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*Review*

# Ameliorative potentials of medicinal plants on the pathophysiological complications of diabetes mellitus: A review

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**Diabetes mellitus is a metabolic disorder with grievous pathophysiological complications which affect various parts of the body and manifesting in different ways which include acute and chronic neuropathy, nephropathy, gastropathy, retinopathy, micro and macro cardiovascular disorders and erectile dysfunction. Incidence and prevalence of diabetes mellitus is fast becoming high in middle and low income countries where about 80% of people living in those countries depend on orthodox medicine. Numerous and varied reports abound in literature on studies conducted to investigate the ameliorative effects of medicinal plants on various pathophysiological complications of diabetes mellitus. This report therefore presents a review of the effects of medicinal plants on the complications of diabetes mellitus stating the components of the plants responsible for these effects and the possible mechanisms.**

**Key words:** Diabetes mellitus, medicinal plants, diabetic complications, neuropathy, nephropathy, gastropathy, retinopathy, cardiovascular diseases, hyperlipidaemia, erectile dysfunction.

## INTRODUCTION

Diabetes mellitus is a metabolic disorder that is marked by elevated blood glucose concentration and excretion of glucose in urine (El-Wakf et al., 2011). The disease occur either because of lack of insulin (a hormone that allows blood glucose to enter the cell of the body to generate energy) or because of the presence of factors that opposes the actions of insulin (Peter, 1993). The result of insufficient action of insulin is an increase in blood glucose concentration higher than 160 mg/dl [8 mmol/L above the normal value of 80 to 120 mg/dl (5.6 mmol/L)] a condition known as hyperglycaemia. The disease is a serious lifelong condition that affects about 8 to 10% of the world's population, out of which about one third do not know they have the disease. International

Diabetes Federation (2011) reported that 366 million people have diabetes in 2011 and by 2030, this would have risen to 552 million. It was also estimated that diabetes caused 4.6 million deaths in 2011 (International Diabetes Federation, 2011).

The commonest symptom of diabetes is thirst, and it is associated with excessive amount of urine as large amounts of glucose are excreted in the urine (Michael, 1999). Other symptoms of the disease include blurry vision from time to time, feeling tired most of the time, losing weight, very dry skin, sores that are slow to heal, getting more infections than usual, slowing of speech and thought, shaking, sweating, unsteadiness, aggressive behaviour, coma and finally unconsciousness (Michael, 1999).

There are three major types of diabetes mellitus; type 1, type 2 and gestational diabetes (International Diabetes Federation, 2011). Type 1 diabetes is caused by an autoimmune destruction of the insulin – secreting beta cells in the pancreas (Lubert, 1995). It is characterized by a partial or complete loss, of insulin producing beta cells and therefore patients require daily injection of insulin. This type of diabetes usually develops during childhood, adolescence or during early adulthood and affects approximately 5 to 10% of all people with diabetes (Dodda and Ciddi, 2014). International Diabetes Federation (2011) reported that Type 1 diabetes affects 78,000 children annually. Although the disease affects only a small percentage of all people with diabetes, it is associated with a greater prevalence of premature complications and mortality than any other forms of the disease (Harris, 1995).

Type 2 diabetes mellitus is the most common type of diabetes mellitus affecting 90 to 95% of people who develop diabetes and it occurs as a result of loss of insulin responsiveness in its target tissues (El-Wakf et al., 2011). Worldwide, about 120 million people suffering from Type 2 diabetes are able to produce insulin but the liver and muscle cells are resistant to its action and most people with type 2 diabetes find out about their diabetic condition after the age of 40, although the numbers of young people, including teenagers, with type 2 diabetes are growing rapidly (Harris, 1995). Increasing age, obesity, diets rich in high glycemic index foods and physical inactivity are risk factors that may enhance the chances of someone developing type 2 diabetes mellitus.

The major complication of diabetes is the damage to the heart and blood vessels which can cause heart attacks, stroke, and poor circulation. These complications are associated not only with elevated blood glucose, but also elevated blood fat (cholesterol) (Ross, 1993). Cholesterol at elevated concentrations tends to deposit on blood vessels, making them narrower, thereby decreasing the delivery of oxygen and nutrients to tissue and increasing the chance of blood to clot (Shor and Phillips, 1999). The effect of narrowing of the blood vessels is the increase of the risk of developing high blood pressure (Mac Mahon, 2000). Diabetic patients also have an increased risk of eyes disease and the damage to the retina associated with diabetes is the leading cause of blindness in adults under age 65 (Ross, 1993). On the other hand, diabetic nephropathy is an important cause of morbidity and mortality, and is now among the most common causes of end-stage renal failure (Peter, 1993). About 30% of patient with type 1 diabetes have developed diabetic nephropathy after 20 years, but the risk after this time falls to less than 1% percent and from the outset, the risk is not equal in all patients (Abbasi et al., 2000).

## PATHOPHYSIOLOGICAL COMPLICATIONS OF DIABETES MELLITUS

Diabetes mellitus is usually accompanied by excessive production of free radicals, and it was recently established that hyperglycaemia induced mitochondrial reactive oxygen species (ROS) production could be a key episode in the progress of diabetic complications (Sayyed et al., 2006). Elevated generation of ROS and the simultaneous decline in antioxidative defence mechanisms observed in diabetic patients could promote the development of complications associated with diabetes mellitus (Sharma et al., 2013). These complications are wide ranging and are due at least in part to chronic elevation of blood glucose levels, which leads to damage of blood vessels (Figure 1). In diabetes, the resulting complications are grouped under “microvascular disease” (due to damage to small blood vessels) and “macrovascular disease” (due to damage to the arteries) (Forbes and Cooper, 2013). Microvascular complications include eye disease or “retinopathy,” kidney disease termed “nephropathy,” and neural damage or “neuropathy,” while the major macrovascular complications include accelerated cardiovascular disease resulting in myocardial infarction and cerebrovascular disease manifesting as strokes (Boon et al., 2006; American Diabetes Association, 2009; Rang et al., 2012). Although the underlying etiology remains controversial, there is also myocardial dysfunction associated with diabetes which appears at least in part to be independent of atherosclerosis. Other chronic complications of diabetes include depression (Nouwen et al., 2011), dementia (Cukierman et al., 2005), and sexual dysfunction (Adeniyi et al., 2011). However, abnormalities of lipoprotein and glucose metabolism are often found in people with diabetes mellitus (Genuth et al., 2003). These abnormalities have been hypothesized to be responsible for the damage to cell membranes which, in turn, results in an elevated production of ROS (Sharma et

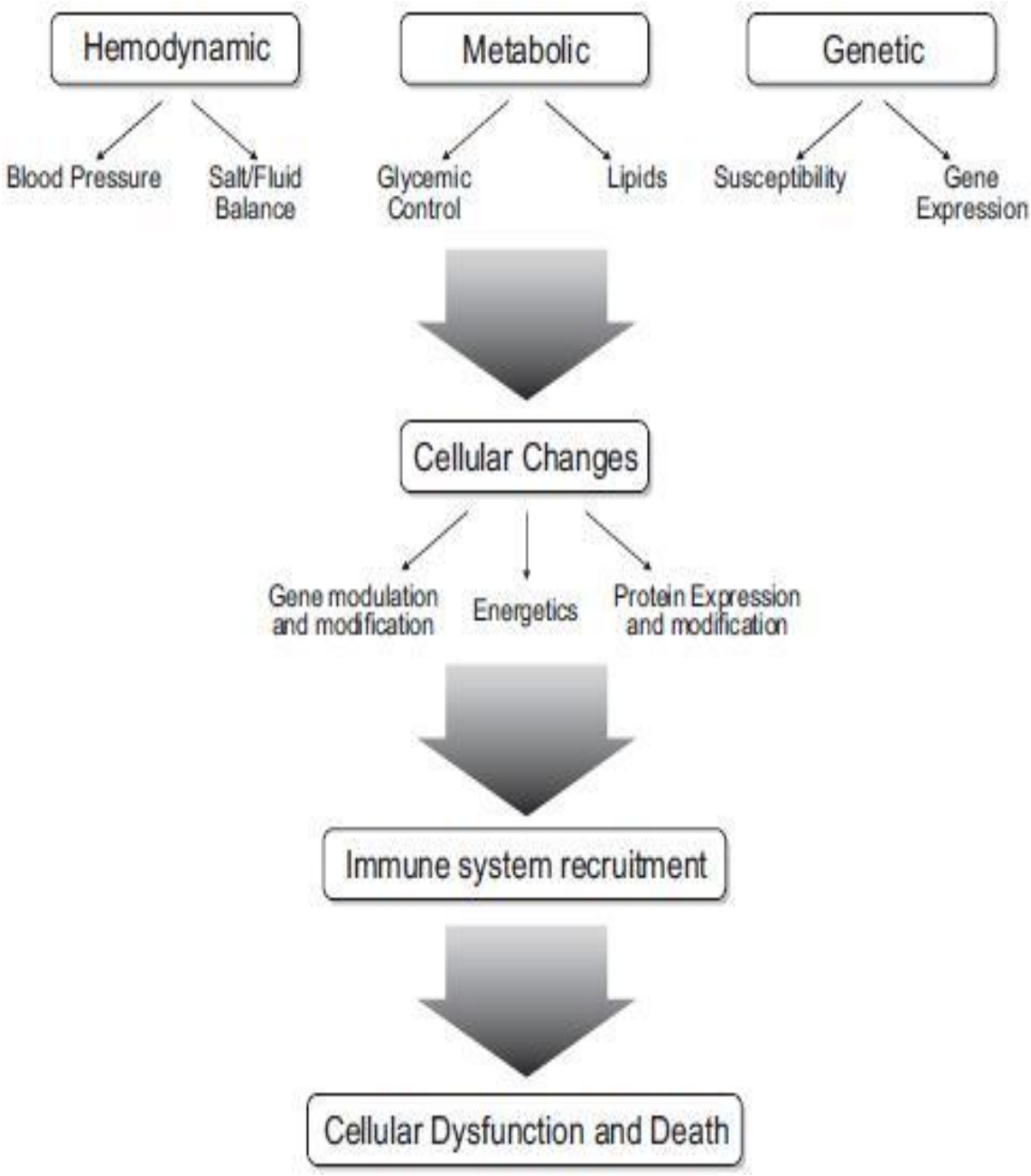


**Figure 1.** Schematic overview of complications of diabetes mellitus. Source: Forbes and Cooper (2013).

al., 2013).

