2

REVIEW OF LITERATURE

Diabetes Mellitus is a serious, chronic disease that occurs either when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Diabetes is an important public health problem, one of four priority non communicable diseases targeted for action by world leaders. Both the number of cases and the prevalence of Diabetes have been steadily increasing over the past few decades (WHO, 2016).

Medicinal plants play an important role in the treatment of Diabetes; especially in the developing countries due to their cost effectiveness (Patel *et al.,* 2012b). Hence the present research entitled "A Comparative study on the antidiabetic potential of alpha amylase inhibitors in *Momordica charantia* and *Trigonella foenum graecum*" is being carried out. The literature pertaining to the present study is discussed under the following headings:

2.1 Diabetes Mellitus

2.1.1 History of Diabetes Mellitus

2.1.2 Aetiology and Classification of Diabetes Mellitus

2.1.3 Complications of Diabetes Mellitus

2.2 Oxidative Stress and Antioxidants in Diabetes Mellitus

2.2.1 Role of Oxidative Stress in Diabetes Mellitus

2.2.2 Antioxidants

2.2.3 Antioxidant Defense Mechanisms

2.3 Management of Diabetes Mellitus

2.3.1 Diagnosis

2.3.2 Treatment of Diabetes Mellitus

2.3.2.1 Diet and exercise

2.3.2.2 Oral antidiabetic drugs

2.3.2.3 Insulin therapy

2.4 Medicinal Plants and Diabetes Mellitus

2.4.1 Antidiabetic, alpha amylase inhibitory and antioxidant compounds from plants

2.4.2 Mechanism of action of plant compounds

2.4.3 *In silico* studies and alpha amylase inhibitors

2.5 Medicinal Plants chosen for the study

2.5.1 *Momordica charantia*

2.5.2 *Trigonella foenum-graecum*

2.1 Diabetes Mellitus

Diabetes Mellitus is a major global metabolic disorder of current century.This pandemic is characterized by excessive sugar in the blood (hyperglycemia) due to deficiency in production of insulin by the pancreas or by the ineffectiveness of the insulin produced. India is the number one danger zone of Diabetes in the World (Aswar and Kuchekar, 2012).

Diabetes Mellitus is one of the most common chronic diseases across the world and number of diabetic patients is on rise. Most people with Diabetes live in low and middle-income countries like India and these countries will also see the greatest increase in numbers to 101 million by the year 2030 (Whiting *et al.,* 2011)

2.1.1 History of Diabetes Mellitus

Diabetes has been recognized for last 3,500 years. The ancient Egyptians knew it very well, as documented in the Ebers Papyrus. The term Diabetes was coined by Aretaeus of Cappadocia (81-138 A.D), which is derived from the Greek “diabainein” that literally means “passing through” or “syphon”, a reference to one of major symptoms of Diabetes-excessive urine production. In 1674, Thomas Willis added the word, “mellitus” to the disease and a word from Latin meaning “honey”, a reference to the sweet taste of urine due to the presence of glucose. Vedic medical treatises from ancient India identified and classified Diabetes Mellitus as Madhumeha or honey urine. The ancient Indians tested for Diabetes by observing whether ants were attracted to a person's urine and called the ailment “sweet urine disease”. Diabetes Mellitus has been known since antiquity: its treatments were known since the middle ages and the elucidation of its pathogenesis occurred mainly in the 20th century (Piero *et al*., 2015).

2.1.2 Aetiology and Classification of Diabetes Mellitus

Diabetes is classified into following four types based on their aetiology (Diabetes Care, 2016)

a) Type 1 Diabetes (due to β-cell destruction, usually leading to absolute insulin deficiency)

b) Type 2 Diabetes (due to a progressive loss of insulin secretion on the background of insulin resistance)

c) Gestational Diabetes Mellitus (GDM) (Diabetes diagnosed in the second or third trimester of pregnancy that is not clearly overt Diabetes)

d) Specific types of Diabetes due to other causes, e.g., monogenic Diabetes syndromes such as neonatal diabetes and maturity-onset diabetes of the young (MODY), diseases of the exocrine pancreas, such as cystic fibrosis and drug or chemical induced Diabetes such as with glucocorticoid use, in the treatment of HIV/AIDS or after organ transplantation.

a) Type1 Diabetes Mellitus

Insulin dependent DM or juvenile onset diabetic patients depend on insulin. There is usually sudden onset and occur in the younger age group and there is an inability of pancreas to produce adequate amount of insulin. This may be caused by virus or due to autoimmunity.

Aetiology

Genetics: The inheritance of human Insulin Dependent Diabetes Mellitus (IDDM) is polygenic. It has been established that over 50% of the heritability is contributed by the HLA class II gene (chromosome 6).

Infection: There is increasing evidence that Type 1 Diabetes especially in younger patients, follows a "*Coxsackie*" or other virus infection. There is sometimes a long interval between the infection and the onset of symptoms. The virus may trigger an autoimmune reaction in the pancreatic islets and this impairs insulin secretion and ultimately destroys the β cells.

Immunological factors: IDDM is slow autoimmune disease associated with other auto immune disorders. Hyperglycemia accompanied by the classical symptoms of Diabetes occurs only when 90% of insulin secreting cells is already destroyed (Kusuma *et al.,* 2015)

b) Type 2 Diabetes Mellitus

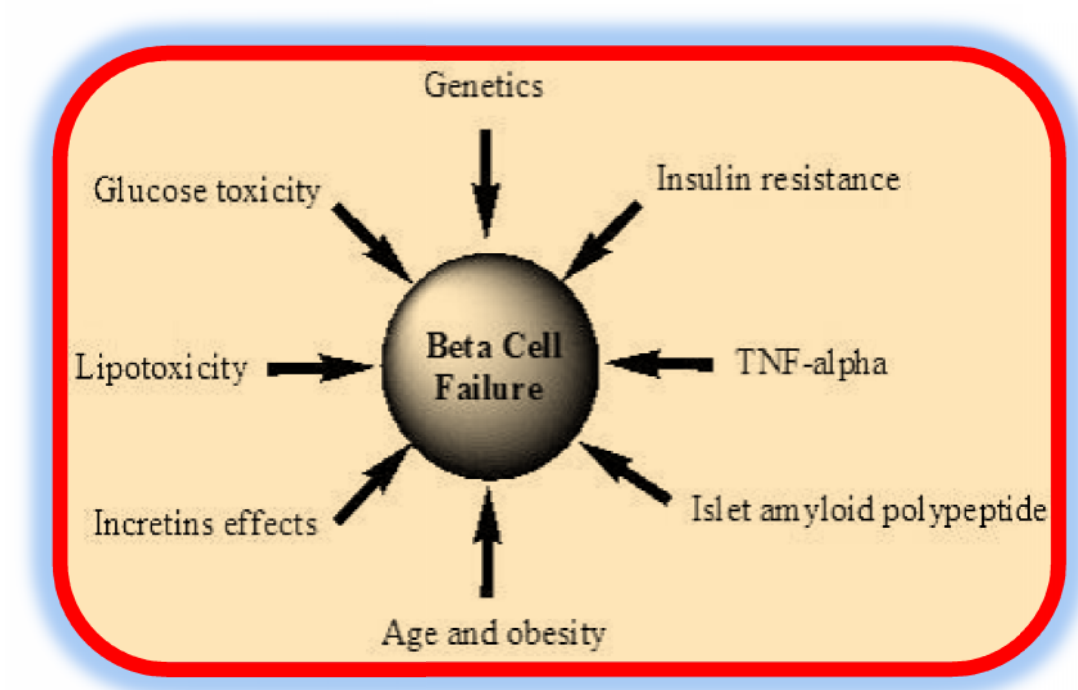
Aetiology

Genetics: Genetic component has a stronger basis for Type 2 Diabetes than Type1Diabetes. Although no definite and consistent genes have been identified, multi factorial inheritance is the most important factor in the development of Type 2 Diabetes.

Constitutional Factors: Certain environmental factors such as obesity, hypertension and level of physical activity play contributory role and modulate the phenotyping of the disease

Insulin Resistance: Insulin resistance is the decreased ability of insulin to act effectively on target tissues (especially liver, muscle and fat). It is one of the most prominent metabolic features of Type 2 Diabetes and results from a combination of genetic susceptibility and obesity.

Impaired Insulin Secretion: The different patho genetic factors are implicated in the progressive impairment of insulin secretion in Type 2 Diabetes as shown in Figure 1.



