of those medicinal plants always depends upon the nature of phytoconstituents present in them. Thus numerous medicinal plants have been studied and reported for antidiabetic activity in the literature (Prakash et al. 2015). At present, about 80% of populations around the world use herbal drugs towards major healthcare delivery. The WHO has listed about 21,000 plants with medicinal properties used around the world for medicinal purposes and among those, about 2500 species of medicinal plants are from India. Hence, India has been known as 'botanical garden of the world' due to large scale producer of plant derived neutraceuticals in the world. These herbal products express beneficial effects in various conditions and activities like antimicrobial, hepatoprotective, antidiabetic, antiarthritic, analgesic, anti-infertility, vasodilatory, antiageing, sedative, antidepressant, antianxiety, antispasmodic, anti-inflammatory, anti-viral, asthma, gall stones, migraine, acne, fatigue, neurodegenerative disease and improvement of memory. The plant based drugs provide an effective and safe treatment in many conditions as their strength differs based on the cultivating conditions, timing and method of harvesting, exposure to environmental conditions, type of conservation and genetic distinction. These raw materials can be further processed by different methods to make it as powder, decoction, hydroalcoholic tincture and fluid extracts based on the mechanism of active chemical constituents.

Diabetes mellitus became the third most dangerous killer of the population with its high prevalence, morbidity and mortality. In the present century people have diverted their interest towards natural medicine like naturopathy as the synthetic drugs seems to have more side effects. The treatment can be done by exploiting
the herbal reliability of India and the process of making them in to a successful alternate to the available drugs. The ethnobotanical information report states that about 1000 or more plants have been identified and studied for their antidiabetic potential which has different type of biological activity. Among various plant constituents, alkaloids, terpenoids, carbohydrates, amino acids, glycosides are important in altering diabetic complications (Sen et al. 2016).

1.1 Medicinal plants

Medicinal plants in terms of various preparations or pure active principles are used for centuries as traditional healers and a safe ailment tool for many disease conditions. The major objective of management is to maintain the blood glucose without causing abnormally low levels and also minimizing the adverse effects. For instance, in case of diabetes mellitus, many plants or plant derivatives have been demonstrated to have multiple beneficial activities including manipulation of the carbohydrate metabolism, improvement of glucose uptake and functioning of β-cells along with antioxidant properties. The mechanisms of action for hypoglycemic activity of herbs are different in different tissues (Chawla et al. 2013).

1.11 Mechanism of action of medicinal plants

In the recent and past, there is a use of plant based herbal medicine for various disease conditions in developed and developing countries due to their origin and less adverse effects. Apart from different natural compounds, many dietary supplements are commercially available in market for combating diabetes but few of them are effective (Rosalie and Ekpe, 2016; Modak, 2007). These phytochemicals are acting mechanistically similar to conventional medicines through various metabolic pathways as substrate or products and influence glucose metabolism effectively. There are many well known medicinal plants with demonstrated anti-diabetic and related beneficial effects such as Acacia arabica (Babhul or Karuvela Maram in Tamil), Aegle marmelos (Bengal Quince
or vilvamaram in Tamil), Allium cepa (Onion), Allium sativum (Garlic), Aloe vera, Azadirachta indica (Neem), Benincasa hispida (Bottle guard), Trigonella foenum-graeca (Fenugreek), Cassia cinnamon, Ocimum sanctum (Holy basil; Tulasi in Tamil), Eugenia jambolana (Jamun; Naval fruit in Tamil) and Agaricus mushroom.

1.12 Flavonoids and Diabetes

Flavonoids are a diverse group of polyphenolic phytonutrient compounds (plant chemicals) and the largest nutrient families known to found in almost all plants, fruits and vegetables. Based on in vitro and in vivo studies, with considerations to their biological properties, polyphenols are well known nutraceuticals and dietary supplements helpful in curing diseases including DM with modulation of carbohydrate and lipid metabolism, alleviation of oxidative stress, and inflammatory process related to metabolic disorders (Testa et al. 2016).

1.13 Role of phytochemicals in diabetes

Chronic diseases like diabetes caused by hyperglycemia or increased blood sugar or uncontrolled regulation of glucose leads to serious damages, disabilities or death to millions of people around the globe.