**Mechanisms for the pathophysiological complications of diabetes mellitus**

Four molecular mechanisms have been studied for their role(s) in causing diabetic complications and they include: (i) increase in the flux of glucose through polyol pathway, (ii) increased intracellular formation of advanced glycation end-products (AGEs), (iii) activation of protein kinase C (PKC) and (iv) increased flux through the hexosamine pathway (Brownlee, 2001). Among these, polyol pathway (Figure 2) plays an important role in the development of

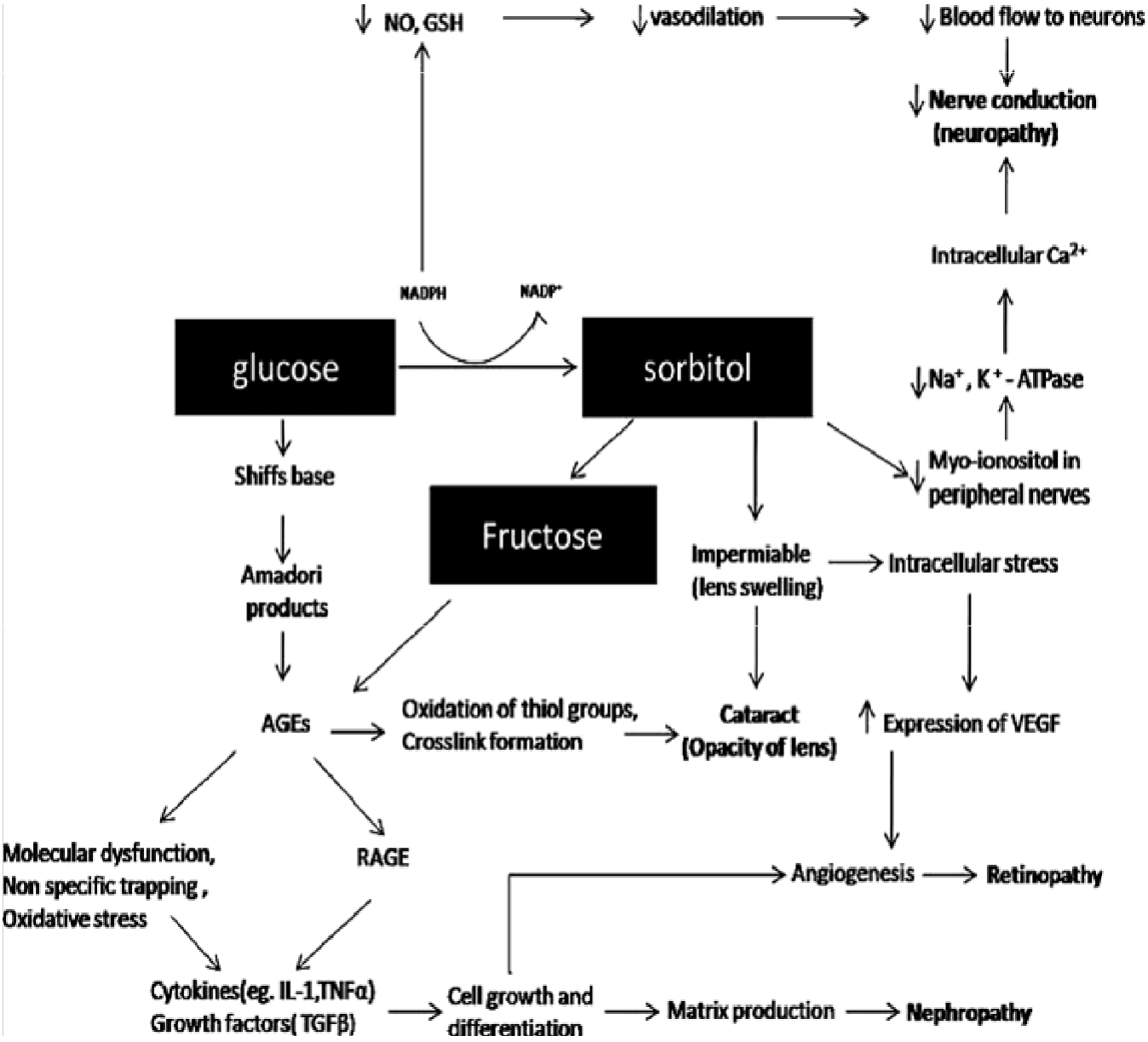


**Figure 2.** Flow diagram illustrating interplay between the polyol pathway, oxidative stress and diabetic complications. Source: Dodda and Ciddi (2014).

complications in DM (Dodda and Ciddi, 2014). Aldose reductase (AR), which is the first enzyme in the polyol pathway, is a cytosolic, monomeric oxidoreductase enzyme that catalyses the NADPH-dependent reduction of glucose (Wilson et al., 1992). In the polyol pathway, sorbitol is oxidised to fructose by the enzyme sorbitol dehydrogenase, with $NAD^+$ reduced to NADH (Dodda and Ciddi, 2014). Hyperglycaemia-induced polyol flux leads to increase in sorbitol-induced osmotic stress, decreased $Na^+$ /$K^+$-ATPase activity, an increase in cytosolic NADH/$NAD^+$ ratio and a decrease in cytosolic NADPH (Lee and Chung, 1999). As NADPH is required for regenerating reduced glutathione (GSH), this could induce or exacerbate intracellular oxidative stress leading to changes in respiration, membrane metabolism and oxidative resistance (Garcia et al., 2001).

Although large varieties of drugs have been developed with potent *in vitro* aldose reductase inhibitor (ARI)

activity, yet, very few of them are clinically available because of undesirable side effects and poor pharmacokinetics (Dodda and Ciddi, 2014). This has led to an increased search for newer therapies with mild or no side effects. Herbal medicines are popularly used remedies for many diseases by a vast majority of the world's population and herbal formulations have attained widespread acceptability as anti-diabetics, hepato-protective and lipid lowering agents because of large number of phytochemicals present in plants (Atawodi et al., 2014). Available literatures show that there are more than 400 plant species showing anti-diabetic activity with the possible use in the treatment of DM complications (Grover et al., 2001; Shafi et al., 2012). Herbal formulation alone or in combination with oral hypoglycaemic agents sometimes produces good therapeautic responses in some resistant cases where modern medicines alone have failed (Adeyi et al., 2012). Many herbal products have been prescribed for the management of diabetes mellitus in ancient and recent literature (World Health Organization, 2010). The present review aims at a critical appraisal of the available literature(s) on the use of herbs in the management of diabetic complications.

## DIABETIC NEPHROPATHY

Diabetic nephropathy (nephropatia diabetica), also known as Kimmelstiel-Wilson syndrome, nodular diabetic glomerulosclerosis or intercapillary glomerulonephritis, is the condition that occurs when diabetes mellitus causes the kidneys to lose their ability to function properly and it is characterized by high levels of protein usually greater than 0.5 g/24 h in the blood (Shafi et al., 2012; Dodda and Ciddi, 2014). It is a progressive condition culminating into a kidney failure and is now among the most common causes of end- stage renal failure (ESRF) in developed countries (Kim et al., 2009). Pathologically, the first changes seen at the time of microalbuminuria are the thickening of the glomerular basement membrane and accumulation of matrix material in the mesangium. Subsequently, nodular deposits are characteristic, and glomerulosclerosis worsens (heavy proteinuria develops) until glomeruli are progressively lost and renal function deteriorates. Microalbuminuria is an important indicator of risk of developing diabetic nephropathy (Lee, 2003). Progressively increasing albuminuria accompanied by hypertension is much more likely to be due to early diabetic nephropathy (Shafi et al., 2012).

Diabetic nephropathy is one of the most important DM complications affecting 20 to 30% of patients with DM (Ayodele et al., 2004). The onset of diabetic nephropathy is found to be 17 years after the diagnosis of DM (Dodda and Ciddi, 2014). The pathogenesis of DM is attributed to the significant increase of the AR in the glomerulus (Kasajima et al., 2001). Hyperactivation of Aldose reductase in renal cells leads to the generation of AGEs. These AGEs along with the generation of ROS results in the expression and activation of transcription factors like nuclear factor NF-κB and PKC, which are implicated in the pathogenesis of diabetic nephropathy. The AGEs also contribute to the release of proinflammatory cytokines, expression of growth factors and adhesion molecules (Oates and Mylari, 1999). Inhibition of AR in kidney can contribute to the protective effect on diabetic kidney.

## THE USE OF MEDICINAL PLANTS FOR THE TREATMENT OF DIABETIC NEPHROPATHY

Some of the medicinal plants reported to be effective in diabetic nephropathy are:

### *Medicago sativa* (Family: Fabaceae; Common name: Alfalfa)

*Medicago sativa* (Alfalfa) is a perennial flowering plant in the pea family - Fabaceae and is usually cultivated as an important forage crop in many countries of the world. Alfalfa has been used as herbal medicine for over 1,500 years and physicians used young alfalfa leaves to treat disorders related to digestive tract and the kidneys. *M. sativa* leaf extract supplementation has been reported to correct diabetes induced dyslipidaemia, oxidative stress and hepatic renal functions and exerts antihyperglycaemic action as effective as metformin. Leaves of *M. sativa* have been used traditionally in South Africa for treating diabetes in the form of tea (Gray and Flatt, 1997). Owing to its rich source of vitamins and phytoestrogens, it is also used as a food additive in several developed countries.

*M. sativa* has been reported to possess antihyperglycaemic property and insulin releasing action. The result obtained by Ramachandran et al. (2010) indicates an effective glycaemic control in diabetic animals treated with *M. sativa* extract (MSE) along with a better serum lipid profile. MSE might have other extra pancreatic mechanisms of action in mediating its antihyperglycaemic effect apart from the promotion of increased insulin secretion and action. The extra pancreatic mechanisms of glucose homeostasis might involve enhanced peripheral glucose transport and metabolism as potent as insulin even in absence of insulin, suggesting the competence of MSE to act through terminal pathways of insulin signaling and the mechanisms of MSE dependent glucose homeostasis might also be attributed to its potential to lower glucose

absorption. So also, increased levels in lipid peroxidation, renal and hepatic markers dysfunction were normalized by MSE treatment and the effects were comparable to those seen with metformin treatment. Further, compromised levels of antioxidant enzymes and $Na^+$- $K^+$ ATPase in diabetic animals was also brought to normal levels by the powdered leaf of *M. sativa*. MSE also reversed the changes in the levels of serum electrolytes in diabetic animals. These ameliorative changes induced by MSE are more potent than with metformin especially with reference to hepatic dysfunction, providing a basis for the contention that the extract has both hepato and reno protective potentials.

***Ginkgo biloba* (Family: Ginkgoaceae; Common Name: Maidenhair Tree)**

Ginkgos are large trees, normally reaching a height of 20 to 35 m, usually deeply rooted and resistant to wind and snow damage. The tree *Ginkgo biloba* has long been believed to have medicinal properties and its extracts are among the most widely -sold herbal supplements in the world. *G. biloba* extract (GbE), prepared from *G. biloba* leaves, is defined as a complex mixture containing 24% Ginkgo flavoneglycoside (quercetin, kaempferol, and isorhamne) and 6% terpene lactones (ginkgolides and bilobalide) (Hassan and Emam, 2012). It has been used as a therapeutic agent in some cardiovascular and neurological disorders. Zhu et al. (2005) studied the effects of three months oral administration of *G. biloba* leaf in treatment of the renal lesions of early diabetic nephropathy. Indexes such as urinary micro-albumin, alpha-1-microglobulin, immunoglobulin, transferring, retinal binding protein and N-acetyl beta-D-glucosaminidase before and after treatment were compared. The levels of urinary micro-albumin, alpha-1-microglobulin, immunoglobulin, transferring, retinal binding protein and N-acetyl beta-D-glucosaminidase decreased significantly after treatment. The beneficial effects of GbE might be channeled through a combination of one or several mechanisms of action. The combined therapeutic effects are probably greater than that of individual mechanisms and are perhaps the result of the synergistic effects of multiple constituents of the total extract (DeFeudis and Drieu, 2000). The chemical structure of GbE 761, both flavonoid and ginkgolide constituents, is responsible for its remarkable antioxidant/reactive oxygen nitrogen species scavenging activity. The flavonoids preferentially react with hydroxyl radicals and chelate pro-oxidant transition heavy metal ions (Gohil, 2002; Zimmermann et al., 2002). Significant antioxidant activity is consequently one of the most analyzed protective effects of GbE on the central nervous system and the circulatory system. GbE has a number of benefits, including ameliorating hemodynamics, suppressing the platelet-activating factor, scavenging reactive oxygen species and relaxing vascular smooth muscles (Akisü et al., 1998). All of these properties offered a pharmacological foundation for testing GbE for diabetic therapy.

***Glycine max* (Family: Fabaceae; Common name: Soyabean)**

The soyabean is a species of legume native to East Asia and is widely grown for its edible bean which has numerous uses. Soyabean has been researched for its nutritional and health benefits. Lunasin is a peptide found in soyabean and some other cereal grains and has been subject of research focusing on its role in the treatment of cancer, cholesterol, cardiovascular diseases and inflammation. Soyabean have been reported to decrease the progression of diabetic nephropathy by preventing the morphological destruction of the kidney associated with diabetes mellitus (Irritani et al., 1997). Soyabean feeding is known to enhance the conversion of polyunsaturated fatty acids to docosahexaenoic acid. Increased production of this complex lipid has been linked to be beneficial in a variety of ways in the treatment of diseases including renal disease (Shafi et al., 2012). Soyabeans have been shown to reduce urinary albumin excretion and total cholesterol in non- diabetic patients with nephritic syndrome. It may prevent weight loss and morphological disruption of the kidney associated with diabetes mellitus. Soyabean diet improves serum glucose and insulin levels, as well as insulin sensitivity in diabetes. Although the exact mechanism has yet to be elucidated, it is possible that the soluble fiber component of soyabeans may be the most important factor (Anderson et al., 1998). Approximately 15% of the soyabean is composed of insoluble carbohydrates and over 30% of the fiber in soyabeans is of the soluble variety. Moreover, soyabeans are slowly digested and have a low glycaemic index and it contain carbohydrates, fat, protein, vitamins and minerals such as calcium, folic acid and iron (Lavigne et al., 2000) as well as a significant amount of omega-3 fatty acid- alpha-linolenic acid and isoflavones.