(DeFronzo, 2004)

Figure1

Pathogenetic factors affecting impairment of insulin secretion

Increased hepatic glucose synthesis: One of the normal roles played by insulin is to promote hepatic storage of glucose as glycogen and suppress gluconeogenesis. In Type 2 Diabetes, as a part of insulin resistance by peripheral tissues, liver also shows insulin resistance i.e. in spite of hyperinsulinaemia in the early stage of disease, gluconeogenesis in the liver is not suppressed. This results in increased hepatic synthesis of glucose which contributes to hyperglycemia in this case.

c) Gestational Diabetes Mellitus

Gestational Diabetes Mellitus refers to the onset or initial recognition of glucose intolerance during pregnancy usually observed in the third trimester. It occurs in about 4% of all pregnancies. The risk factors associated with GDM are obesity, glycosuria and family history that includes Diabetes. If the GDM develops during pregnancy, the women have a 50% risk of developing Type 2 Diabetes in the future and a 50% risk of experiencing GDM in subsequent pregnancy (Mahesh *et al.,* 2016).

d) Other specific types (Monogenic Diabetes)

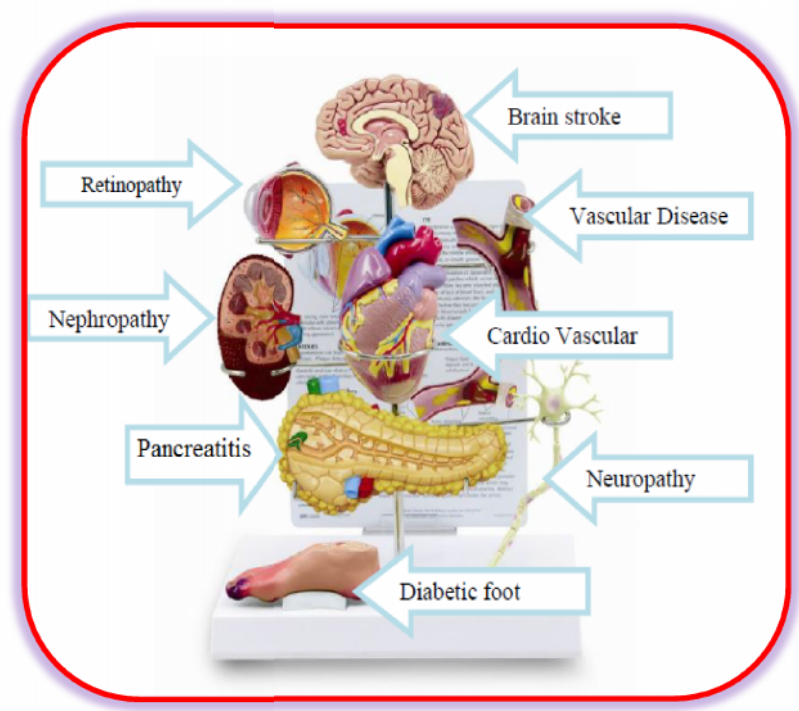
Types of Diabetes Mellitus of various known etiologies are grouped together to form the classification called “Other Specific Types”. This group includes persons with genetic defects of beta-cell function (this Type of Diabetes was formerly called MODY or maturity-onset Diabetes in youth) or with defects of insulin action; persons with diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis; persons with dysfunction associated with other endocrinopathies (e.g. acromegaly); and persons with pancreatic dysfunction caused by drugs, chemicals or infections and they comprise less than 10% of DM cases (Baynest, 2015)

2.1.3 Complications of Diabetes Mellitus

Type1 Diabetes can affect major organs in our body, including heart, blood vessels, nerves, eyes and kidneys. Keeping our blood sugar level close to normal most of the time can dramatically reduce the risk of many complications. Long-term complications of type1 Diabetes develop gradually, over years as shown in Figure 2. Diabetes complications may be disabling or even life-threatening like

- Heart and blood vessel disease
- Nerve damage (Neuropathy)
- Kidney damage (Nephropathy)
- Diabetic cardiomyopathy

- Coronary artery disease
- Stroke (Mainly the ischemic type)
- Diabetic myo-necrosis (Muscle wasting)
- Diabetic encephalopathy
- Eye damage
- Foot damage (Diabetic foot)
- Skin and mouth functions
- Osteoporosis
- Pregnancy complications
- Hearing problems (Harikumar *et al*., 2015)



(Kusuma *et al.,* 2015)

Figure 2

Complications of Diabetes Mellitus

Diabetic Retinopathy (DR) is a well recognized complication occurring both in Type1 and Type 2 Diabetes Mellitus and has been shown that nearly all Type1 and 75% of Type 2 Diabetes will develop DR after 15 years duration of Diabetes. DR is classified into Non Proliferative Diabetic Retinopathy (NPDR) or background retinopathy and Proliferative Diabetic Retinopathy (PDR). NPDR is characterized by vascular closure with

the earliest visible signs as micro aneurysms and retinal haemorrhages. Progressive capillary non perfusion is accompanied by development of cotton-wool spots, venous beading and intra retinal micro vascular abnormalities. PDR which occurs with further retinal ischemia is characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous. Risk for developing retinopathy is greater in diabetics with poor control of blood sugar level, high blood pressure, high cholesterol, pregnancy, smoke etc (Deepraj *and* Karthika*,* 2012)

Diabetic nephropathy causes glomerular basement membrane thickness, micro aneurism formation and mesangial nodule formation, all which are reflected in proteinuria and in the end, renal insufficiency. The mechanisms for injury also involve the increased polyol pathway and Advanced Glycation End Products (AGE) formation. AGE binding to its receptors has been proved to play a role in renal damage, fibrosis and inflammation associated with diabetic nephropathy. These actions of AGE also potentiate oxidative stress, while synergizing with rennin-angiotensin system activation, which leads to a vicious cycle causing kidney failure (Thomas, 2011).

Diabetic neuropathy is defined as the presence of symptoms and signs of peripheral nerve dysfunction in diabetic patients after exclusion of other causes. Peripheral neuropathy in Diabetes may manifest in several different forms, including sensory, focal/multifocal and autonomic neuropathies. Diabetic neuropathy may be associated with foot ulcers, amputations, non-healing skin wounds and sexual dysfunction. The neuropathy results in loss of protective sensation in the feet, which leads to callus formation, ulceration and other injury and may also result in the infection of the skin (e.g. cellulitis) and bones of the foot (e.g. osteomyelitis) and gangrene. Sexual dysfunction usually occurs in young-aged diabetic patients because of oxidative stress in cavernous tissues (Yanling *et al.,* 2014).

Cardiovascular disease is one of the common complications of Diabetes Mellitus. In developed countries, it is the most common cause of death in diabetic patients. Cardiovascular disease in Diabetes is linked to the development of atherosclerosis. Patients with Diabetes are classified as being high risk for cardiovascular disease and Diabetes Mellitus is regarded as a coronary disease equivalent. Cardiovascular disease in Diabetes Mellitus may be associated with hypertension, heart failure, diabetic cardiomyopathy, coronary artery disease, myocardial infarction and stroke (Young *et al.,* 2016).

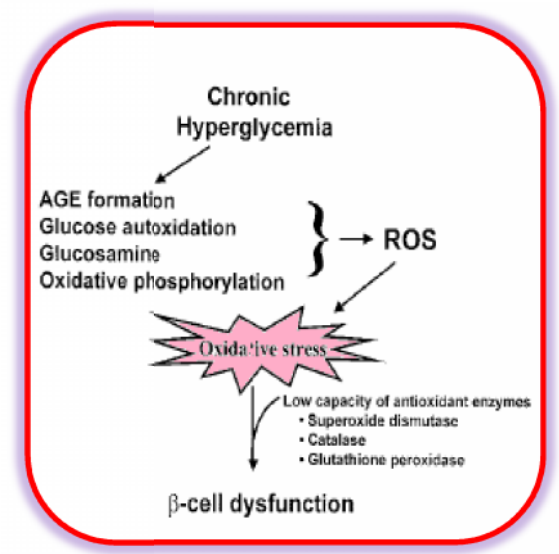
2.2 Oxidative Stress and Antioxidants in Diabetes Mellitus

2.2.1 Role of Oxidative Stress in Diabetes Mellitus

Oxidative stress can be defined as a disturbance in the balance between oxidants and antioxidants due to different factors such as aging, drug actions, toxicity, inflammation and addiction. It is in general, excess formation or insufficient removal of highly reactive molecules. Oxidative stress is increased in Diabetes because of multiple factors. Among these factors, glucose auto-oxidation is a dominant factor leading to the production of free radicals. Other factors include cellular oxidation or reduction imbalances and reduction in antioxidant defenses including decreased cellular antioxidant levels and a reduction in the activity of antioxidant enzymes that dispose of free radicals. Moreover, levels of some pro-oxidants such as ferritin and homocysteine are elevated in Diabetes. Another important factor is the interaction of Advanced Glycation End Products (AGEs) with specific cellular receptors called AGE Receptors (RAGE). Elevated levels of AGE are formed under hyperglycemic conditions. Their formation is initiated when glucose interacts with specific amino acids on proteins forming a compound that then undergoes further chemical reactions. Glycation of protein alters protein and cellular function and binding of AGEs to their receptors can lead to modification in cell signalling and further production of free radicals.

Oxidative stress plays an important role in the development of vascular complications in Diabetes particularly Type2 Diabetes. Reactive oxygen species (ROS) level elevation in Diabetes may be due to perturbations in antioxidant defense system. The variation in the levels of antioxidant enzymes makes the tissues susceptible to oxidative stress leading to the development of diabetic complications as indicated in the Figure 3.