The synthetic drugs which are used for the management of diabetes mellitus may be divided into insulin and insulin preparations taken by parenterally, and as oral hypoglycemic drugs (Gaikwad et al. 2014) as mentioned elsewhere in this section. Although numerous synthetic chemical entities were developed for the management of diabetes mellitus their use may be limited due to various adverse effects. So there is still an unmet need for the determination of alternative remedies against the complications of diabetes.
As per recommendation of WHO, the evaluation of traditional plants and plant based therapeutics for various conditions like diabetes due to their effectiveness, non-toxic nature, with less or no side effects. Phytoconstituents obtained from different plant sources such as polyphenols, alkaloids, flavonoids, tannins and steroids are reported as potent hypoglycemic agents. Plant extracts or individual phytochemical or group of phytochemicals has contributed mechanistically to reduce the diabetes status in both animals as well as humans (Gaikwad et al. 2014; Govindappa, 2015).

Figure 1.8 Action sites of herbs in diabetes treatment (Hui et al. 2009)

1.14 Curcumin
1.14.1 History

Curcuma longa (turmeric or curcuma), a plant of the ginger family (Zingiberaceae), commonly present in Asian countries especially in India being the native habitat of turmeric as a spice remedy, it is the important producer, consumer and exporter. In combination, turmeric with other spices and used as a curry powder for cooking purpose (Trujillo et al. 2013).
1.14.2 Taxonomic profile

Turmeric has been described by Linnaeus and its taxonomic profile of *C. longa* belongs to:

- Class: Liliopsida
- Order: Zingiberales
- Family: Zingiberaceae
- Genus: Curcuma
- Species: longa
- Scientific name: *Curcuma longa*

1.14.3 Chemistry of curcumin

Curcuma, a crystalline orange-yellow powder insoluble in water contains 60–70% carbohydrate, 8.6% protein, 5–10% fat, 2–7% fiber, 3–5% curcuminoids (50–70% curcumin) and up to 5% essential oils and resins. Vogel and Pelletier (1815) first isolated in an impure form and reported the name curcumin around two centuries ago as a yellow colour compound found in turmeric (*curcuma longa*). The structure of curcumin a diferuloylmethane or 1,6-heptadiene-3,5-dione-1,7-bis (4-hydroxy-3-methoxyphenyl)-(1E, 6E), was confirmed by Lampe and Milobedeska in 1910. Srinivasan (1953) reported that curcumin was a mixture of curcuminoids and then separated and quantified. The composition of curcuminoids is approximately 70% curcumin (curcumin I), 17% demethoxycurcumin (curcumin II), 3% bis-demethoxycurcumin (curcumin III) and the rest (10%) is called cyclocurcumin (curcumin IV) (Tokusoglu *et al.* 2015). Studies indicate that the functional groups associated to curcumin's chemical structure includes bis- α, β unsaturated β-diketone, two methoxy groups, two phenolic hydroxy groups and two double-conjugated bonds (Lee *et al.* 2013; Tokusoglu *et al.* 2015). The first study with curcumin on human was published in 1937 by Albert O in Lancet. Srimal and Dhawan (1973) reported that curcumin a non-steroidal and anti-inflammatory agent and several studies
demonstrated that curcumin has the multi-target capacity in curing many diseases especially diabetes and its complications (Arafa, 2005; Ak, Gulcin, 2008; EI-Moselhy et al. 2011; Ghorbani et al. 2014; Bulboaca, 2016; Kato et al. 2016).

Figure 1.9 *Curcuma longa* Linn. plant, rhizome powder and structure of curcumin (Alrawaig and Abdullah, 2014)

Curcumin is a hydrophobic polyphenol compound extracted from the rhizome of the herb *Curcuma longa* used as food supplement that possess many pharmacological activities including anti-inflammatory, anti-cancer properties, powerful anti-oxidant and as an anti-diabetic agent. On this basis, the present study was focused the preventive effect of curcumin against high fructose diet fed on biochemical, oxidative stress parameters and their association with potential changes in insulin sensitivity in adult male Wistar rats.