***Anacardium occidentale* (Family: Anacardiaceae; Common name: Cashew Tree)**

The cashew tree is a tropical evergreen plant that grows as high as 14 m, but the dwarf cashew growing up to 6 m and many parts of the plants are used in the traditional medicine for the treatment of diseases. In some cases, the seeds are ground into poultice and used in the

treatment of snakebites, the fruits, barks and leaves are used as antifungal, antipyretic and antidiarrheal agents (Akash et al., 2009). Furthermore, Leonard et al. (2006) reported that cashew seed can reduce diabetes induced functional and histological alterations in the kidneys and the hypoglycaemic action of this plant is mostly seen in experimental type I diabetes. Streptozotocin induced diabetes in rats has been reported to be associated with functional and morphological changes in the kidney (Leonard et al., 2006). Albino rats receiving graded doses of hexane extract of this plant (150 and 300 mg/kg/day) showed a significant reduction in blood glucose level, total protein excreted, glycosuria and urea in diabetic rats as reported by Leonard et al. (2006). Leonard et al. (2006) further observed that the histopathological study showed significant reduction in accumulation of mucopolysaccharides in the kidneys of diabetic animals. Phytochemical analysis of the cashew seed has revealed the presence of alkaloids, polyphenols and saponins.

***Vernonia amygdalina*** **(Family: Asteraceae; Common Name: Bitter Leaf)**

*Vernonia amygdalina*, a member of the Asteraceae family, is a small shrub that grows in the tropical Africa. *V. amygdalina* typically grows to a height of 2 to 5 m and the leaves are elliptical and up to 20 cm long with a rough bark (Ijeh and Ejike, 2011). African common names of *V. amygdalina* include *grawa* (Amharic), *ewuro* (Yoruba), *etidot* (Ibibio), *onugbu* (Igbo), *ityuna* (Tiv), *oriwo* (Edo), *chusar-doki* (Hausa), *mululuza* (Luganda), *labwori* (Acholi), and *olusia* (Luo) and *Ndolé* (Cameroon) (Egedigwe, 2010; Kokwaro, 2009). *V. amygdalina* is among medicinal plants reported to be used in traditional settings for the management of ailments. Report by Atangwho et al. (2010) showed *V. amygdalina* to restore the damage previously done to the beta cells of the pancreas that is, protective ability of the extracts on the pancreas, as the probable mechanism of action in exerting anti-diabetic action.

Iwara et al. (2013) investigated the effects of combined extracts of *V. amygdalina* (VA) and *Moringa oleifera* (MO) on streptozotocin induced kidney damage in experimental rat models. Significant increases ($p < 0.05$) were observed in $K^+$, $Na^+$, $Cl^-$ and urea concentration in groups treated with VA, MO, and MO/VA. This observation may be attributed to the reported presence of bioactive component that are present in these plants and consistent with findings of Musabayane (2012) and Mapanga et al. (2009), which shows that combined leaf extracts of *V. amygdalina* and *M. oleifera* which possess hypoglycemic effect, has the ability to excrete electrolyte in streptozotocin diabetes mellitus, suggesting that this plant may be beneficial in the management of renal dysfunction associated with diabetes mellitus. The result therefore suggests the synergistic effects of the plants in amelioration of nephrotoxicity associated with diabetes mellitus.

***Camellia sinensis*** **(Family: Theaceae; Common name: Green tea, Chaay)**

*Camellia sinensis* is the species of plant whose leaves and leaf buds are used to produce the popular beverage tea and it is native to East, South and Southeast Asia, but it is today cultivated across the world in tropical and subtropical regions (Ming, 1992). *C. sinensis* is an evergreen shrub or small tree that is usually trimmed to below 2 m when cultivated for its leaves. The seeds of *C. sinensis* and *Camellia oleifera* can be pressed to yield tea oil, an essential oil that is used for medical and cosmetic purposes. The leaves of the plant however have been used in traditional Chinese medicine and other medical systems to treat asthma (functioning as a bronchodilator), angina pectoris, peripheral vascular disease, and coronary artery disease. Recent medical research on tea (most of which has been on green tea) has revealed various health benefits, including anti-cancer potential, effects on cholesterol levels, antibacterial properties and positive effects for weight loss (Ming, 1992). It is considered to have many positive health benefits due to tea's high levels of catechins, a type of antioxidant. Among other interesting bioactivities, (-)-catechin from *C. sinensis* was shown to act as agonist of PPARgamma, nuclear receptor that is current pharmacological target for the treatment of diabetes type 2 (Wang et al., 2014).

Ribaldo et al. (2009) reported that green tea can prevent diabetes and hypertension-related renal oxidative stress as well as attenuate renal injury. In their experiment, spontaneously hypertensive rats (SHR) with streptozotocin induced diabetes and nondiabetic SHR were treated daily with tap water or freshly prepared green tea. After 12 weeks, the systolic blood pressure did not differ between treated and untreated nondiabetic or diabetic rats. However, body weight was less and glycaemia was greater in diabetic SHR rats than in no diabetic rats. Renal oxidative stress variables were greater in diabetic rats. The oxidative stress parameters were significantly less in rats treated with green tea. These findings suggest that the consumption of green tea may reduce nephropathy in diabetic hypertensive patients.

***Cinnamomum zeylanicum*** **(Family: Lauracaeae; Common name: Dalchini)**

*Cinnamomum zeylanicum* (new botanical name:

*Cinnamomum verum*) trees can grow up to a height of 10 to 15 m and the leaves are ovate-oblong in shape, with flowers that are greenish in colour which are arranged in panicles. In addition to its culinary uses, in native Ayurvedic medicine Cinnamon is considered a remedy for respiratory, digestive and gynaecological ailments. Almost every part of the cinnamon tree including the bark, leaves, flowers, fruits and roots, has some medicinal or culinary use. The volatile oils obtained from the bark, leaf and root barks vary significantly in chemical composition, which suggests that they might vary in their pharmacological effects as well (Shen et al., 2002). The different parts of the plant possess the same array of hydrocarbons in varying proportions, with primary constituents such as; cinnamaldehyde (bark), eugenol (leaf) and camphor (root) (Gruenwald et al., 2010). Thus cinnamon offers an array of different oils with diverse characteristics, each of which determines its' value to the different industries. For example the root which has camphor as the main constitute, has minimal commercial value unlike the leaf and bark (Paranagama et al., 2010). It is this chemical diversity that is likely to be the reason for the wide-variety of medicinal benefits observed with cinnamon. The ameliorative effect of the cinnamon oil upon early stage diabetic nephropathy due to its antioxidant and antidiabetic effect has been studied against alloxan (150 mg/kg intraperitonally) induced diabetic nephropathy by Mishra et al. (2010).

Histological studies of the kidney revealed the protecttive effect of cinnamon oil by reducing the glomerular expansion, eradicating hyaline casts and decreasing the tubular dilatations. The results indicated that the volatile oil from cinnamon contained more than 98% cinnamaldehyde and that it confers dose-dependent significant protection against alloxan induced renal damage. The maximum decrease in fasting blood glucose has been achieved at the dose of 20mg/kg (Mishra et al., 2010).

***Curcuma longa*** **(Family: Zingiberaceae; Common name: Turmeric)**

Turmeric is a rhizomatous herbaceous perennial plant of the ginger family, Zingiberaceae and it is native in southeast India (Chan et al., 2009). The most important chemical components of turmeric are a group of compounds called curcuminoids, which include curcumin (diferuloylmethane), demethoxycurcumin, and bisdemethoxycurcumin of which the best studied compound is curcumin, which constitutes 3.14% (on average) of powdered turmeric (Tayyem et al., 2006). In addition, there are other important volatile oils such as turmerone, atlantone, and zingiberene and some general constituents such as sugars, proteins, and resins (Nagpal and Sood, 2013). In India, turmeric has been used traditionally for thousands of years as a remedy for stomach and liver ailments, as well as topically to heal sores, basically for its supposed antimicrobial property (Chaturvedi, 2009). In the Siddha system (since c. 1900 BCE) turmeric was a medicine for a range of diseases and conditions, including those of the skin, pulmonary, and gastrointestinal systems, aches, pains, wounds, sprains, and liver disorders. A fresh juice is commonly used in many skin conditions, including eczema, chicken pox, shingles, allergy, and scabies (Khalsa, 2013). The active compound curcumin is believed to have a wide range of biological effects including anti-inflammatory, antioxidant, antitumour, antidiabetic, antibacterial, and antiviral activities, which indicate potential in clinical medicine (Aggarwal et al., 2007). Chronic treatment with curcumin obtained from *Curcuma longa* significantly attenuates both renal dysfunction and oxidative stress in streptozotocin induced diabetic rats.

The results confirmed evidence of oxidative stress in diabetic nephropathy and point towards the possible anti-oxidative mechanism being responsible for the nephroprotective action of curcumin (Sharma et al., 2006).

***Brassica oleracea*** **(Family: Brassicaceae; Common name: Red Cabbage)**

*B. oleracea* has become established as an important human food crop plant, used because of its large food reserves, which are stored over the winter in its leaves. It is rich in essential nutrients including vitamin C and a diet rich in cruciferous vegetables (for example, cabbage, broccoli, cauliflower) is linked to a reduced risk of several human cancers (Verhoeven et al., 1996). It is mainly used as a vegetable and it has anti-oxidant and antihyperglycaemic activities (Shafi et al., 2012). Main constituents are the isothiocyanates and anthocyanins, reduces oxidative diabetic nephropathy (Evans et al., 2002). It contains anthocyanin pigments that are described as free radical scavenging and antioxidant agents. Its extract contains vitamins A, B and C all of which have protective roles against oxidative damage (Fowke et al., 2003). It also contains substantial quantities of isothiocyanates some of which are very potent anti-oxidants. Daily ingestion of red cabbage polar extract (g/kg body weight) ameliorates oxidative stress and diabetic nephropathy (Shafi et al., 2012).

***Ganoderma lucidum*** **(Family: Ganodermataceae; Common name: Lingzhi Mushroom)**

Lingzhi is a mushroom that is soft (when fresh), corky

and flat, with a conspicuous red-varnished, kidney-shaped cap and, depending on specimen age, white to dull brown pores underneath (Arora, 1986). *Ganoderma lucidum*, an oriental fungus has a long history of use for promoting health and longevity in China, Japan and other Asian countries. In Chinese, the name lingzhi represents a combination of spiritual potency and essence of immortality, and is regarded as the "herb of spiritual potency," symbolizing success, well-being, divine power and longevity. Among cultivated mushrooms, *G. lucidum* is unique in that its pharmaceutical rather than nutritional value is paramount. The specific applications and attributed health benefits of lingzhi include control of blood glucose levels, modulation of the immune system, hepatoprotection, bacteriostasis and more. Various polysaccharides have been extracted from the fruit body, spores, and mycelia of lingzhi; they are produced by fungal mycelia cultured in fermenters and can differ in their sugar and peptide compositions and molecular weight (for example, ganoderans A, B, and C). *G. lucidum* polysaccharides (GL-PSs) are reported by Bao et al. (2001) and Wachtel-Galor et al. (2004) to exhibit a broad range of bioactivities, including anti-inflammatory, hypoglycemic, antiulcer, antitumorigenic and immunostimulating effects.

The effects of *G. lucidum* polysaccharide on renal complication in streptozotocin induced diabetic mice were studied by He et al. (2006). From their findings, extract of *G. lucidum* was able to reduce the serum creatinine and blood urea nitrogen levels and urinary albumin excretion compared with diabetic model mice in a dose dependent manner. Increasing serum glucose and triglyceride levels in diabetic mice could also be lowered by *G. lucidum* polysaccharide. It has a capacity to improve the metabolic abnormalities of diabetic mice and prevent or delay the progression of diabetic renal complications (He et al., 2006).