Various mitochondrial, enzymatic and non-enzymatic pathways mainly comprise oxidative stress in Diabetes Mellitus. The imbalance in an antioxidant and pro oxidant is due to auto-oxidation of glucose level in diabetes that usually leads to high energy particle generation. In cells, there usually exists a balance between antioxidants elimination and free radical development. The gradual increase in free radicals and diminishing antioxidant defense mechanism is also the fact linking Diabetes Mellitus with oxidative stress.



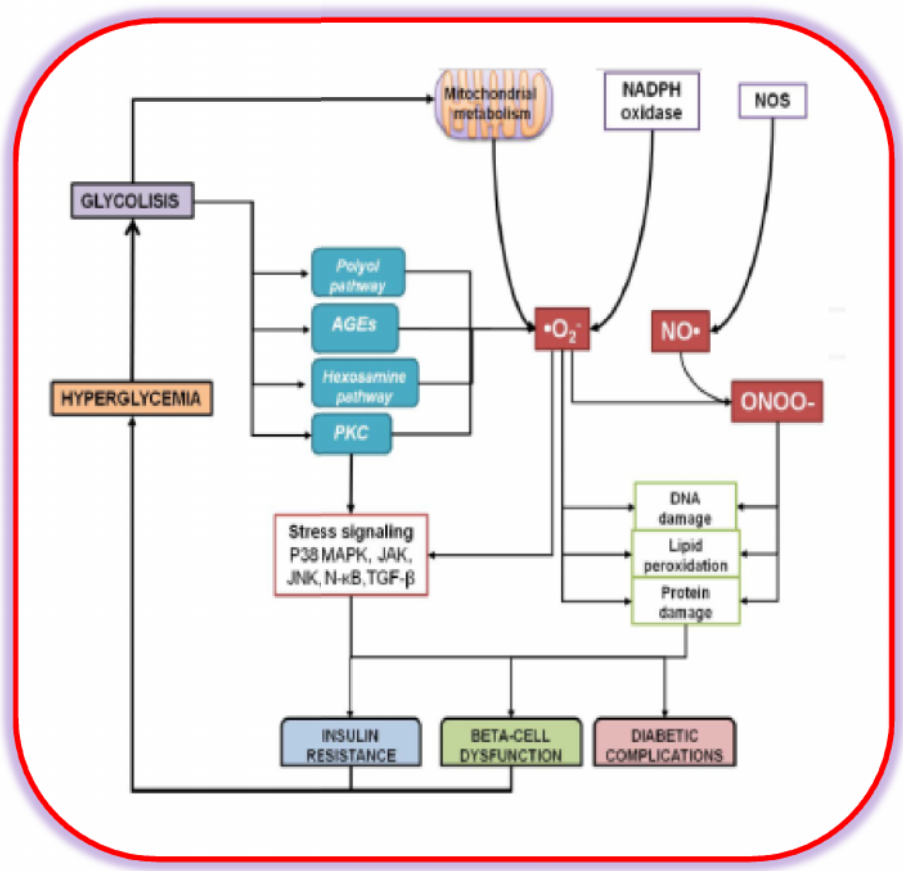
(El-Demerdash *et al*., 2016)

Figure 3

Oxidative stress in Diabetes

Free radical species are superoxide molecules, hydroperoxyl molecules and hydroxyl molecules. Reactive nitrogen species having free radicals are nitrogen dioxide and nitric oxide while non-radical is peroxynitrates and peroxynitrites. By the physical, physiological and chemical factors, the reactive radicals, nitric oxide peroxynitrite and superoxide molecules cause tissue damage. There are a variety of different defense mechanisms by which human body works against oxidative stress induced by free radicals as tissue repair, anticipatory mechanism, physical resistance and antioxidant defense (Ahmad *et al*., 2015).

Hyperglycemia and free fatty acid intake are among the causes for oxidative stress conditions. Diabetic subjects tend to have more oxidative cell and organism environments than healthy subjects, i.e. an increase in ROS generation. Moreover, diabetic patients present a decrease in antioxidant defenses. The antioxidant enzyme levels are affected by Diabetes, which further increase oxidative stress. Oxidative stress has been proposed as a major participant in the pathophysiology of diabetic complications. Nevertheless, regarding Diabetes onset and development, oxidative stress has also shown to affect the two major mechanisms failing during Diabetes: insulin resistance and insulin secretion as indicated in Figure 4.Oxidative stress plays a pivotal role in the development of Diabetes complications, both at the micro vascular and macro vascular levels (Maria-Luisa and Cristina, 2013).



(Maria- Luisa and Cristina, 2013)

Figure 4

Oxidative stress pathways in Diabetes Mellitus

2.2.2 Antioxidants

Antioxidants are chemical or biological agents able to neutralize the potentially damaging action of free radicals such unstable molecules as peroxyl radical, hydroxyl radical and singlet oxygen and peroxynitrate radicals. The oxidation process of other macromolecules is avoided or slows down by antioxidants. The destructive effect of free radicals in cells is minimized or terminated by antioxidants. The tissues or cell damage by toxic metabolites is minimized by antioxidants. In recent studies, there is strong relation found between oxidative stress and reactive oxygen species for human disorders/diseases. So antioxidants and free radical studies are very important in today's research for understanding the relationships of diseases such as cancer, neurodegenerative diseases, Diabetes Mellitus and cardiac arrest (Agnieszka *et al*., 2011).

Plants are a potential source of natural antioxidants. Natural antioxidants or phytochemical antioxidants are secondary metabolites of plants which produce a very impressive array of antioxidant compounds. Natural products especially from plant sources have the ability to reduce oxidative stress by acting as antioxidants (Latifou *et al.,* 2015). Antioxidants obtained from nature, helps in neutralization of reactive oxygen species and significantly reduce the probability of progression of diabetic complications. A variety of nutritionally important vitamins, supplements and constituents of natural food sources, naturally reduce the injury caused by oxidative stress in Diabetes Mellitus (Ahmad *et al*., 2015). The complications in the existing diabetic treatment have led to the employment of natural resources either as a food supplement or as a medicinal formulation, as alternatives to the synthetic drugs. Indian traditional medicine formulates several herbs and is used in the treatment of various diseases since time immemorial (Ramith *et al*., 2014).

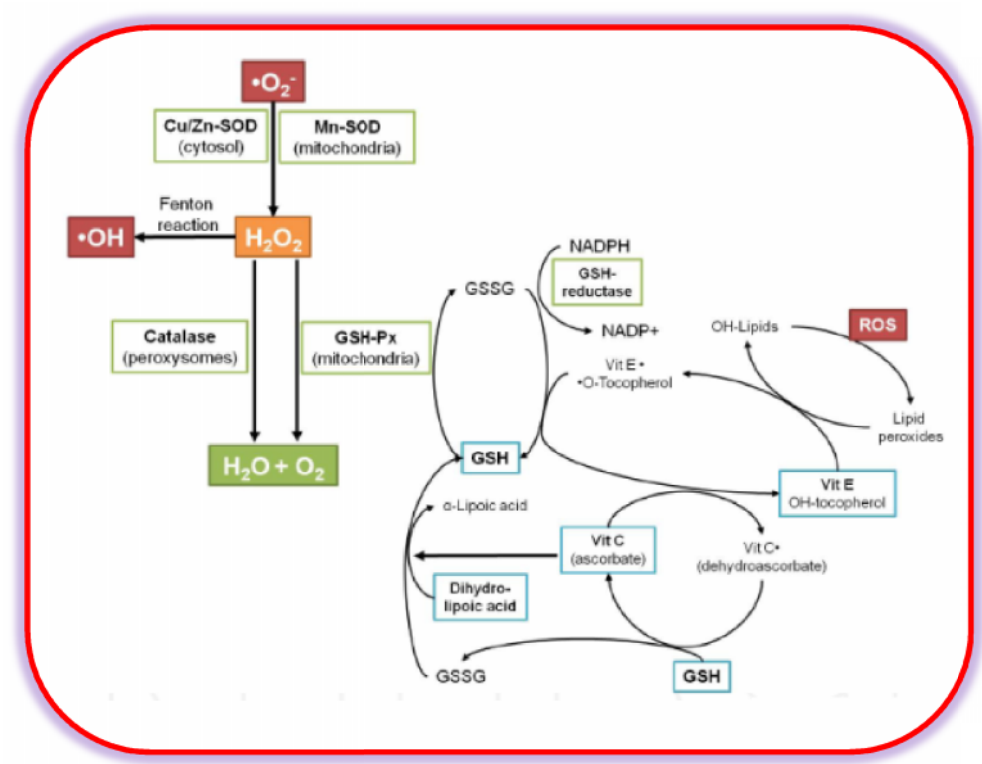
2.2.3 Antioxidant Defense Mechanisms

As a small part, the oxygen consumed for aerobic processes will be converted into superoxide anion, which will have to be scavenged or converted into less reactive (and harmful) molecules. The main enzymes that regulate this process are superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase as shown in Figure 5. When reactive oxygen species (ROS) overproduction or chronic hyperglycemia occurs, the activity of these enzymes is insufficient, leading to more ROS and reactive nitrogen species (RNS) formation and activation of oxidative stress pathways.

SOD is considered a first-line defense against ROS. This enzyme is present in nearly all cells and converts $\bullet O_2^-$ into H_2O_2. Mitochondrial and bacterial SOD contains Mn, while cytosolic SOD is a dimer containing Cu and Zn. As the H_2O_2 may still react with other ROS, it needs to be degraded by either one of the other two antioxidant enzymes, GSH-Px or catalase. GSH peroxidase is located in the mitochondria. It catalyzes degradation of H_2O_2 by reduction, where two gluthathione (GSH) molecules are oxidized to glutathione disulfide (GSSG).Regeneration of GSH by GSH-reductase, requires NADPH, which is oxidized to NADP+. Catalase, on the other hand, is localized primarily in peroxisomes, and therefore it detoxifies the H_2O_2 that diffuses from the mitochondria to the cytosol, converting it into water and molecular oxygen.

There are also nonenzymatic antioxidant mechanisms, which mostly help regenerate GSSG back into GSH. Antioxidant vitamins such as A, C, E and alpha-lipoic acid are among these mechanisms. Although all these antioxidant defenses work together to eliminate H_2O_2 (and thus superoxide) from the cell, in the presence of reduced

transition metals (Cu, Fe), H_2O_2 can be transformed into •OH, which is a highly reactive ROS, by the Fenton reaction.



(Maria-Luisa and Cristina, 2013)

Figure 5

Antioxidant defense mechanisms

2.3 Management of Diabetes Mellitus

The starting point for living well with Diabetes is an early diagnosis – the longer a person lives with undiagnosed and untreated Diabetes, the worse their health outcomes are likely to be. Easy access to basic diagnostics, such as blood glucose testing, should therefore be available in primary health-care settings. Established systems for referral and back-referral are needed, as patients will need periodic specialist assessment or treatment for complications.

For those who are diagnosed with Diabetes, a series of cost-effective interventions can improve their outcomes, regardless of what type of Diabetes they may have. These interventions include blood glucose control, through a combination of diet, physical activity and, if necessary, medication; control of blood pressure and lipids to reduce cardiovascular risk and other complications; and regular screening for damage to the

eyes, kidneys and feet, to facilitate early treatment. Diabetes management can be strengthened through the use of standards and protocols (WHO, 2016).

2.3.1 Diagnosis

The diagnosis of Diabetes carries considerable consequences. If the patient has classical symptoms (such as increased thirst and urine volume, unexplained weight loss, pruritus vulvae or balanitis) or drowsiness or coma, associated with marked glycosuria, the diagnosis can be readily established by demonstrating fasting hyperglycaemia. The identification of patients with Diabetes or Pre-Diabetes by screening allows for earlier intervention, with potential reductions in future complication rates.

Random plasma test

The simplest test does not require fasting before taking the test. If 200 or more than 200 mg/dl of blood glucose it probably indicates Diabetes but has to be reconfirmed.

Fasting plasma glucose test

There should be eight hours fasting before taking this test. Blood glucose more than 126 mg/dl on two or more tests conducted on different days confirms a Diabetes diagnosis.

Oral glucose tolerance test

This blood test evaluates body's response to glucose. This test requires fasting at least eight but not more than 16 hrs. Fasting glucose level is determined, and then given 75 gm of glucose, 100 gm for pregnant women. The blood is tested every 30 minutes to one hr for two or three hrs. This test is normal if glucose level at two hrs is less than 140 mg/dl. A fasting level of 126 mg/dl or greater and two hour glucose level of 200 mg/dl or higher confirms a Diabetes diagnosis (Gillett, 2009)

Glycated haemoglobin

The life span of hemoglobin in vivo is 90 to120 days. During this time glycated hemoglobin A forms, being the ketoamine compound formed by combination of hemoglobin A and glucose. Several subfractions of glycated hemoglobin have been isolated. Of these glycated hemoglobin A fraction HbA1c is of most interest serving as a retrospective indicator of the average glucose concentration. HbA1c is recommended as an essential indicator for the monitoring of blood glucose control. The blood HbA1c ≥6.5% is considered as Diabetes (Selvin *et al.,* 2010).

2.3.2 Treatment of Diabetes Mellitus

2.3.2.1 Diet and exercise

Balanced diet plays key role in the better management of Diabetes. Lifestyle changes can control blood sugar. Calories count is a major factor in the determination of emergency in Diabetes. A calorie is a unit of energy. Age, size and duration of activity decide the need of calories. Physically active people need more calories than inactive people. Treatment can also affect metabolism. For example, a person with a thyroid gland that does not secrete enough thyroid hormone will have a slower metabolism. People who are 20% heavier than their ideal weight are medically "obese." To reduce weight, they should eat fewer calories than their body needs (Saini *et al.,* 2015).

Diet therapy

Research Society for the Study of Diabetes in India (RSSDI) (2015) has given the following recommendations for management of Diabetes through diet:

- High-carbohydrate diets with relatively large amounts of unrefined carbohydrate and fibre such as legumes, unprocessed vegetables and fruits are recommended
- Protein intake equivalent to at least 15% of daily total calories is recommended
- Intake of non-nutritive artificial sweeteners in moderate amounts may be considered
- Combining foods with high and low glycaemic indices, such as adding fibre-rich foods to a meal or snack, improves the glycaemic and lipaemic profiles
- Cardio-protective diet should include:
    - More: leafy vegetables, vegetable salads, coarse grains, sprouted grams, spices and all other foods, which are rich in fibre and antioxidants
    - Moderate amounts of: low fat milk and milk products, vegetable oils with mono unsaturated fatty acid (MUFA) and poly unsaturated fatty acid (PUFA), flesh foods (fish, chicken without skin, white of the egg) and artificial sweeteners
    - Avoid: Alcohol, sugar, saturated fats and foods that are refined, processed, salt-rich, cholesterol-rich and deep-fried

- Provide access to a dietician (nutritionist) or other health-care professionals trained in the principles of nutrition, at or around the time of diagnosis offering an initial consultation with follow-up sessions as required, individually or in groups
- Individualise advice on food/meals to match needs, preferences and culture
- Advise on reducing energy intake and control of foods with high amounts of added sugars, fats or alcohol

Exercise

Person with Diabetes should exercise regularly. This can include brisk walking, jogging, cycling, swimming and playing badminton or tennis. Depending on one's interest, any of these can be selected. It should become a part of regular life. It is recommended that diabetic should do exercise of moderate intensity for a minimum period of 150 minutes a week (Kusuma *et al.,* 2015).

WHO recommendations on physical activity are provided for different age groups

- It is recommended that children and youth aged 5–17 years should do at least 60 minutes of moderate- to vigorous-intensity physical activity daily.
- It is recommended that adults aged 18–64 years should do at least 150 minutes of moderate-intensity aerobic physical activity (for example brisk walking, jogging, gardening) spread throughout the week, or at least 75 minutes of vigorous-intensity aerobic physical activity throughout the week, or an equivalent combination of moderate- and vigorous-intensity activity.
- For older adults, the same amount of physical activity is recommended, but should also include balance and muscle strengthening activity tailored to their ability and circumstances (WHO, 2016).

Exercise can improve glucose uptake by improving insulin sensitivity and reducing body adiposity in both patients of Type1 and Type 2 DM. Yoga is an ancient discipline designed to bring balance and health to the physical, mental, emotional and spiritual dimensions of the individual. A comprehensive yoga therapy program has the potential to enhance the beneficial effects of standard medical management of DM and can be used in an effective complementary or integrative therapy program. The improvement in various biochemical indices and stress reduction by practicing yoga can enable a person with a better healthy living. Numerous studies have shown positive benefits of yoga in the management of Diabetes with good impact on glycemic control, lipid profile and cardiovascular status (Senthilraj *et al*., 2015).

2.3.2.2 Oral antidiabetic drugs

Anti-diabetic drugs treat Diabetes Mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs and their selection depends on the nature of the Diabetes, age and situation of the person, as well as other factors (Prashant *et al.,* 2012).

Insulin secretagogues

Sulfonylureas (Glibenclamide, Gliclazide, Glipizide and Glimepiride)

The sulphonylureas (SUs) were initially developed in the 1920s and have become indispensable in the management of Type 2 DM. The mechanism of action involves a direct secretory effect on the pancreatic islet beta-cells. Adenosine triphosphate (ATP)-sensitive potassium channels (K^+ ATP) of the beta-cells play an essential role in the release of insulin.

Glibenclamide is considered an intermediate-acting drug (12 - 24 hours) with active metabolites of which approximately 50% are eliminated by the liver.

Gliclazide (Diamicron) also has duration of action of 12 - 24 hours, but up to 65% of active metabolites are excreted mainly by the kidneys.