***Indigofera tinctoria* (Family: Fabaceae; Common name: True Indigo)**

True indigo is a shrub, one to two metres high and it may be an annual, biennial, or perennial, depending on the climate in which it is grown. It has light green pinnate leaves and sheafs of pink or violet flowers. The herb is widely used in the Indian system of medicine for epilepsy, nervous disorders, bronchitis and liver ailments (Singh et al., 2001). Extensive research of the last few decades has revealed that the herbal extract is used as an anticardiovascular agent (Narender et al., 2006). It has been used so as to protect rat against hepatoxicity induced by $CCl_4$ and as a liver antioxidant (Sreepriya et al., 2001). The family of bis-indoles known generically as indirubins is the main constituents of *I. tinctoria;* a product from Chinese material medica used to treat myelogenous leukemia and possesses cytotoxic activity (Cragg and David, 2005). The study carried out by Bangar and Saralay (2011) shows that the extract from leaves improved renal creatinine clearance and reduced renal total protein loss demonstrating nephroprotective properties. The organ to body weight ratio studies carried out showed pancreas and liver specific effects of *I. tinctoria* leaves. These results were also supported by histo-pathological studies. It was concluded from the studies that alcoholic extract of leaves in long-term treatment may be beneficial in the management of type-1 and type-2 diabetes.

***Panax quinquefolius* (Family: Araliaceae; Common name: American Ginseng)**

American ginseng (*Panax quinquefolius*) is a perennial herbaceous plant, commonly used in Chinese or herbal medicine and the effects of American ginseng and heat-processed American ginseng on diabetic renal damage using streptozotocin induced diabetes was studied by Kim et al. (2009). The diabetic rats have shown a loss of body weight gain and increase in kidney weight, food intake, and urine volume, whereas the oral administration of heat processed American ginseng at a dose of 100 mg/kg body weight per day for 20 days attenuated these diabetes- induced physiological abnormalities. Among the renal function parameters, the elevated urinary protein levels in diabetic control rats were significantly decreased by the American ginseng or heat processed American ginseng administration, and the decreased creatinine clearance level was significantly increased in rats administered with heat processed American ginseng. These findings indicated that heat processed American ginseng may have beneficial effect on pathological conditions associated with diabetic nephropathy.

## DIABETIC NEUROPATHY

Diabetic neuropathy (DN) is a secondary microvascular complications of diabetes mellitus causing damages to the nerves and is characterized by fall in nerve conduction velocity, severe pain, impaired sensation and degeneration of nerve fibres (Anjaneyulu and Chopra, 2004). It is also characterized by hyper responsiveness to pain typically originating in the extremities, followed by progressive loss of neuronal function in a distal to proximal gradient (Feldman et al., 1997).

There are many different diabetic neuropathies involving different nerve types, which are mainly featured by diffuse or focal damage to peripheral somatic or

autonomic nerve fibres. Hence, DN can be classified into diffuse and focal neuropathies with diffuse neuropathy being more common, chronic and progressive, whereas focal neuropathies are less common and acute in nature (Anjaneyulu and Chopra, 2004). However, all these neuropathies are thought to occur from hyperglycaemia-induced damage to nerve cells and from neuronal ischaemia resulting from hyperglycaemia-induced changes (Edwards et al., 2008).

The exact etiopathogenesis of DN is multifactorial and involves various factors such as hyperglycaemia, neuronal loss, alterations in neurotransmitters and growth factors etc (Anjaneyulu and Chopra, 2004). Other mechanisms of DN include insulin deficiency, oxidative stress, nitrosative stress, ischaemia, osmolyte accumulation, neurotropic factor deficiency, autoimmune nerve destruction, alterations in cellular signaling pathways and gene expression of protein (Kannan, 2000). Increase in sorbitol concentrations by polyol pathway can lead to cellular injury and decrease of myo-ionositol in the peripheral nerves and thereby leading to decrease in $Na^+/K^+$-ATPase activity, which is essential for nerve conduction (Oka and Kato, 2001). Moreover, decreased NADPH results in decreased nitric oxide and reduced GSH production resulting in decreased vasodilatation and increased ROS production and oxidative damage. Thus, substances containing aldose reductase inhibitors are likely to ameliorate the development of diabetic neuropathy.

Although, the precise records of neuropathic pain sufferers are not available, it is estimated that more than one million people worldwide are suffering from this condition (Hall et al., 2006). At present there is no definitive course of treatment available for diabetic neuropathy, as it is not clearly understood. Tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI), anticonvulsants, opioids and topical capsaicin have been used in the management of painful diabetic neuropathy.

The use of all these classes of drugs is restricted by their cost and side effects. Furthermore, these are only moderately effective, produce potential toxicity and develop tolerance, so the need for newer, better tolerated and efficacious treatment is in high demand (Ziegler, 2008). There is now enormous support that herbal drugs may be helpful in the cure and control of neuropathy and this may translate directly or indirectly to the management of diabetic complications.

## The use of medical plants in the treatment of diabetic neuropathy

Some of the medicinal plants with potential use in the treatment of DN are described:

### *Cleome viscosa* (Family: Capparadiceae; common name: Dog mustard)

*Cleome viscosa* is an annual, sticky herb with yellow flowers and lengthy slender pods containing seeds which bear a resemblance to those of mustard with strong penetrating odour (Parimala Devi et al., 2004). The plant contains lignans, flavonoids, saponins, ascorbic acid and polyunsaturated fatty acid, and some other chemical constituents such as glucosinolates, cleomeolide, Stigmasta-5, 24 (28)-diene-3β-*O*-α-L-rhamnoside, kaempferide-3-glucuronide and naringenin glycoside (Sudhakar et al., 2006). Traditionally, herbal formulations of *C. viscosa* are used as laxative, anti-helminthic, stomachic, diuretic and hypoglycemic agents (Rukmini, 1978; Yaniv et al., 1987; Gupta et al., 2009). Rao et al. (2014) investigated the neuroprotective effect of ethanolic extract of *C. viscosa* (EECV) against streptozotocin induced diabetic neuropathy in Wistar rats. Intraperitoneal injection of streptozotozin resulted in significant increase in thermal hyperalgesia and hyperlipidaemia after four weeks. Antioxidant enzyme (superoxide dismutase (SOD), glutathione (GSH) and catalase) levels were reduced and malondialdehyde (MDA) level was increased significantly in diabetic rats as compared to the vehicle control rats. Four weeks of treatment with EECV (100, 200 and 400 mg/kg) attenuated the level of nociceptive threshold significantly ($p < 0.05$) and dose dependently, thus suggesting the role of ROS mediated oxidative stress in nociceptive changes in STZ induced diabetic rats. It also significantly ($p < 0.05$) decreased the elevated levels of lipids, lipid peroxidation and oxidative stress and this was also dose dependent. *C. viscosa* is already proved to have antioxidant properties, and this may trim down the susceptibility of lipids to oxidation and cause the membrane lipids stabilization, thus reducing oxidative stress. The study of Rao et al. (2014) therefore provides investigational evidence of the protective effect of EECV on nociception, hyperlipidaemia and oxidative stress in streptozotocin induced diabetic neuropathy.

### *Aegle marmelos* (Family: Rutaceae; common name: Stone apple/golden apple/wood apple/Bengal quince/bael)

The tree grows throughout deciduous forest of India and ripen fruits are commonly used for delicacy and are also widely used in Indian Ayurvedic medicine for the treatment of diabetes mellitus (Kamalakannan and Stanley, 2003). *A. marmelos* is well known for its antihyperglycemic, analgesic, anti-inflammatory and anti-oxidant properties (Sabu and Kuttan, 2004). Bhatti et al.

(2012) investigated the effect of *A. marmelos* leaf extract (AME) on hyperalgesia in alloxan-diabetic rats. The diabetic animals exhibited first symptoms of hyperalgesia from 7th day of alloxan injection and maximal hyperalgesia was observed between 12th to 14th day of inducing diabetes. The diabetic animals were treated with vehicle (diabetic control), varying doses of AME (25, 50, 100, 200 and 400 mg $kg^{-1}$), fluoxetine (20 mg $kg^{-1}$), propanolol (30 mg $kg^{-1}$) followed by AME (100 mg $kg^{-1}$) and yohimbine (2 mg $kg^{-1}$) followed by AME (100 mg $kg^{-1}$) from 3rd to 14th day of induction of diabetes. AME was found to increase the paw licking and tail flicking latency ($p < 0.05$) as compared to the vehicle treated diabetic controls. The effect of AME was found to be dose dependent with maximum dose dependent increase observed at a dose of 100 mg $kg^{-1}$. Aegeline found in the alcohol extract of *A. marmelos* has been proposed to have a structural similarity to adrenergic receptor ligands and it has been generally accepted that both α and β adrenergic receptors allocated on the membrane surface of beta cells of pancreas regulate the insulin release (Narener et al., 2007). The $\alpha_2$ adrenergic receptors are proposed to be the major adrenergic receptor involved in the modulation of insulin release in pancreatic beta cells (Nakadate et al., 1981). The pretreatment with propanolol did not alter the *perse* effect of AME. On the other hand administration of yohimbine prior to AME was found to attenuate the protective effect of AME. Also, the antinociceptive effect of *A. marmelos* may involve interplay between adrenergic neurons and other neurotransmitters. From the findings, Bhatti et al. (2012) tentatively concluded that AME provides protection against alloxan induced diabetic neuropathy in rats and this effect might be mediated via the autonomic nervous system**.**

***Momordica charantia* (Family: Cucurbitaceae; common name: Bitter melon/bittergourd/balsam pear)**

Bittergourd is one of the popular herbs found in Nigeria and is known in some tribes of Nigeria as Ejirin wewe (Yoruba), Ndeme (Igbo) and Garafun (Hausa) (Komolafe et al., 2012). Various parts of *M. charantia* such as the seed, fruits and even the whole plants has been reported to have beneficial effects in the prevention and treatment of DM in individuals with non-insulin dependent diabetes (Platel and Srinivasan, 1997). It has hypoglycaemic properties as it significantly suppressed the rise in blood glucose concentrations in albino rats (Nicholas et al., 2006).

The first clinical study into the influence of the fresh juice of bittergourd on the management of DM was Akhtar et al. (1981). These findings suggested that the intervention would effectively treat all symptoms of diabetes including polyuria, polydipsia and polyphagia.

Bitter melon contains an array of biologically active plant chemicals including triterpenes, proteins and steroids. In numerous studies, at least three different groups of constituents found in all parts of bitter melon have clinically demonstrated hypoglycemic properties or other actions of potential benefits against DM and these chemical include a mixture of steroidal saponins known as charantins, insulin-like peptides and alkaloids (Tan et al., 2007).

The hypoglycemic effect is more pronounced in the fruits of bitter melon where these chemicals are found in greater abundance (Komolafe et al., 2012). However, administration of a *M. charantia* fraction with potent ARI activity in diabetic rats has been reported to lead to a slight increase in myelinated fibre area, even though, the mechanism for this beneficial effect of *M. charantia* on the structural abnormalities of peripheral nerves in experimental DM was not established (Celia et al., 2003). Furthermore, Komolafe et al. (2012) investigated the effects of *M. charantia* on the histological changes of the left ventricle of the heart in STZ-induced diabetic wister rats.

Histologically, there was evidence of architectural alteration in the myocardium of diabetic animals and the effects were abrogated with the administration of *M. charantia* extract and glimepiride for four weeks and this observation may have been possible due to a reduction in blood glucose level leading to enhanced peripheral glucose utilization. Tripathi and Chandra (2009) also reported that *M. charantia* extracts potentiate the insulin effect by rejuvenation of damaged beta cells. So also, distribution of elastic fibres were observed to be sparsely distributed as evident by the staining intensity in the left ventricle of diabetic rats when compared with the control group and this observation suggests a reduction in the tensile strength and elasticity of the heart. Administration of *M. charantia* and glimperide gradually restored the integrity of these fibres thereby reducing the susceptibility to cardiovascular complications. All these evidences suggest cardio-protective effects of *M. charantia* against anatomical derangements observed in the diabetic group, thus, the findings of Komolafe et al. (2012) showed that the methanolic extract of *M. charanta* has a promising ameliorative effects on the associated cardiac complications implicated in the STZ induced diabetes in rats.