Glimepiride has duration of action of about 24 hours and is eliminated by the liver. (Bosenberg and Zyl, 2008).

Non-Sulfonylureas

Meglitinide analogues, benzoic acid derivatives, structurally unrelated to the sulfonylurea's, are a different class of insulin secretagogues, stimulate prandial insulin release by inhibiting ATP-sensitive potassium channels of the beta-cell membrane via binding to a receptor distinct from that of sulphonylureas (SUR1/KIR6.2). Meglitinides have a very short onset of action and a short half-life.

Repaglinide, first clinically available insulin secretagogue, specifically enhances early-phase prandial insulin response by increasing the sensitivity of β-cells to elevated glucose levels, producing a greater insulin release under hyperglycaemic conditions (Durgaprasad *et al.,* 2016).

Insulin sensitisers

Metformin has been available since the 1950s. It has variety of clinical actions that extend beyond just the glucose lowering effects such as weight reduction, improving lipid profiles and vascular effects, which include improving endothelial function, as well as decreasing PAI-1 levels.

Thiazolidinedione derivatives (Troglitazone,Rosiglitazone,Pioglitazone) are synthetic ligands for peroxisome proliferative activated receptor (PPARγ) and improve Insulin sensitivity. PPARγ is mainly expressed in adipose tissue and increases insulin sensitivity by acting on adipose, muscle and liver to increase glucose utilization and decrease glucose production. Thiazolidinediones have also been shown to exert potent antioxidant effects. Various thiazolidinediones have differential effects on PPAR-gamma and PPAR-alpha. Pioglitazone exerts some PPAR-alpha effects. Troglitazone was introduced in 1997 but withdrawn from the market in 2000 due to increased risk of hepatic necrosis (Vaishali *et al*., 2017).

Alpha-glucosidase inhibitors (AGI's) and alpha amylase Inhibitors delay break down of complex carbohydrates by inhibiting action of enzyme glucosidase in the brush border of upper part of small intestine thereby reducing intestinal absorption of carbohydrates like starch, dextrin and disaccharides and blunts the rate of rise of postpradial plasma glucose, without increasing insulin levels. Acarbose, emiglitate, miglitol and voglibose of this class are available. All AGI's act on α-glucosidases. However, acarbose is minimally absorbed and most effective in inhibiting glucoamylase, whereas miglitol is a more potent inhibitor of disaccharide-digesting enzymes (Durgaprasad *et al.,* 2016).

Acarbose is of microbial origin and it was the first alpha-glucosidase inhibitor commercially available for Diabetes treatment which inhibits the activities of alpha amylase, sucrase and maltase (Prashant and Ritika, 2016).

Incretins (Amylin Agonists/GLP-1 Agonists)

Incretins, are the gut hormones, released in response to nutrient ingestion (Mainly glucose and fat) and exert a wide range of effects, including pancreatic insulin secretion in a glucose-dependent manner and also influence local gastrointestinal and whole-body physiology. Two gut hormones, Glucose-dependent Insulinotropic Peptide (GIP) secreted from L-cells of the distal ileum and colon and Glucagon Like Peptide–1 (GLP-1) secreted from the K-cells in the duodenum and jejunum were found to mediate

the "Incretin Effect" (Higher insulin release in response to an oral glucose challenge compared with an equal intravenous glucose load) The two hormones equally contribute to the incretin effect and have cumulative outcomes (Durgaprasad *et al.,* 2016).

Di Peptidyl Peptidase- 4 Inhibitors (DPP 4) (Gliptins)

Oral DPP4 inhibitors increase the availability of endogenous GLP1, thus enhancing glucose-induced insulin secretion and inhibiting glucagon release. These agents have no effect on gastric emptying and do not affect body weight (Buse *et al*., 2009 and Ahren, 2007).

2.3.2.3 Insulin therapy

Insulin has a major role in the control of hyperglycemia for Type1 diabetic patient while it may be required at a later stage or in selective individuals suffering from Type 2 Diabetes. Insulin analogues were developed in an attempt to overcome the problems associated with human insulin. They include short (rapid)-acting (aspart, lispro, glulisine), long-acting (glargine, detemir), ultralong acting (degludec) and premixed insulin formulations (75% neutral protamine lispro + 25% lispro; 50% neutral protamine lispro + 50% lispro and 70% protamine aspart+ 30% aspart). These formulations allow a closer replication of a normal insulin profile. Insulin analogues are classified according to their duration of action and their pharmacokinetic characteristics are shown in Table1.

Table 1

Pharmacokinetic characteristics of insulin preparations

Preparation	Analogues	Onset of action	Peak action	Duration of action
Short acting	Aspart Glulisine Lispro	<15 minutes	30-90 minutes	3-4 hours
Long acting	Detemir Glargine	1-4 hours	Peakless	20-24 hours
Ultralong acting	Degludec	30-90 minutes	Peakless	> 24 hours
Premixed	75%Protamine Lispro +25% Lispro 50%Protamine Lispro +50% Lispro 70%Protamine Aspart+ 30% Aspart	<15 minutes	90 minutes	Up to 10-16 hours

(Sharma and Sharma, 2013)

Table 2 shows some of the properties of available glucose-lowering agents and their adverse effects used in the treatment of Diabetes Mellitus.

Table 2
Properties of available glucose-lowering agents and their adverse effects used in the treatment of Diabetes Mellitus

Class	Compound (s)	Cellular mechanism(s)	Primary physiological action(s)	Side effects
Biguanides	Metformin	Activates AMP-kinase	↓ Hepatic glucose production	Gastrointestinal side effects (diarrhoea, abdominal cramping, nausea) Vitamin B12 deficiency, acidosis, hypoxia, dehydration and lactic acidosis
Sulfonylureas	2nd generation Glyburide Glipizide Glimepiride	Closes K^+ ATP channels on β-cell plasma membranes	↑ Insulin secretion	Hypoglycemia ↑ Weight
Meglitinides (glinides)	Repaglinide Nateglinide	Closes K^+ ATP channels on β -cell plasma membranes	↑ Insulin secretion	Hypoglycemia,↑ Weight,Frequent dosing schedule
Thiazolidinedione Derivatives	Pioglitazone Rosiglitazone	Activates the nuclear transcription factor PPAR-g	↑ Insulin sensitivity	↑ Weight Edema/heart failure Bone fractures ↑ LDL-C (rosiglitazone)
alpha-Glucosidase inhibitors	Acarbose Miglitol	Inhibits intestinal α-glucosidase	Slows intestinal carbohydrate digestion/absorption	Generally modest A1C efficacy Gastrointestinal side effects (flatulence, diarrhoea),Frequent dosing schedule
DPP-4 inhibitors	Sitagliptin Saxagliptin Linagliptin Alogliptin	Inhibits DPP-4 activity, increasing postprandial incretin (GLP-1, GIP)	(glucose dependent) ↓ Glucagon secretion (glucose dependent)	Angioedema/ urticaria and other immune-mediated dermatological effects Acute pancreatitis ↑ Heart failure hospitalizations
Amylin mimetics	Pramlintide	Activates amylin receptors	↓ Glucagon secretion Slows gastric emptying ↑ Satiety	Modest A1C efficacy Gastrointestinal side effects (nausea/ vomiting),Hypoglycemia , Injectable,Frequent dosing schedule,training requirements
Insulins	Rapid-acting analogs Inhaled insulin Short-acting Human Regular Intermediate-acting Human NPH	Activates insulin receptors	↑ Glucose disposal ↓ Hepatic glucose production Suppresses ketogenesis	Hypoglycemia.Weight gain Training requirements,Patient and provider reluctance, Injectable (except inhaled insulin) Pulmonary toxicity (inhaled insulin)

(American Diabetic Foundation, 2017)

Methods of insulin administration

Single unit disposable syringes with microfine needles are available for injection of insulin. Pen devices combine the insulin container and the syringe into a single unit. They eliminate the inconvenience of carrying insulin and syringes separately- Continuous subcutaneous Insulin Infusion pump (CSII). Pump therapy is capable of producing a physiological profile of insulin replacement. It provides constant basal infusion with an option of different infusion rates as well as bolus injection programmed according to size and nature of the meal (Minaxi *et al.,* 2015).

2.4 Medicinal Plants and Diabetes Mellitus

Diabetes Mellitus, being a multifactorial disease, demands multiple therapeutic approaches. Although synthetic oral hypoglycemics together with insulin are the main route for controlling Diabetes, however, they exhibited prominent side effects and failed to reverse the course of its complications. This constitutes the major force for finding alternatives, mainly from plant kingdom that is of less severe or even no side effects. Natural products are the major source for discovering promising lead candidates, which play an important role in future drug development programs (Asharani *et al.,* 2016).

Many indigenous Indian medicinal plants have been found to be useful to successfully manage Diabetes. One of the great advantages of medicinal plants is that these are readily available and have fewer side effects. The ethnobotanical information reports about 800 plants that may possess antidiabetic potential (Arumugam *et al*., 2013).