***Moringa oleifera* (Family: Moringaceae, common name: Drumstick tree)**

*Moringa oleifera* is the most widely cultivated species of a monogeneric family, the Moringaceae, which is native to the sub-Himalayan tracts of India, Pakistan, Bangladesh and Afghanistan. It is used in traditional folklore for

treating many ailments such as asthma, spasm, enlarged liver and spleen, infection and nervous debility, ulcer, inflammation and for wound healing (Mishra et al., 2011; Promkum et al., 2010). This tree has in recent times been advocated as an outstanding indigenous source of highly digestible protein, calcium, iron, vitamin C, and carotenoids suitable for utilization in many of the so-called "developing" regions of the world where undernourishment is a major concern. Studies have also shown that the extract of *M. oleifera* leaves also possesses antidiabetic and antioxidant activities (Pari et al., 2007; Jaiswal et al., 2009). Khongrum et al. (2012) investigated the activity of leaf extract of *M. oleifera* in improving neuropathic pain induced by diabetic condition. Diabetic (induced with STZ) rats were induced with neuropathic pain by constricting the right sciatic nerve (CCI) permanently.

Thereafter, all rats were administered the extract of *M. oleifera* leaves at doses of 100, 200 and 300 mg/kg BW once daily in a period of 21 days. The analgesic effect of the plant extract was evaluated using Von Frey filament and hot plate tests every 3 days after CCI throughout 21-day experimental period.

At the end of the experiment, the alteration of oxidative damage markers including malondialdehyde (MDA) level and the activities of superoxide dismutase (SOD), catalase (CAT) and reduced glutathione peroxidise (GSH-Px) in the injured sciatic nerve were also evaluated. The results obtained showed that rats subjected to *M. oleifera* leaves extract at doses of 100 and 200 mg/kg BW significantly reversed the decreased withdrawal threshold intensity and withdrawal latency in Von Frey filament and hot plate tests, respectively. In addition, rats subjected to the medium dose extract also reversed the decreased activities of SOD and GSH-Px and the elevation of MDA level in the injured nerve. Therefore, the decreased MDA level in rats subjected to *M. oleifera* leaves extract at low dose might be due to either the decreased oxidative stress formation or due to the enhanced non-enzymatic scavenging activity. In addition, the possible underlying mechanism contributing the important role on the analgesic effect of *M. oleifera* leaves extract may be attributed not only to the decreased oxidative stress damage but also to other mechanisms.

Based on the previous finding that both the inhibition of calcium channel and cyclo-oxygenase 2 (COX-2) are also playing the role on the hyperalgesia and allodynia in neuropathic pain condition (Muthuraman and Singh, 2011), it was suggested that the mechanism just mentioned may also contribute to the role in the analgesic effect of *M. oleifera* extract especially at a low dose concentration (100 mg/kg). The results obtained therefore suggest that *M. oleifera* leaves extract can attenuate neuropathic pain in diabetic condition.

***Coccinia indica* (Family: Curcubitaceae; common name: Little gourd)**

*Coccinia indica* has been used extensively in Ayurvedic and Unani practice in the Indian subcontinent (Kohli and Kumar, 2014). Ivy plant has been used in traditional medicine as a household remedy for various diseases, including biliary disorders, anorexia, cough, diabetic wounds, hepatic disorders. For the last few decades, some extensive work has been done to establish the biological activities and pharmacological actions of Ivy Gourd and its extracts. Polyprenol (C60- polyprenol (1)) is the main yellow bioactive component of Ivy Gourd and has been shown to have antidyslipidaemic of biological actions. Kohli and Kumar (2014) investigated the use of combined *C. indica* with low dose of acarbose treating diabetic neuropathic pain as well as restoring blood glucose level and antioxidant status. The essence of administering low dose of acarbose to the experimental animals was to reduce hypoglycemic effect due to DM induction. Diabetic rats treated with C*. indica* alone and in combination with low dose of acarbose produced significant decrease in the blood glucose level after 7 weeks of treatment. Blood glucose lowering activity may be due to the inhibition of intestinal glucose uptake, insulin secreting property, insulinotropic activity of the component present in the extract.

Hypoglycaemic action of *C. indica* could be due to its ability to potentiate the insulin effect of plasma by increasing the pancreatic secretion of insulin from the existing beta cells (Venkateswaran and Pari, 2002; Shakya, 2008). Treatment with combined *C. indica* leaf and acarbose showed a significant decrease in blood glucose levels of the diabetic rats. Oxidative induced damage to the beta cells can be prevented by herbal therapy due to potential antioxidant property. It has been reported that saponins, cardenolides, quercetin, terpenoids, flavonoids and polyphenols present in *C. indica* leaf posses the antioxidant, anti-inflammatory properties (Pari and Venkateswaran, 2003). *C. indica* leaf extract decreased the thiobarbituric acid reactive substances (TBARS) level and increased the SOD and CAT level in the diabetes neuropathic rats. Quercetin proved to be capable of stimulating beta cell and inducing insulin secretion. Terpenoids were also found to be responsible for antidiabetic activity of the *C. indica* leaf extract. Untreated diabetic rats showed significant hypersensitivity towards thermal stimuli when compared with normal control.

In preventive therapy the acarbose, CI and combinations produced increase tail flick latency in tail immersion test and paw withdrawal in hot plate test. The increased tail flick latency may be due to their property to control blood glucose level and its analgesic and inflame-matory property (Kamble et al., 1998). Histopathological

studies proved that there is no damage in the sciatic nerve of the groups treated with the ethanolic extract of *C. indica* and its combination with low dose of acarbose. Hence based on the result, it is concluded that ethanolic extract of *C. indica* leaf with low dose of acarbose can be used as antinociceptive agent due to its antidiabetic and antioxidant property.

***Astragalus membranaceus* Bunge (Fisch.) (Family: Leguminosae; common name: Astragalus)**

*Astragalus membranaceus* is an important herb commonly used in Chinese homeopathic homes. It has been used in a wide variety of herbal blends and 'natural' remedies. *A. membranaceus* has been researched for its cardioprotective, anti-inflammatory, and longevity effects. The flavonoid content of *A. membranaceus* may also contribute to its cardioprotective effects. Its poly-saccharide content also protects the heart because it is a potent anti-inflammatory agent, and it is able to reduce cholesterol levels. The main mechanism of *A. membranaceus* is a result of its active ingredients. The protective mechanism of AGS-IV, a new glycoside of cycloartane-type triterpene isolated from the root of *A. membranaceus* (Fisch.) decreases the blood glucose concentration and HbAlC levels, and increases plasma insulin levels. AGS-IV increases the activity of glutathione peroxidase in nerves, depress the activation of aldose reductase in erythrocytes, and decreases the accumulation of advanced glycation end products in both nerves and erythrocytes. Moreover, it elevates $Na^+$, $K^+$-ATPase activity in both the nerves and erythrocytes of diabetic rats. These results indicate that AGS-IV exerts protective effects against the progression of peripheral neuropathy in STZ-induced diabetes in rats through several interrelated mechanisms (Yu et al., 2006).

**DIABETIC RETINOPATHY**

Diabetic retinopathy (DR) is the most common ocular complication in DM and is an important cause of preventable blindness. DR is broadly classified as nonproliferative DR involving intraretinal microvascular changes and proliferative DR involving the formation of new vessels or fibrous tissue or both on the retina. DR primarily effects the microvascular circulation of the retina. The factors leading to these changes are thickening of basement membrane of the capillary wall, increased platelet stickiness and changes in red blood cells (RBCs) resulting in sluggish microvascular circulation and biochemical changes in the form of activation of polyol pathway resulting in tissue damage. Since the retinal ganglionic cells and endothelial cells are endowed with aldose reductase (AR) enzyme, these cells are more prone to damage caused by the activation of polyol pathway leading to DR. Early development of cataract of lens is due to the increased rate of sorbitol formation, caused by hyperglycaemia (Eshrat and Hussain, 2002). Glycosylation of retinal proteins and retinal micro vascular abnormalities lead to retinopathy and blindness (Kelvin and Moss, 1992). Glycosylation of lysine residues of lens proteins also causes cataract formation.

**THE USE OF MEDICINAL PLANTS IN THE TREATMENT OF DIABETIC RETINOPATHY**

A variety of plant preparations have been mentioned in Ayurveda and other indigenous systems of medicine, which are claimed to be useful in diabetes mellitus and their complications (Shukla et al., 2000) and they include the following:

***Azadirachta indica* (Family: Meliaceae; common name: Neem)**

Neem is a fast-growing tree that can reach a height of 15 to 20 m (49 to 66 ft), rarely to 35 to 40 m (115 to 131 ft). It is an evergreen tree, but in severe drought, it may shed most or nearly all of its leaves. *A. indica* Juss leaves have been reputed to possess cardiovascular, antimicrobial, immunomodulatory, hypoglycemic and a number of other effects (Chattopadhyay, 1996). A bitter principle, *nimbi din*, isolated from seeds of neem tree was reported to be effective in reducing fasting blood glucose at a dose of 200 mg/kg in alloxan diabetic rabbits (Sonia and Srinivasan, 1999). Aqueous extract of tender neem leaves was also reported to reduce blood glucose and this effect was due to its ability to block the actions of epinephrine on glycogenolysis and peripheral utilization of glucose (Chattopadhyay et al., 2000). Eshrat and Hussain (2002) carried out a study to investigate the effect of oral feeding of aqueous extract of fresh leaves of *A. indica* in streptozotocin induced diabetes and its associated retinopathy in rats. The streptozotocin injected rats developed not only diabetes as indicated by increased fasting blood glucose values, but also showed external signs of retinopathy by 10 days. The eyes of diabetic rats looked opaque even from outside. After treatment for 16 weeks, the eyes of the treated group of rats appeared normal from outside. Photograph of the retina indicated that the laser spots has disappeared, therefore pointing out that the treatment reversed the changes in the eye, that is, abnormal changes of retinopathy almost disappeared. Treatment of the diabetic rats with aqueous extract of leaves of *A. indica* at

a dose of 250 mg/kg body weight for 16 weeks resulted in gradual but significant fall in blood glucose and improvement in total serum, low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol and triacylglycerol which increased in diabetic rats. Thus, the present study indicates that treatment with water extract of neem leaves has favorable effect not only on blood glucose and glucose tolerance but also on lipid profile and body weight. Another interesting feature of this plant product is that it completely reversed the abnormal change in retina and inflammation of paws. This shows the promising effects of *A. indica* being a useful anti-diabetic agent and its ability to reverse complications of retinopathy and cardiovascular changes in diabetes.

### ***Tinospora cordifolia*** **(Family: Menispermaceae; common name: Giloe)**

*Tinospora cordifolia* is an Ayurvedic plant and it is distributed throughout tropical Indian subcontinent, Sri Lanka and China, ascending to an altitude of 300 m (Sharma et al., 2014). The plant is commonly used in rheumatism, urinary disease, dyspepsia, general debility, syphilis, skin diseases, bronchitis, spermatorrhea and impotence. The arabino-galactan polysaccharide isolated from *T. cordifolia* has been reported to have an anti-oxidant effect in normal animals as well as in diabetic animals. It also reported to be used in treatment of diabetic complications like retinopathy and neuropathy (Agrawal et al., 2012; Nadig et al., 2012). The phytoconstituents of *T. cordifolia* including alkaloids are known to have hypoglycemic effect (Grover et al., 2000; Patel and Mishra, 2011; Patel and Mishra, 2012; Sangeetha et al., 2013). Various chemical constituents have been isolated from different part of *T. cordifolia* and they belong to different classes such as flavanoids, saponin, glycosides, steroids, alkaloids, sesquiterpenoid, polysaccharides diterpenoids lactones, phenolics and aliphatic compounds (Jasuja et al., 2014). Three major groups of compounds; protoberberine, alkaloids, terpenoids and polysaccharides are considered as putative active constituents of *T. cordifolia* (Jasuja et al., 2014).

## DIABETIC INDUCED HEPATOPATHY

Diabetic hepatopathy also known as glycogen hepato-pathy is a disease of the liver which causes lesions to develop on the liver. It is associated with diabetes mellitus, and for unknown reasons, this type of liver disease is also associated with lesions on the skin. One of the possibilities may be a link to metabolic system and a change in the organ systems. Glycogen hepatopathy (GH) has been characterized as a pathologic overloading of hepatocytes with glycogen that is associated with poorly controlled type 1 diabetes mellitus (Fridell et al., 2007). Clinically, it presents with a spectrum of clinical signs and symptoms, including abdominal discomfort, tender hepatomegaly and elevated transaminases.

## THE USE OF MEDICINAL PLANTS IN THE TREATMENT OF DIABETIC INDUCED HEPATOPATHY

Medicinal plants are good source of natural antioxidants believed to exert their effects by reducing the formation of the final active metabolite of the drug- induced systems or by scavenging the reactive molecular species to prevent them from reaching a target site (Kaleem et al., 2005). It has been documented that several medicinal plants have great hypoglycemic effects which is mainly associated with a significant alteration in the activity of liver hexokinase (Bopanna et al., 1997) and glucokinase (Kumari et al., 1995). In addition, Mansour et al. (2002) demonstrated that the administration of several herb extracts could restore the changes in the activities of serum liver enzymes, like transaminases (AST and ALT) as well as alkaline phosphatase (ALP) and lactate dehydrogenase (LDH) of diabetic rats**.** Aminotransferases (AST and ALT) mediate the catalysis of aminotransfer reactions and they are markers for clinical diagnosis of liver injury (Li et al., 2007). ALP is a hydrolase enzyme responsible for removing phosphate group from nucleotides and proteins, it is produced primarily in liver and brain (Han et al., 2006), and it is a marker of hepatic functions (Yoo et al., 2008). LDH is a general indicator of acute or chronic hepatic damage, as well as determining organ, cell and tissue condition (Yoo et al., 2008). Some of the herbs that can be used in the treatment of diabetic induced hepatopathy are described.

### ***Cichorium*** **spp (Family: Asteraceae; common name: Sun flower)**

*Cichorium* spp is a bushy perennial plant and the rhizome is light yellow outside, white from within, containing milky, bitter juice. *Cichorium endivia* is a very highly nutritious plant, with a high content of dietary fibres, potassium and vitamin C (Kopeck, 1998). The antibacterial, antimalarial, cytotoxic, antidiabetic, no-mutagenic and other activities of chicory were evaluated previously by Petrovic et al. (2004). Earlier studies have reported that ethanolic extract of *Cichorium intybus* has antidiabetic and hypolipidaemic activities in STZ-induced diabetic rats (Pushparaj et al., 2007). Similarly, Upur et al. (2009) reported that *Cichorium glandulosum* extract can reduce serum AST, ALT and ALP activities after $CCl_4$ and

galactosamine administration, which induced acute hepatotoxicity in mice, and this suggest that *C. glandulosum* is a potent hepatoprotective agent that could protect liver against the acute injury and this ability might be attributed to its antioxidant potential. Furthermore, from the research carried out by Kamel et al. (2011), the leaf powder of *C. endivia* produced significant hepatoprotective effects by decreasing the activities of serum aminotransferases (AST and ALT), ALP, LDH and liver malondialdehyde (MDA) level as well as liver superoxide dismutase (SOD) and catalase (CAT) activities, and increasing the liver glutathione peroxidase (GPx) and glutathione-S-transferase (GST) activities and reduced glutathione (GSH) level of streptozotocin-induced diabetic rats.

### *Gongronema latifolium* Endl. (Family: Asclepiadaceae; common name: Bush buck)

The origin of the plant is traced to Nigeria in West Africa and the Efiks and Quas in Calabar use *G. latifolium* crude leaf extract in the treatment of malaria, diabetes, hypertension, and as laxative and it is also used as a spice and vegetable (Morebise et al., 2002). Scientific studies have established the hypoglycaemic, hypolipidaemic and antioxidative effects of aqueous and ethanol extracts of *G. latifolium* leaf (Ugochukwu et al., 2003; Ogundipe et al., 2003). Ugochukwu and Babady (2002) reported that *G. latifolium* leaves could exert antidiabetic activities through their antioxidant properties. Morebise et al. (2002) showed that the leaf extract has anti-inflammatory properties. So also, Eleyinmi (2007) investigated the roles of the leaf extract in preservation of food. Some phytochemicals such as B-sistosterol, lupenyl esters, pregnane ester, glycosides, essential oils and saponins are associated with different parts of this herb (Morebise et al., 2002). It is plausible that one or more of these phytochemicals that are found in *G. latifolium* is likely to influence its medicinal activities. Edet et al. (2009) investigated the effect of *G. latifolium* on serum cardiac enzymes in alloxan induced diabetic rat models and normal control rats using graded doses of 80% ethanolic leaf extract of *G. latifolium*. Serum creatine kinase isoenzyme (CKMB) and lactate dehydrogenase (LD) activities increased significantly ($p > 0.001$) in diabetic rats when compared to non-diabetic rats. Serum CK and LD decreased significantly in diabetic and non-diabetic rats treated with *G. latifolium* leaf extract when compared with the control. Moreover, the significantly lowered activities of CK, CKMB and LD at 200 mg/kg body weight and CK and LD at 400 mg/kg body weight scientifically suggest that the leaf extract of *G. latifolium* may have the potential of reducing the factors that produce infarction in the myocardium. This is so because the metabolism of alloxan-induced infarct myocardium may be studied by assessing the level of marker enzyme proteins in the serum. It is interesting to know that as myocardial diseases are rich sources of CKMB, so are skeletal muscular diseases good sources of creatine kinase isoenzyme (Hamm et al., 1992).

Pathological value has been estimated in injured skeletal muscle, therefore the significant reduction in CK enzyme at the dose of 400 mg/kg body weight of *G. latifolium* extract may be due to some physiological effects on muscular activity. This fact may be associated with the efficacy of *G. latifolium* crude leaf extract in the treatment of muscular pains, arthritis and inflammation (Morebise et al., 2002). These data suggest that the effects of *G. latifolium* leaf extract are not dose dependent and hepatotoxic.

## DIABETIC INDUCED HYPERLIPIDAEMIA

Hyperlipidaemia is a known complication of DM and coexists with hyperglycaemia and is characterized by increased levels of cholesterol, triglycerides and marked changes in lipoprotein fractions and the control of hyperlipidaemia is a prerequisite for the prevention of diabetic microangiopathy (retinopathy, nephropathy and neuropathy) and macroangiopathy (ischemic heart disease), cerebral vascular disease and arteriosclerosis obliterans in diabetes (Sharma et al., 2013). Oxidative stress in cells and tissues results from the increased generation of reactive oxygen species and/or from diseases in antioxidant defense potentials (Gumiieniczek et al., 2002). Lipid peroxidation of cellular structures, a consequence of free radical activity in turn seemed to play an important role in aging and late complications of diabetes (Ugochukwu and Cobourne, 2003), disrupting natural antioxidant defence systems and altering antioxidant enzyme activities in various tissues like the liver (Rauscher et al., 2001). On the other hand, an increase in circulating lipids may be a reason for increased lipid peroxidation in diabetes.

Currently, there is a renewed and growing interest in the use of plant-based products as drugs or as ‘leads’ in the manufacture of more potent drugs (Ogbonnia et al., 2008). Several secondary plant metabolites have been shown to modify biological processes, which may reduce the risk of chronic diseases in humans (Ugochukwu et al., 2003).

## THE USE OF MEDICINAL PLANTS IN THE TREATMENT OF DIABETIC INDUCED HYPERLIPIDAEMIA

Some medicinal plants that have been used in the treatment

of Diabetic Induced Hyperlipidaemia are described.

***Helicteres isora* (Family: Sterculiaceae; common name: Indian screw tree)**

*Helicteres isora* is a species of small tree or large shrub found in Asia including India, South china, Malay Peninsula, Java and Saudi Arabia. The bark of *H. isora* has been used in indigenous systems of medicine in India for the treatment of diabetes mellitus since time immemorial. The plant is a shrub or small tree available in forests throughout the Central and Western India. The roots and the bark are expectorant and demulcent and are useful in colic, scabies, gastropathy, diabetes, diarrhoea and dysentery (Kirtikar and Basu, 1995). The fruits are astringent, refrigerant, stomachic, vermifugal, vulnerary and useful in griping of bowels and flatulence in children and possess an antispasmodic effect (Pohocha and Grampurohit, 2001). From the roots, cucurbitacin B and isocucurbitacin B were isolated and reported to possess cytotoxic activity (Bean et al., 1985). The roots have a significant hyperglycaemic effect (Venkatesh et al., 2003). The aqueous extract of the bark showed a significant hypoglycaemic effect (Kumar et al., 2006a), hypolipidaemic activity (Kumar and Murugesan, 2008), lowering effect of hepatic enzymes (Kumar et al., 2006b), and glycoprotein levels (Kumar and Murugesan, 2007) and an antiperoxidative effect (Kumar et al., 2007). The aqueous extract of *H. isora* bark (100 mg, 200 mg/kg body weight) was screened for its antioxidant effect in streptozotocin induced diabetic rats by Kumar et al. (2008). An appreciable decrease in peroxidation products, thiobarbituric acid reactive substances (TBARS), conjugated dienes (CD), and hydroperoxides (HP) was observed in the heart tissues of *H. isora* (HI) treated diabetic rats. The decreased activities of key antioxidant enzymes such as SOD, catalase (CAT), GPx, GST and GSH in diabetic rats were brought back to near normal range upon HI treatment. The results suggest that the effectiveness of the drugs depends, probably, on the accumulative effect of active principles (Peungvicha et al., 1998). From the roots and barks of HI, betulic acid, daucosterol, sitosterol, isorin were isolated (Qu et al., 1991). Furthermore, the present study of Kumar et al. (2008) therefore provides some useful insight into the cardiac antioxidant and antiperoxidative potency of bark of HI in STZ induced diabetes.

***Eleucine coracana* (Family: Poaceae; common name: Black finger millet)**

*Eleucine coracana* is an annual widely grown cereal in the arid areas of Africa and Asia. The millet seed coat contains several phenolic compounds like phenolics, flavonoids, polymeric tannins and anthocyanins, some of which are effective inhibitors of pancreatic amylase and intestinal α-glucosidase (Chethan and Malleshi, 2007). It is also a rich source of phytates and minerals (Shobana et al., 2006). Traditionally, finger millet food preparations are known for their higher sustaining power, lower glycaemic response and higher satiety scores compared with other cereal foods which are usually recommended for diabetic patients. Dietary polyphenols and phytates are known for their ability to reduce carbohydrate digestibility and thereby regulate postprandial glycaemic response (Thompson et al., 1987). Moreover, polyphenols are known to inhibit glucose absorption and prevent advanced glycation end product (AGE) formation (Scalbert et al., 2005).

Okoyomoh et al. (2013) evaluated the antioxidant and antidiabetic properties of seed coat matter (SCM) of grains of black finger millet on 20 and 40% in streptozotocin induced diabetic rats. *E. coracana* exhibited significant antidiabetic activity resulting to a 45% reduction in the diabetic experimental group treated with 40% SCM. Apart from being a rich source of dietary fibre, phytates and minerals, the millet seed coat is a reserve of many health-beneficial phenolic compounds (Shobana et al., 2006; Chethan and Malleshi, 2007). It has been reported that polyphenols reduce fasting hyperglycaemia and attenuate the postprandial blood glucose response in rats (Scalbert et al., 2005). Feeding the experimental rats with various concentration of the SCM exhibited significant protective effect by lowering the serum levels of ALT, AST and ALP. Catalase (CAT) and superoxide dismutase (SOD) activities were increased while the concentration of thiobarbituric acid reactive substances (TBARS) was significantly lowered. Phytate is known to have amylase- inhibitory properties (Knuckles and Betschart, 1987) and a regulatory role in insulin secretion from pancreatic beta cells.