Plants have yielded directly or indirectly many important medicines in the past. For Diabetes, the discovery of the widely used hypoglycemic drug, metformin, came from the traditional approach of using *Galenga officinalis*. These traditional Indian medicines have great potential for scientists to find active compounds and develop new drugs for anti-Diabetes. Thus, there is an increasing requirement and the feasibility to screen and obtain active compounds including plant extracts from Indian traditional medicinal plants for the treatment of Diabetes and its complications. The lack of scientific and experimental evidence about effective constituents, toxicity, pharmacokinetics, effectiveness and efficacy resulted in deficiency of belief in effectiveness, quality and safety of Indian medicines. The need for adequate standards of herbal preparations to ensure quality, safety and efficacy has been highlighted since the use of herbal medicines and phytotherapy (Prakash *et al.,* 2015).

2.4.1 Antidiabetic, Alpha amylase Inhibitory and Antioxidant Compounds from Plants

Ayurveda and other traditional system of medicine have described a number of medicinal plants used for the treatment of Diabetes. Plant derived active principles represent numerous chemical compounds and has established activity constant with their possible use in the treatment of Diabetes (Seema and Chanchal, 2014).

Secondary metabolites could act as lead compounds for the discovery of different new classes of possibly potent and safe antidiabetic agents. Further attention should be given for the identification of the typical modes of action of their extracts and the isolated pure compounds (Abdel *et al*., 2014).

A number of plant extracts and natural biomolecules have been tested for their antidiabetic properties using both *in vivo* and *in vitro.* Some of them show very promising effects, which indicate that the dietary intake of phytochemicals could be a promising strategy for Diabetes prevention. Additionally, therapies based on phytochemicals could constitute a novel pharmacological approach for treatment or an approach that would reinforce existing treatments (Cristina *et al.,* 2012).

Inhibition of α-glucosidase activity was demonstrated as a good strategy for controlling glycemia and in consequence, glucosidase inhibitors have been used in medicine for Diabetes treatment. Inhibition of α-amylase is a possibility for treating Type 2 Diabetes Mellitus by phytotherapy. Amylase inhibitors retard the liberation of glucose from carbohydrates, delaying its intestinal absorption and consequently postprandial glycemia, thus reducing hyperglycemia (Akshatha *et al.,* 2014).

Most of the commercially available amylase and glucosidase inhibitors are of microbial origin. Though these drugs help in maintaining constant level of glucose in blood by delaying the breakdown of starches, their usage have been limited due to their side-effects such as flatulence and diarrhoea due to colonic fermentation of non-absorbed sugar. When compared to the microbial counterparts, amylase inhibitors from medicinal plant are considerably safe and effective (Alagesan *et al*., 2012).

Antioxidants or inhibitors of oxidation are compounds which retard or prevent the oxidation and in general prolong the life of the oxidizable matter. A plant-based diet protects against chronic oxidative stress-related diseases. Dietary plants contain variable chemical families and amounts of antioxidants. It has been hypothesized that plant antioxidants may contribute to the beneficial health effects of dietary plants (Chirag *et al*., 2013)

Antioxidants are abundantly present in leaf vegetables, fruits and natural food sources. Phytoconstituents with antioxidant potential include some cinnamic acids, coumarin derivatives, diterpenes, flavonoids, monoterpenes, phenylpropanoids, tannins and triterpenes. Natural antioxidants are present in all parts of higher plants like wood, bark, stems, pods, leaves, fruit, roots, flowers, pollen, and seeds. The occurrence of such oxidative mechanisms in plants clarifies why a plenty of antioxidant compounds have been recognized in plant tissue. Plants mostly those with elevated levels of powerful antioxidant compounds have an essential role in the cure and treatment of illness concerning oxidative stress including Diabetes Mellitus (Patel and Sharma, 2014).Some of the medicinal plants with their active constituents and mode of action are shown in Table 3.

Table 3

Medicinal plants with their active constituents and mode of action

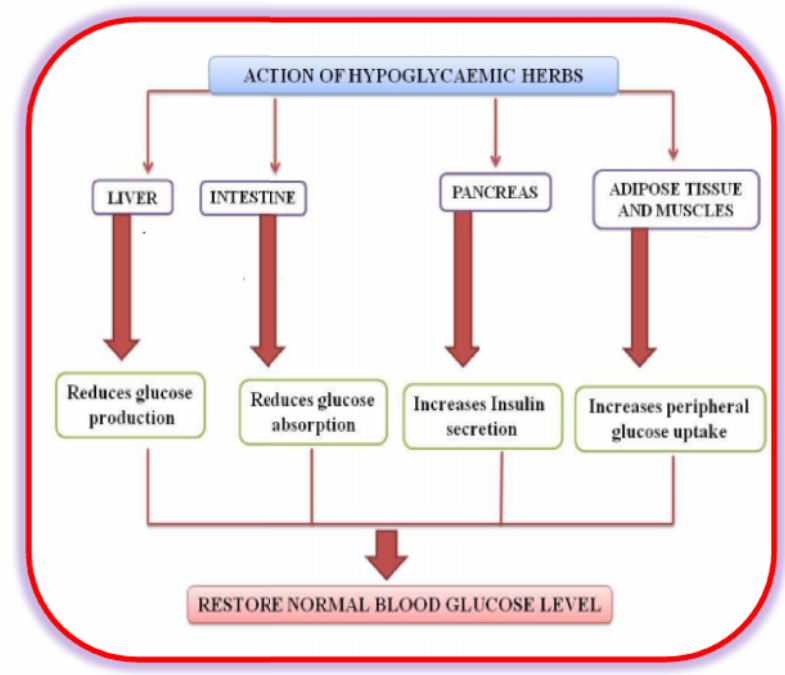
Botanical name and Family	Part of plant used	Active constituents	Mode of action
Acacia arabica (Indian Gum) Fabaceae	Seed and bark	Polyphenols, Tannins	Initiate insulin release from pancreatic beta cells (Raju *et al.,*2011).
Aegle marmelos (Bel, Golden Apple) Rutaceae	Leaf	Again , marmelosin	Increases either the glucose utilization or directly stimulates insulin release from pancreatic beta cells (Arumugam, *et al.,*2008, Yaheya *and* Ismail, 2009).
Allium cepa (onion) Alliaceae	Bulb	Allyl propyl disulphide, S- methyl cysteine Sulphoxide	Stimulates insulin secretion and also increases HMG CoA reductase activity and liver hexokinase activity (Ozougwu, 2011).
Allium sativum (Garlic) Alliaceae	Bulb	Allyl propyl disulphide, allicin	Control the blood glucose and lipids in serum as well as in tissues and altered the activities of liver hexokinase, glucose 6- phosphatase and HMG CoA reductase (Thomson *et al.,* 2007, Poonam *et al*., 2013).

Botanical name and Family	Part of plant used	Active constituents	Mode of action
Aloe barbadensis (Aloe vera) Liliaceae	Leaf	Alloin and barbaloin	Stimulates synthesis and/or release of insulin from the beta cells of the islets of Langerhans of pancreas and also the action of hepatic gluconeogenesis/ glucogenolysis (Jafri *et al*.,2011).
Biophytum sensitivum (Sikerpud) Oxalidaceae	Entire plant	Unknown	Stimulates the synthesis/release of insulin from the beta cells (Ananda *et al.,* 2012).
Boerhavia diffusa Nyctaginaceae	Whole plant	Punarnavine and ursolic acid	Improves the glucose tolerance (Patel *et al*, 2012 c).
Coccinia indica (Ivy guard kundru) Cucurbitaceae	Leaf	Resins, starch, glucose, fatty acid and carbonic acid	Inhibits the key gluconeogenic enzyme glucose-6-phosphatase (Jose and Usha 2010, Deokate and Khadabadi, 2011).
Cuminum cyminum (Jira) Umbellifereae	Seed	Cuminaldehyde, phellandrene, hydrocumine	Causes a reduction in blood glucose, glycosylated hemoglobin, creatinine, blood urea nitrogen and improved serum insulin and glycogen (liver and skeletal muscle) content (Jagtap and Patil, 2010).
Momordica charantia (karela) Cucurbitaceae	Leaf	Charantin, sterol	Increases the beta cells production in the pancreas or may permit the recovery of partially destroyed cells and also stimulates the insulin secretion from the beta cells (Savula *et al.,* 2012, Garau *et al.,* 2003).
Tinospora cordifolia Menispermaceae	Root	Tinosporone, tinosporic acid	Inhibits the alpha-glycosidase activity (Gupta and De, 2012).
Syzygium cumini Myrtaceae	seeds, leaves, flower	Mycaminose Betulinic acid and 3,5,7,4`-tetrahydroxy flavanone	Stimulate insulin secretion from pancreatic cells (Kumar *et al.,* 2008) Inhibit alpha amylase (Karthic *et al*.,2008)