Earlier reports have shown that finger millet phenolics are non-competitive inhibitors of intestinal α-glucosidase and pancreatic amylase (Shobana et al., 2009). As these inhibitors are proven modulators of postprandial glycaemia, they play a significant role in the management of diabetic complications. Phenolic compounds are also known to enhance insulin activity (Anderson and Polansky, 2002), regulate intestinal glucose transporter (GLUT2) (Shimizu et al., 2000), increase muscle glucose uptake and reduce hepatic gluconeogenesis (Liu et al., 1999). Hence, the phytate of the SCM may have complemented the positive role of polyphenols towards regulation of postprandial glycaemia and ameliorating complications associated with diabetes via impeding glucose absorption in the small intestine. There was significant reduction in liver enzyme activity; this could be attributed to the polyphenolic content of the seed coat

matter. Histopathological observations also revealed that SCM of *E. coracana* offered protection to the animals against pancreatic, kidney and liver STZ induced damages. The result indicates that the various concentrations of *Eleusine coracana* grains possess antioxidant and antidiabetic potentials in STZ induced diabetic rats (Okoyomoh et al., 2013).

***Pterocarpus santalinus* (Family: Fabaceae; common name: Red sandal wood)**

*Pterocarpus santalinus* Linn (Fabaceae) (PS), commonly known as "Red sanders", is a small to medium sized deciduous tree, 7.5 m high, with an extremely hard, dark purple heart-wood with a bitter flavor. In the traditional system of medicine, the decoction prepared from the heartwood is attributed to various medicinal properties. It has been used as a cooling agent, antipyretic, anti-inflammatory, antihelmintic, tonic, hemorrhage, dysentery, aphrodisiac, diaphoretic as well as to induce vomiting, to treat eye diseases, mental aberrations and ulcers (Kiritikar and Basu, 1987). The wood in combination with other drugs is also prescribed for snake-bites and scorpion-stings (Warrier et al., 1995). Decoction of the heartwood has been reported as a central nervous system (CNS) depressant and also shown to have anti-inflammatory activity for induced hind paw edema in rats when prepared in formalin (3%). Himoliv, a polyherbal Ayurvedic formulation containing PS as one of the ingredients, has been reported to possess hepatoprotective activity (Bhattacharya et al., 2003).

Heartwood contains pterocarpol, santalin A, B, pterocarptriol, ispterocarpolone, pterocarpo-diolones with *β*-eudeslol and cryptomeridol (Yoganarasimham, 2000). In addition, Aurone glycosides viz., 6-OH-1-Methyl-3', 4', 5'-trimethoxyaurone-4-*O*-rhamnoside and 6, 4'-dihydroxyaurone-4-*O*neohesperidoside, and isoflavone glycoside 4', 5-dihydroxy 7-*O*-methyl isoflavone 3'-*O*-beta-*D* -glucoside are also present (Krishnaveni and Rao, 2000). In addition, the bark extract has a blood glucose level lowering effect in experimental animals (Varma et al., 1991). Methanol and aqueous extracts of heartwood of PS have shown anti-hepatotoxicity in $CCl_4$-induced hepatoxicity (Rane and Gramarc, 1998). Halim et al. (2011) reported that treatment with *P. santalinus* caused significant lowering of blood sugar and improvement in glucose tolerance tests and a decrease HbA1c on regular long term control over blood glucose levels was observed. The antioxidant properties of the red sandal wood extract was also evident, as it caused a reduction in MDA in the brain, liver and muscle tissues. The extract also caused a decrease in the formation of lipid per-oxidase, estimated by TBARS and increased antioxidants SOD, CAT, glutathione peroxidase and glutathione transfers in erythrocytes. Serum creatinine and urine albumin showed decreased levels after treatment with *P. santalinus* and thereafter returned to control values. The kidneys examined histologically for diabetic nephropathy showed regression following treatment. Furthermore, sixteen weeks combination therapy also resulted in decreases in LDL-C/HDL-C, TC, TG and an increase in HDL-C of treated diabetic rats. The use of the aqueous extract of *P. santalinus* caused improvements in glycaemia, lipid peroxidation and brain, liver and heart masses due to its antioxidant properties (Halim et al., 2011).

***Physalis angulata* (Linn) (Family: Solanaceae; common name: Ground cherry)**

*Physalis angulata,* a branched erect annual plant, is widely distributed throughout tropical and subtropical regions of the world and mostly abundant as a weed in gardens, waste lands and pastures, plantations, along roads, in forest along creeks near sea levels and even in cultivated fields (Smith, 1991; Januario et al., 2002). It is a medicinal plant employed in herbal medicine around the world for the treatment of various diseases such as hepatitis, asthma, malaria, dermatitis and rheumatism (Soares et al., 2003). The plant was reported to possess central nervous system depressant effects (Oladele et al., 2013). Some compounds such as physalin A, B, D and F, and glycosides (myricetin-3-o-neohesperidoside) have been isolated from the organic fractions of the plant. Oladele et al. (2013) studied the antidiabetic potentials of the ethanolic root extract of the plant using alloxan induced diabetes mellitus in rats. The 400 and 800 mg/kg of the extract significantly ($p < 0.05$) reduced the blood glucose, cholesterol, triglycerides and low density lipo-proteins, while the high density lipoproteins significantly ($p < 0.05$) increased. This may suggest that the mecha-nisms of actions of ethanolic root extract of *P. angulata* could be by beta cell regeneration in addition to the possibility of stimulation of glucose utilization in the liver and peripheral tissues through the keyenzymes partici-pating in glucose metabolism. It was therefore concluded that the ethanolic root extract of the plant possesses antidiabetic properties as well as anti hyperlipidaemic effects.

***Bauhinia forficata* Link. (Family: Caesalpinaceae; common name: Orchid Tree)**

Orchid tree is a perennial shrub that can be found in the rain forest. It is frequently used as anti-diabetic herbal medicine. It is also used as diuretic for kidney and urinary

disorders (including polyuria, cystitis and kidney stones), as a blood cleanser, to build blood cells and for high cholesterol. Oral administration of kaempferilrin, a major flavonoid compound of the n-butanol fraction from *B. forficata* leaves leads to a significant hypoglycemic effect in normal and in alloxan-induced diabetic rats. In normal rats, kaempferitrin lowers blood glucose only with the higher dose of 200 mg/kg at 1 h after treatment and also shows antioxidant properties (de Sousa et al., 2004). Administration of aqueous, ethanolic and hexanic extracts daily for 7 days at doses of 200 and 400 mg/kg, to the alloxan-diabetic rats, shows significant reductions in plasma glucose, triglycerides, total cholesterol and HDL-cholesterol after treatment with the extracts and glibenclamide (standard drug) as compared to the diabetic controls (Lino et al., 2004).

***Vitex doniana* (family; Verbanaceae; Common Name: Vitex)**

*Vitex doniana* is a perennial shrub widely distributed in tropical West Africa, and some East African countries including Uganda, Kenya and Tanzania (Yakubu et al., 2012). It is found in the middle belt of Nigeria particularly Kogi, Benue, and parts of the savannah regions of Kaduna, Sokoto and Kano states. It is variously called *dinya* (Hausa), *dinchi* (Gbagyi), *ucha koro* (Igbo), *oriri* (Yoruba), *ejiji* (Igala) and *olih* (Etsako) in Nigeria (Yakubu et al., 2012). *V. doniana* is employed in the treatment of a variety of diseases. Hot aqueous extracts of the leaves are used in the treatment of stomach and rheumatic pains, inflammatory disorders, diarrhea, dysentery and diabetes indicating that the plant's leaves may possess antidiabetic properties among others and in North-Central and eastern parts of Nigeria, the young leaves are used as vegetables or sauces and porridge for meals, especially for diabetic patients (Yakubu et al., 2012). Yakubu et al. (2012) investigated the effect of aqueous leaf extract of *V. doniana* on oxidative stress and lipid peroxidation in streptozotocin-induced diabetic and non diabetic rats.

The results indicated that the concentrations of TBARS, AST, ALT, ALP and bilirubin were significantly ($p < 0.05$) increased while the activities of CAT and SOD were reduced in the diabetic animals. The extract significantly increased CAT and SOD activity and reduced TBARS, ALT, AST, ALP and bilirubin concentrations ($p < 0.05$). These reductions in TBARS, ALT, AST, ALP and bilirubin concentrations could lead to a decrease in oxidative stress and hence a reductions in the rate of progression of diabetic complications in the liver. The study concluded that the extract reversed diabetes - induced oxidative changes in the hepatocytes, thus suggesting its use for the management of diabetic complications.

***Albizia lebbeck* Benth (Family: Fabaceae; common name: Lebbek, woman's tongue tree, flea tree, fry wood and koko)**

*Albizia lebbeck* Benth. is a deciduous tree with compound leaves and flat oblong fruits. It is distributed throughout India from the plains upto 900 m in the Himalayas. The bark and flowers of *A. lebbeck* were used to treat arthritis according to the Siddha system of Medicine (Jain, 1991). Hypoglycaemic and/or anti-hyperglycaemic activities have been recorded with numerous plants, many of which are used as traditional herbal treatments of diabetes. *A. lebbeck* Benth. stem bark have been used in traditional medicine along with some preliminary reports on its hypoglycaemic action. Ahmed et al. (2014) evaluated the antidiabetic and antioxidant activities of methanolic extract of stem bark of *A. lebbeck* in streptozotocin induced diabetic rats. Streptozotocin in-duced diabetic rats depicted the increased blood glucose levels, TC, TG, LDL-c, diminished HDL-c level and perturb level of antioxidant markers. Oral administration of methanolic extract of stem bark of *A. lebbeck* at a concentration of 100, 200, 300 and 400 mg/kg b.w daily for 30 days results in a momentous decrease in fasting blood glucose, glycated haemoglobin and enhancement of plasma insulin level as compared with STZ induced diabetic rats. Furthermore, it significantly ($p < 0.05$) decreased the level of TC, TG, and LDL-c, VLDL-c, while it increased the level of HDL-c to a significant ($p < 0.05$) level. The treatment also resulted in a marked increase in reduced glutathione, glutathione peroxidase, catalase and superoxide dismutase and diminished level of lipid peroxidation in liver and kidney of STZ induced diabetic rats.

Histopathological studies suggest the diminution in the pancreatic, liver and cardiac muscle damage. Their research exertion clearly indicates the considerable antihyperglycemic, antihyperlipidaemic, antioxidant and pancreas/renal/hepatic/cardiac protective action of methanolic extract of stem bark of *A. lebbeck*.

***Caesalpinia bonducella* (L) Roxb. (Family: Caesalpinaceae; common name: Fever nut)**

*Caesalpinia bonducella* F. (Leguminosae) is a medicinal plant, widely distributed throughout India and the tropical regions of the world. Its seed kernels are used in the management of diabetes mellitus, in the folklore medicine of Andaman and Nicobar as well as the Caribbean Islands. It has been reported that seeds of the plant possess antidiarrhoeal, antiviral, antibacterial, anti-microbial, antifungal, antidiabetic, antitumor, antipyretic and analgesic, antifilarial, anxiolytic, anti- inflammatory,

antioxidant, immunomodulatory, adaptogenic, anticonvulsant, antispasmodic, nootropic, antifeedant, antiamoebic, antioestrogenic, diuretic, insecticidal, as well as trypsin and chymotrypsin inhibitor proper-ties (Nazeerullah et al., 2012; Moon et al., 2010; Kshirsagar, 2011; Emmanuel and Swaran, 2006). Phyto-chemical analysis of *C. bonducella* seeds has revealed the presence of alkaloids, flavonoids, glycosides, saponins, tannins, and triterpenoids. Phytochemical studies on ethanolic extracts of the bark of *C. bonducella* yielded two new homoisoflavonoids along with five known natural products and all of these compounds exhibited different levels of GST inhibitory and antifungal potentials (Ata et al., 2009). The oral administration of the extracts (300 mg/kg) produces significant antihyperglycemic action as well as lowers the bilirubin levels significantly.

The action of the extracts on diabetes induced hyper-lipidaemia significantly lowers the elevated cholesterol as well as LDL level. The antihyperglycemic action of the extracts may be due to the blocking of glucose absorp-tion. The drug has the potential to act as antidiabetic as well as antihyperlipidaemic (Kannur et al., 2006).