Botanical name and Family	Part of plant used	Active constituents	Mode of action
Petrea volubilis Verbenaceae	Root	Unknown	Inhibit alpha amylase (Parul and Rekha,2015)
Ipomoea batatas Convolvulaceae	tubers	Saponins Coumarin	Antioxidant activity (Nazareth *et al.,*2014)
Coriandrum sativum Apiaceae	Aerial part	Umbelliferone and Beta-Ionone	α-amylase and α-glucosidase inhibitors (Rayar and Rajamanickam, 2016)
Musa cavendishi Musaceae	leaves	Flavonoid diglucosides; kaempferol rutinoside and quercetin-3-O-rutinoside	Inhibit alpha amylase (Abdel- Raziq *et al.,* 2016)
Persea Americana Lauraceae.	Peel and seed	Unknown	Inhibition of alpha amylase and Antioxidant activity (Smitha *et al*.,2016)
Croton bonplandianum Euphorbiaceae.	Leaf	Phytol, Heptadecanol, 1-Nonadecene, Phenol, 2,4-bis (1,1dimethylethyl), Cyclotetracosane	Inhibition of alpha amylase and Antioxidant activity (Sumathy *et al.*, 2013)

2.4.2 Mechanism of Action of Plant Compounds

Various types of mechanisms are associated with phytocompounds like causing a change in carbohydrate metabolism, preventing and restoring the function of beta-cells, insulin releasing activity, improving glucose uptake and utilization and also the antioxidant properties which offer an exciting opportunity to develop them into novel therapeutics as indicated in Figure 6. Therefore, a proper scientific evaluation and screening of plant by pharmacological tests followed by chemical investigations is necessary.



(Seema and Chanchal, 2014)

Figure 6

Mechanism of action of antidiabetic herbs

Through various studies, it has been shown that the effects of the main component of antidiabetic plants was with direct action on insulin secretion from the pancreas. They established that improvement of β cell function and insulin secretion is possible with antioxidant compounds via suppression of oxidative stress, although other mechanisms are also important such as cytokine-induced impairment, suppression of NF-κB, activation of uncoupling protein 2, insulin-like activity and increasing intracellular calcium (Tabatabaei-Malazy *et al.*, 2012).

The potential mechanisms of natural products as antidiabetic agents are established through inhibition of glucose absorption in the gut, enhancement of glucose uptake and upregulation of glucose transports, activation of nuclear receptors, increasing adiponectin release, modification of glycogen metabolism, insulinomimetic and insulinotropic effects, elevation of D-chiro-inositol, incretin mimetic and incretin enhancers, role of endogenous opioids on glucose homeostasis and antioxidants. New types of antidiabetic drugs have been introduced in treatments in recent years, such as DDP-4 inhibitors, GLP-1 analogs, and cannabinoid receptor Type1 antagonist. Several studies reported that some natural products could act by these mechanisms (El-Abhar and Schaalan, 2014).

Ramírez *et al*. (2012) screened the inhibitory effect of hydroethanolic extracts from 23 medicinal plants used in Mexico as antidiabetics on glucosidase obtained from rat intestinal mucosa. Li *et al*. (2014) recently investigated and established a ligand screening method based on enzyme-immobilized magnetic nanoparticles integrated with high performance liquid chromatography for studying new α-amylase inhibitors of plant origin. The most widely used antidiabetic herbs and their therapeutic action are summarized in Table 4.

Table 4

Classification of herbal antidiabetics according to their therapeutic action

Botanical name	Therapeutic action
Panax ginseng *Allium cepa* *Azadirachta indica* *Eugenia jambolana* *Pterocarpus marsupium* *Medicago sativa*	Increasing insulin secretion from beta cells of pancreas
Morusbomoysis *Pterocarpus marsupium* *Tinospora cordifolia* *Gymnema sylvestre*	Regeneration of γ-cells of the islets of Langerhans
Cyamposis tertragonoloba *Ocimum sanctum*	Reduction in absorption of glucose from gastrointestinal tract
Aralia elata	Inhibition of aldose reductase activity
Zingiber officinale *Cyamospsis tetragonolobus* *Grewia asiatica*	Increased glucose utilization
Lythrum salicaria	Reduction of lactic dehydrogenase and γ-glutamyl transpeptidase
Allium sativum	Inhibition of glycogen-metabolizing enzymes
Trigonella foenum graecum	Increased glyoxalase 1 activity in liver Increased the creatine kinase levels in tissues
Bauhinia megalandra	Inhibition of glucose-6-phosphate system
Momordica charantia	Oxygen radical scavengers
Morus alba	Protection of pancreatic beta cells from degeneration and diminish lipid peroxidation

Tripathi *et al*. (2011) and Singab *et al.* (2005)

2.4.3 *In silico* Studies and Alpha amylase Inhibitors

In silico methods can be used for the estimation of chemical interactions with drug metabolizing enzymes including prediction of possible metabolites (Kirchmair *et al.,* 2012). A computer simulation method that assists in the prediction of conformation of a receptor-ligand complex is called as molecular docking. The receptor is frequently a protein molecule whose X-ray crystallography arrangement is known while a ligand may be either a small molecule or active pharmacophore. It is thus used in virtual screening events where a large amount of compounds are docked against one target molecule and the excellent hit is gained. The molecular docking methods were developed with a purpose to acquire a rapid procedure for the detection of new lead compounds or to reproduce an experimental conformation at elevated accuracy for the justification with experimental data (Arumugam *et al.,* 2014).

In silico techniques help identifying drug target via bioinformatics tools. They can also be used to explore the target structures for possible active sites, generate candidate molecules, dock these molecules with the target, rank them according to their binding affinities and further optimize the molecules to improve binding characteristics (Amuthalakshmi and Anton, 2013).

Docking programs simulate how a target macromolecule (receptor, enzyme, or nucleic acid) interacts with small molecule ligands, such as substrates, inhibitors, or other drug candidates. To model the binding between the ligand and the target molecule, their known three dimensional structures are superimposed and the fit between the key sites of the target molecule and the ligand is then analyzed. By using molecular mechanics, the programs usually determine the binding energy between the host's binding site and the ligand, a feature used to predict and describe the efficacy of the binding (Thomas, 2007).

The computational methodology, involving molecular docking analysis could be an easy gate-way for searching effective drugs of natural origin against diseases (Mohapatra *et a*l., 2015). Management of Type 2 Diabetes by conventional therapy involves the inhibition of degradation of dietary starch by glucosidases such as α-amylase and α-glucosidase. Understanding the mechanism of action and inhibition mechanism of the target enzyme is critical in the early discovery and development of drug candidates. The purpose of a mechanism of action is to characterize the interaction of a compound with its target, to understand how the compound interacts with the target and how natural substrates at physiological concentrations will modulate this activity. Studies regarding

interaction between inhibitor and α- amylase have significance in obtaining a better insight in the mechanism of α-amylase inhibition. Thus, the molecular docking predictions are used to find the probable inhibition mechanism (Wulan *et al.,* 2015).

2.5 Medicinal Plants Chosen for the Study

2.5.1 *Momordica charantia*

Momordica charantia belongs to the family Cucurbitaceae and is commonly known as bitter melon. Bitter melon grows in tropical and subtropic areas, including parts of East Africa, Asia, the Caribbean and South America, where it is used as a food as well as a medicine. It produces beautiful flowers and prickly fruit .The fruit of this plant lives up to its name-it tastes bitter. Although the seeds, leaves and vines of bitter melon have all been used, the fruit is the safest and most prevalent part of the plant used medicinally (Saifi *et al.,* 2013). *Momordica charantia* is recognized by different local names in the tropics and subtropics as shown in Table 5.

Table 5

Local names of *Momordica charantia*

Language	Local names of *Momordica charantia*
English	Bitter gourd, Balsam pear, Balsam apple
Tamil	Pakal, Pavaka, Paharkai
Hindi	Karela, Kardi
Malayalam	Kaipp, Kaippavlli, Paval
Telugu	Koekara, Kaaya
Kannada	Hagal

(Ariyawansa, 2011)

Medicinal value of *Momordica charantia* has been attributed to phenols, flavonoids, isoflavones, terpenes, anthroquinones and glucosinolates, all of which confer a bitter taste (Snee *et al*., 2011).Some of the major phytochemical compounds of various parts of *Momordica charantia* are presented in Table 6 and Ethno botanical uses of different of parts of *Momordica charantia* and their medicinal application are given in Table 7.