***Aloe arborescens* (Family: Liliaceae; common name: Aloe vera)**

*Aloe arborescens* is a cactus like plant that grows readily in hot, dry climates and currently, because of demand, is cultivated in large quantities (Grieve, 1975). There are some preliminary studies to suggest that oral administration of *Aloe vera* might be effective in reducing blood glucose levels in diabetic patients and in lowering blood lipid levels in hyperlipidaemia (Rajasekaran et al., 2004). Sharma et al. (2013) examined the potential anti-hyperlipidaemic and antihyperlipidaemia efficacy of the aqueous extract from *A. vera* leaf gel in alloxan-induced diabetic mice. Various biochemical parameters, including lipid profile and serum glucose were decreased as well as HDL-C increased. It may be followed that the extract acts as an antioxidant blocking the formation of the reactive oxygen species; mechanism of which remains to be elucidated. This result however demonstrates the anti-diabetic and antihyperlipidaemic activities of *A. vera* leaf extract in diabetic mice.

***Nigella sativa* L (Family: Ranunculaceae; common name: Black cumin)**

*Nigella sativa* Linn. (NS) is a small medicinal herb whose different parts have been reported as therapeutic agents in traditional system of medicines. The seeds of NS are considered carminative, stimulant, diuretic and used in the treatment of mild cases of puerperal fever; they are externally applied for eruptions of skin. Oral administration of ethanol extract of *N. sativa* seeds (300 mg/kg body weight/day) to streptozotocin induced diabetic rats for 30 days significantly reduces the elevated levels of blood glucose, lipids, plasma insulin and improved altered levels of lipid peroxidation products (TBARS and hydroperoxides) and antioxidant enzymes like catalase, superoxide dismutase, reduced glutathione and glutathione peroxidase in liver and kidney. The results confirm the antidiabetic activity of *N. sativa* seeds extract (Kaleem et al., 2006).

***Ficus exasperata* (Family: Moraceae; common name: Sandpaper leaf tree)**

The sandpaper leaf tree is a terrestrial afro-tropical shrub or small trees. In traditional medicine, different parts of this plant (fruit, leaf, sap, bark, and root) are considered medicinally important. In Africa, Yemen and India, various parts of the plant are used as analgesic, antiarthritic, diuretic vermifuges, febrifuge, abortifacient, ecbolic, wound healing, animal fodder and also in general debility, malnutrition, parasitic infection (cutaneous, subcutaneous), leprosy, ophthalmic and oral infections, nasopharyngeal afflictions, arthritis, rheumatism, gout, edema, kidney disorders, diarrhea, dysentery, hemorrhoids and venereal diseases.

The effects of treatment with aqueous extract of *Ficus exasperata* on the pathophysiology and histopathology in alloxan-induced diabetic rats was studied by Adeyi et al. (2012). Hyperglycaemia was recorded in all induced rats after alloxan induction, while treatment with the different concentrations of the plant extract reversed hyperglycaemia within four days. Values of packed cell volume (PCV), haemoglobin concentration (Hb) and RBC were higher in rats treated with the extract than in rats treated with glibenclamide, while ionoregulatory distruptions observed in the diabetic groups reduced significantly ($p < 0.05$) in rats treated with the extract. Lipid profile parameters were higher in rats treated with glibenclamide compared to groups treated with the extract.

Treatment with the plant extract ameliorated the various degenerations observed in the pancreas, liver and kidney in contrast to untreated group and group treated with glibenclamide. Results from this study demonstrated the ameliorative effects of aqueous leave extract of *F. exasperata* on the pathophysiological and histopathological complications of diabetes mellitus.

***Ocimum sanctum* L. (Family: Lamiaceae; common name: Holy Basil)**

It is a tropical annual herb grown all over India and use

for household remediation (Mukherjee et al., 2006). Since ancient times, this plant has been known for its medicinal properties. The aqueous extract of the leaves show significant reduction in blood sugar level in both normal and alloxan induced diabetic rats (Vats et al., 2002). Significant reduction in fasting blood glucose, uronic acid, total amino acid, total cholesterol, triglyceride and total lipid indicate the hypoglycemic and hypolipidaemic effects of tulsi in diabetic rats (Rai et al., 1997). *Ocimum sanctum* leaf powder produced potent hypoglycemic and hypolipidaemic effect in normal and diabetic rats (Ravi et al., 2004).

***Pterocarpus marsupium* Roxb. (Family: Papilionaceae; common name: Indian kino tree)**

*Pterocarpus marsupium*, also known as Vijayasar or the Indian Kino Tree, is a medium to large tree that can grow up to 30 m tall. It is widely used in 'Ayurveda' as 'Rasayana' for management of various metabolic disorders. An aqueous extract of *P. marsupium* wood, at an oral dose of 250 mg/kg, shows statistically significant hypoglycemic activity (Mukhtar et al., 2005). Marsupin, pterosupin and liquiritigenin obtained from this plant show antihyperlipidaemic activity (Jahromi and Ray, 1993). (-)Epicatechin, its active principle, has been found to be insulinogenic, enhancing insulin release and conversion of proinsulin to insulin *in vitro*. Like insulin, (-)epicatechin stimulates oxygen uptake in fat cells and tissue slices of various organs, increases glycogen content of rat diaphragm in a dose dependent manner (Ahmad et al., 1989).

***Trigonella foenum graecum* L. (Family: Papilionaceae; common name: Fenugreek/Menthi)**

*Trigonella foenum - graecum* (Linn.) belonging to the family Papilionaceae commonly known as Fenugreek is an aromatic, 30 to 60 cm tall, annual herb, cultivated throughout the country (Yadav et al., 2014). Menthi is used both as a herb (the leaves) and as a spice (the seed) and cultivated worldwide as a semi-arid crop. Oral administration of 2 and 8 g/kg of plant extract produces dose dependent decrease in the blood glucose levels in both normal as well as diabetic rats (Khosla et al., 1995). Administration of fenugreek seeds improves glucose metabolism and normalizes creatinine kinase activity in heart, skeletal muscle and liver of diabetic rats. It also reduces hepatic and renal glucose-6-phosphalase and fructose -1,6-biphosphatase activity (Gupta et al., 1999). Compounds extracted from the plant have shown cardiotonic, hypoglycaemic, diuretic, antiphlogistic, hypotensive activity and hypocholesterolemic properties. Its major free amino acid 4-hydroxyisoleucine stimulates insulin secretion from perfused pancreas *in vitro* (Al-Habbori and Raman, 1998). The galactomannan-rich soluble fiber fraction of fenugreek may be responsible for the antidiabetic activity of the seeds (Yadav et al., 2014). Insulinotrophic and antidiabetic properties also have been associated with the amino acid 4-hydroxyisoleucine that occurs in fenugreek at a concentration of about 0.55%. *In vitro* studies have indicated that this amino acid causes direct pancreatic betacell stimulation. Delayed gastric emptying and inhibition of glucose transport also have been postulated as possible mechanisms (Yadav et al., 2014).

**DIABETES INDUCED ERECTILE DYSFUNCTION (DIED)**

Impotence or erectile dysfunction is defined as inability to achieve and/or maintain an erection sufficient to permit satisfactory sexual intercourse (Barve, 2013). Erectile dysfunction often is seen as a result of diseases such as diabetes, kidney disease, chronic alcoholism, multiple sclerosis, atherosclerosis, vascular diseases and neurological diseases. Amongst these disorders, diabetes and associated oxidative stress are major contributors for impotency in males. An association with diabetes and erectile dysfunction has been documented since 1798 (McCulloch et al., 1980). It has been reported that 35 to 50 percent of men with diabetes experience erectile dysfunction (National Institutes of Health (NIH) Erectile Dysfunction, 2004). It is usually present within 10 years of diagnosis. The presence of diabetes mellitus not only increases the risk for ED but also other aspects of sexual dysfunction which include sexual drive, ejaculatory function and sexual satisfaction (Burke et al., 2007). The pathophysiology for DIED is multifactorial and it is associated with hyperglycaemia and protein glycosylation thus leading to the production of AGEs (Wolff and Dean, 1987)

These might contribute to DIED either by generating free radicals which in turn quench nitric oxide or damage the potassium channels, both of which are required for the cavernosal smooth muscle relaxation (Giuseppe et al., 2006). There is an elevation of endothelins, which are potent vasoconstrictors in the penis, which inhibit the relaxation (Mills et al., 2001). RhoA/Rho kinase is implicated in decreased production of NO in the penis, which in turn might be responsible for ED (Rees et al., 2002). DIED might also be a consequence of neuropathic damage (Costabile, 2003). Impairment of cGMP dependant protein kinase 1 (PKG-1) plays an important role in DIED (Chang et al., 2004).

Although there are several drugs available in the market, there are limitations in their use either due to high

cost or side effects like hypoglycaemia, weight gain, gastrointestinal disturbances, liver toxicity etc (Dey et al., 2002). In search of first line treatment with better safety and efficacy, research efforts have to be made to find a complete treatment of DIED. The ideal drug to combat DIED is one which involves the NO/cGMP pathway, but a combination of drugs affecting multiple peripheral intracellular targets could also be an option available for treatment.

## THE USE OF MEDICINAL PLANTS IN THE TREATMENT OF DIABETES INDUCED ERECTILE DYSFUNCTION

Medicinal plants are currently being researched for the treatment of diabetes and its complications. The World Health Organizatiobn (WHO) has listed 21,000 plants which are used for medicinal purposes around the world. Of these, 2500 species are found in India (Seth and Sharma, 2004). Some of the herbs used in traditional systems of medicine in India and world over are reviewed in detail for their aphrodisiac and antidiabetic effect. These herbs could be promising candidates for exploring their potential in the treatment of DIED, due to their combined effects on erectile dysfunction and diabetes.

### *Chlorophytum borivilianum* (Family: Asparagaceae; common name: Safed musli)

Safed musli (*Chlorophytum borivilianum*) is a herb, and belongs to family Liliaceae. It was originally grown in thick forests of India (Singh et al., 2012). About 300 species are distributed throughout the tropical and subtropical parts of the world. Tropical and subtropical zones of Africa are the probable centres of origin of the genus. The tubers have been traditionally used for various therapeutic applications. It is used as an aphrodisiac, treatment of diabetes and arthritis, curative for prenatal and postnatal problems etc. The roots contain two major constituents-saponins and mucilage. The roots (tubers) are considered rich in alkaloids, vitamins, minerals, proteins, carbohydrates, saponins, polysaccharides and steroids. It has various therapeutic values as total rejuvenator, antioxidant and Immunomodulator (Singh et al., 2012). It has been found that the fructo-oligopolysaccharide fraction is effective in treatment of streptozotocin induced diabetes (Narsimhan et al., 2006). Furthermore, it is found that the same fraction is also effective in the treatment of sexual dysfunction in hyper-glycemic male rats. The probable mechanism behind this effect is improved steroidogenesis and rejuvenation of the entire system that helps in restoring the failing sexual function in diabetes (Thakur et al., 2009).

### *Dioscorea bulbifera* (Family: Dioscoreaceae; common name: Shoebutton air potato, air yam, bitter yam)

Air potato, *Dioscorea bulbifera*, is an invasive plant not native to Florida but whose present-day distribution includes most of the state (Hammer, 1998). It is a vigorously twining, long-stemmed herbaceous vine which may arise from an underground tuber, although often tubers are inconspicuous or absent. The stems are round to slightly angled in cross section and they twine counter-clockwise. Conspicuous aerial tubers (called bulbils) are pale, round to globose in shape, up to 13 cm wide and are formed in leaf axils. It is these bulbils that give *D. bulbifera* the common name "air potato' (Langeland, 2001). *D. bulbifera* containing steroidal saponin based on diosgenin is also believed to act on the seminiferous tubules presumably by exerting a testosterone like effect (Park et al., 2006). Extract prepared from the bulbs of *Dioscorea* is found to inhibit alpha-amlyase and alpha-glucosidase, thus helping to manage post prandial hyperglycaemia (Ghosh et al., 2012).

## CONCLUSION

Diabetes mellitus is a chronic metabolic disorder of impaired carbohydrates, fat and protein metabolism. Limiting diabetes mellitus without any side effects is a challenge still to the medical system. In recent years, herbs have become a subject of interest because of their beneficial effects on human health. Several plant extracts have been examined for their antidiabetic properties in an attempt to recognize alternative treatment strategies that pose less of a hazard for diabetics. The present review article therefore explored the roles of herbs in treatment of diabetes and diabetic complications such as neuro-pathy, nephropathy, gastropathy, retinopathy, cardio-vascular diseases, hyperlipidaemia and erectile dysfunction.

## Conflict of interests

The author(s) have not declared any conflict of interests.

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