Table 6

Major phytochemical compounds of various parts of *Momordica charantia*

Source	Phytochemicals
Plant body	Momorcharins, momordenol, momordicilin, momordicins, momordicinin, momordin, momordolol, charantin, charine, cryptoxanthin, cucurbitins, cucurbitacins, cucurbitanes, cycloartenols, diosgenin, elaeostearic acids erythrodiol, galacturonic acids, gentisic acid, goyaglycosides, goyasaponins, multiflorenol, glycosides, saponins, alkaloids, fixed oils, cucurbitane-Typetriterpenes, proteins and steroids, momordicine, charantin, polypeptide-p insulin and ascorbigen.
Fruit	**Amino acids** – aspartic acid, serine, glutamic acid, threonine, glutamic acid, threonine, alanine, g-amino butyric acid pipecolic acid and luteolin. **Fatty acids** – Lauric, myristic, palmitic, palmitoleic, stearic, oleic, linoleic and linolenic acid
Seeds	**Enzyme**-Urease **Amino acids** – valine, threonine methionine, isoleucine, leucine, phenylalanine and glutamic acid

(Anilakumar *et al.,* 2015)

Table 7

Ethnobotanical uses of different parts of *Momordica charantia*

Plant Part	Ethnobotanical uses	Type of extract
Leaf	Purgative in children Anti-helmintic, treatment of leprosy, piles and jaundice; treatment of ringworm, bowel movement, cough, congestion and chest pain	Oral Hot water extract
Vein and shoots	Emmenagogue; shoots used to treat pneumonia and leucorrhagia	Hot water extract
Root	Used as an abortifacient, root paste administered in milk to reduce the scars in small pox	Decoction
Fruit	Used for jaundice, piles, leprosy, rheumatism, gout, Diabetes, hydrophobia; treatment of malarial fevers Anti-helminthic	Fruit juice
Seed	Seeds are boiled and the extremely bitter effusion is said to produce instantaneous vomiting and used to reduce fat	Hot water extract or oral

(Anilakumar *et al.,* 2015)

Ali *et al.* (2016) had reported that the accumulation of advanced glycation end products (AGEs) and oxidative stress underlie the pathogenesis of diabetic complications. Antiglycation and antioxidant properties of aqueous extracts of *M*omordica *charantia* pulp, flesh and charantin were studied *in vitro.* It was found that *M*omordica *charantia* extracts were capable of preventing AGE formation *in vitro*. This activity may be due to the antioxidant properties, particularly the total phenolic content of the extracts. Thus, the use of *M*omordica *charantia* deserves more attention, as it may not only reduce hyperglycaemia but also protect against the build-up of tissue AGEs and reduce oxidative stress in patients with Diabetes.

Dhivya and Rajasimman, (2015) had reported that silver nano particles synthesized from water extracts of *Momordica charantia* had significant effect on inhibition of the enzyme alpha amylase. The synthesized silver nanoparticles showed significant effect on antidiabetic activity. Zuraini *et al*. (2012) have reported *in vitro* anti-diabetic activities of Polypeptide-k and oil Isolated from seeds of *Momordica charantia*. Both polypeptide k and seed oil showed potent inhibition of α-glucosidase enzyme and α-amylase. Collectively, the *in vitro* assay strongly suggests that both polypeptide k and seed oil from *Momordica charantia* are potent potential hypoglycemic agents.

Copper nanoparticles prepared by green synthesis from ethanol extract of bitter gourd were investigated for its carbohydrate digestibility efficacy. The assay results of copper nanoparticles showed dose dependent activity against α - amylase enzyme and α - glucosidase enzyme. Therefore, it was suggested that colloidal copper nanoparticles could be used as an effective material for the treatment of Diabetes by controlling blood glucose level (Chizoba, *et al*., 2016).

Momordica charantia plant and fruit extracts and different compounds seem to exert their beneficial effects via several mechanisms like 5’ AMP-activated protein kinase (5’adenosine monophosphate-activated protein kinase (AMPK), Peroxisome proliferator-activated receptor (PPARs), Liver X receptors (LXRs), Sterol regulatory element-binding protein (SREBPs), Sirtuin (Sirts) mediated glucose and fat metabolism in various tissues which are directly related to the beneficial effect of controlling and treating Diabetes Mellitus, dyslipidemia and obesity related cardiovascular complications. However, a knowledge gap in research was observed in the field of any direct effect of this plant on cardiac function, hypertension and hypercholesterolemia induced atherosclerosis. Further researches are also advocated for eliciting the effect of different dose of bitter gourd in diabetic heart failure and hypertension both in animal and in patients with Diabetes, obesity and cardiovascular complications (Ashraful *et a*l., 2015).

Protein extracts from the fruits of the two varieties of bitter gourd inhibited α-amylase and α-glucosidase *in vitro* and lowered the blood glucose level *in vivo* on par with acarbose when orally administrated to Streptozotocin-induced diabetic rats (Sundar and Madasamy, 2016).

The concept of food as medicine has been a central theme in dietetic and nutritional sciences. In Asian society, *Momordica charantia* has always been treasured as a bitter 'panacea' for different ailments. In addition, thorough screening of literature available on *Momordica charantia* depicted the fact that apart from few case reports, safety and interactions of *Momordica charantia* have remained largely unexplored in human population. *Momordica charantia* may have hypoglycemic effects, but data are not sufficient to recommend its use in the absence of careful supervision and monitoring. Till now no scientific body has issued definite guidelines and clear recommendation for the use of *Momordica charantia* in Diabetes Mellitus (Dipesh *et al*., 2015).

2.5.2 *Trigonella foenum-graecum*

*Trigonella foenum graecum (*Fenugreek) is an annual leguminous bean and belongs to Fabaceae family. The seeds and green leaves of *Trigonella foenum graecum* used as food possess many medicinal applications. India is the largest producer of fenugreek in the world. Total fenugreek production in India was 113 thousand metric tonnes in the year 2012- 2013.In India; it is extensively used as ayurvedic medicine and in China as traditional medicine (Prasad *et al.,* 2014). Fenugreek is consumed in various parts of the world in different forms and has been regarded as a treatment for many ailments known to man (Laila *et al*., 2014). Local names of *Trigonella foenum graecum* are given in Table 8.

Table 8

Local names of *Trigonella foenum-graecum*

Language	Local names of *Trigonella foenum-graecum*
English	Fenugreek
Tamil	Vendayam, Meti
Hindi	Methi, Sag methi (fresh leaves), Kasuri methi (dried leaves)
Malayalam	Uluva
Telugu	Menthulu
Kannada	Menthya

Medicinally, the fenugreek seeds are the most important and useful part of fenugreek plant. These seeds are golden-yellow in colour, small in size, hard and have four-faced stone like structure. The biological and pharmacological actions of fenugreek seeds are mostly attributed to the variety of its bioactive chemical constituents that serve as raw materials for the manufacture of various hormonal and therapeutic drugs (Mehrafarin *et al,* 2010; Priya *et al,* 2011).

Research reports indicate fenugreek to possess immunomodulatory, anti-carcinogenic, anti-helmintic, anti-nociceptive, antioxidant, anti-microbial, anti-ulcer, gastro- hepatoprotective, anti-obesity, anti-hyperglycemic, antidiabetic and hypocholesterolemic effects (Kumar *et al*, 2013). It has been shown to normalize the blood circulation, thereby making the body active and energetic (Laila *et al.*, 2014).

The biological and pharmacological effects of fenugreek has related to the variety of its components namely, steroids, N-compounds, polyphenolic substances, volatile constituents, and amino acids. The compounds identified in fenugreek are galactomannans, proteins high in lysine, tryptophan, lipids, pyridine alkaloids, trigonelline, choline, carpaine, gentianine, flavonoids- luteolin, apigenin, quercetin, orientin, isovitexin vitexin, amino acids 4- hydroxyisoleucine, histidine, arginine, calcium, saponins, glycosides steroidal sapogenins (yamogenin, diosgenin, neotigogenin, tigogenin), sitosterol, cholesterol and vitamins A, B1 and C (Devasena *et al.,* 2014)

Talobi *et al.* (2013) had reported in their studies that fenugreek seed predominantly contains simple alkaloids consisting mainly of trigonelline, choline, gentianine and carpaine; much of the trigonelline is degraded during roasting to nicotinic acid and other pyridines and pyrroles, which probably account for much of the flavour of roasted fenugreek. Hamden *et al*. (2013) demonstrated that the administration of trigonelline to diabetic rats can make it a potentially strong candidate for industrial application as a pharmacological agent for the treatment of hyperglycemia, hyperlipidemia and liver-kidney dysfunctions.

Ethyl acetate and water extracts of *Trigonella foenum graecum* leaves demonstrated its hypoglycemic activity to be mediated through its dose dependent inhibitory activity on carbohydrate hydrolysing enzymes, α-amylase and α-glucosidase (Ganeshpurkar *et al,* 2013). Animal studies have shown that fenugreek seed extracts have the potential to slow enzymatic digestion of carbohydrates, reduce gastrointestinal absorption of glucose and thus reduce post-prandial glucose levels. In addition to this,

fenugreek stimulates glucose uptake in peripheral tissues and has proved to have insulinotropic properties in isolated rat pancreatic cells (Neelakantan *et al.,* 2014).

Ethanolic extract of fenugreek seeds and its major alkaloid, trigonelline both are promising natural antioxidants that act by lowering plasma MDA or increasing the plasma GSH markers and may be used in the treatment of many diseases especially Diabetes Mellitus (Salim and Hamadi, 2012). Seeds also lower the lipid peroxidation in liver of ethanol intoxicated and diabetic rats by scavenging of hydroxyl radicals (-OH) and inhibition of hydrogen peroxide induced lipid peroxidation in rat liver mitochondria (Acharya *et al*., 2011).