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Some Selected Medicinal Plants with Antidiabetic Potentials

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1. Introduction

1.1. General overview of diabetic mellitus

Diabetes mellitus is a metabolic disorder that is characterized by hyperglycemia associated with impairment in insulin secretion and/or insulin action as well as aberrations in intermediary metabolism of carbohydrates, proteins and lipids. Several reports indicate that annual incidence rate of diabetes mellitus will increase in the future worldwide, especially in the developing countries [1]. The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. Diabetes mellitus may present with classical characteristic features such as blurring of vision, excessive thirst (polydypsia), excessive feeding (polyphagia) excessive urination (polyuria), and weight loss. In its most severe forms, ketoacidosis may develop leading to stupor, coma and, in absence of effective treatment death ensues [2].

Often symptoms are not severe, or may be absent, and consequently hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before the diagnosis is made. On the other hand, other chronic features of diabetes mellitus include progressive development of the specific complications of retinopathy with potential blindness. Nephropathy that may lead to renal failure with risk of foot ulcers, amputation, including reproductive dysfunction [3-6]. People with diabetes are at increased risk of developing cardiovascular, peripheral vascular and cerebrovascular disease [7-8]. These include processes which destroy the beta cells of the pancreas with consequent insulin deficiency and ultimately

resulting in insulin resistance. The abnormalities of carbohydrate, fat and protein metabolism have also been shown to result in deficient action of insulin on target tissues resulting from insensitivity or lack of insulin [9-10].

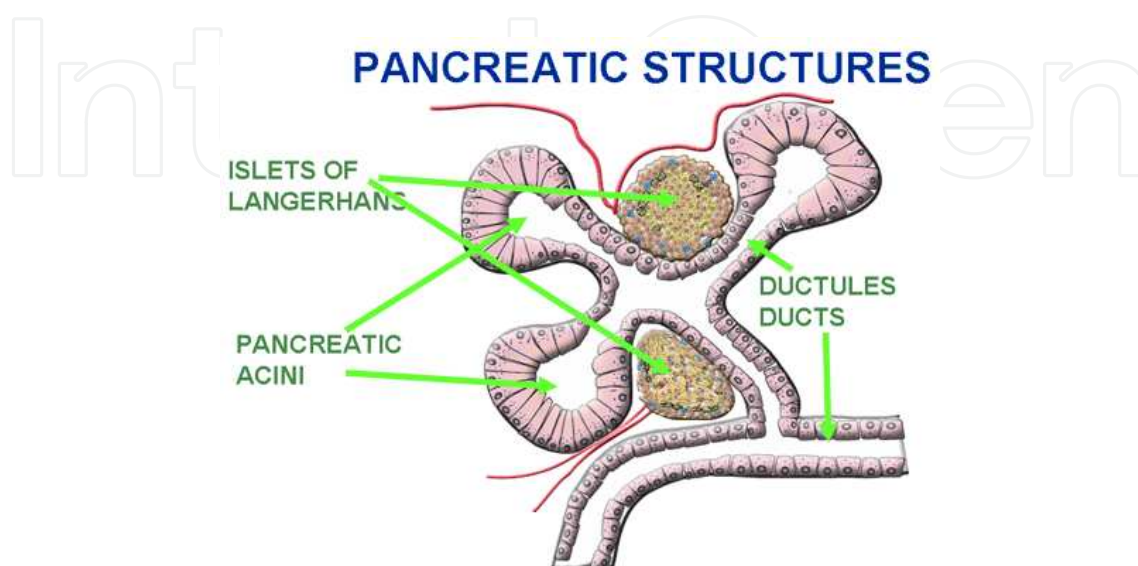


Figure 1. The structure of the pancreas which houses islets of Langerhans

Insulin resistance was recently reported to be associated with obesity and type 2 diabetes[11]. Recent studies suggest that a complex interaction between inflammation, endoplasmic reticulum stress, oxidative stress, mitochondrial dysfunction and autophagy dysregulation play an important role in insulin resistance. The stress-activated c-Jun N-terminal kinase (JNK) has been increasingly recognized as a central mediator of insulin resistance [11] and suppression of the JNK pathway has been shown to improve insulin resistance and glucose tolerance. Also, hyperhomocysteinemia (HHcy) was found to induce insulin resistance in adipose tissue via activation of JNK pathway [12].

2. Classifications of diabetic mellitus

The terms type 1 and type 2 are used for classification based on aetiological factors. The terms insulin-dependent and non-insulin-dependent are used for classifying pathophysiological conditions of diabetes mellitus regardless of the aetiological factors. However, it has been noticed that failure to administer insulin in an insulin-dependent condition can lead to ketosis and with resultant life threatening condition. In the same vein patients whose conditions do not require insulin treatment for prevention of ketosis or for survival are known to require insulin for glycaemic control and such patients are considered to be in a non-insulin-dependent state [13].

2.1. Type 1 diabetes mellitus

Type 1 diabetes mellitus is caused by insulin deficiency due to destruction of pancreatic β -cells principally via an autoimmune reaction that can be triggered by different factors [14]. It can also develop in association with certain hereditary factors, such as Human Leukocyte Antigen (HLA) alleles. Typically, destruction of pancreatic β -cells progresses to absolute deficiency in insulin. This condition develops rapidly in young people and has been found to occur in any age group [14]. Similarly, autoantibodies against islet antigens (islet-associated antibodies) have been shown to increase in the early phase of the disease. Hence, pancreatic β -cell destruction involves autoimmune mechanisms. Therefore, type 1 diabetes mellitus is also known as 'autoimmune' type 1 diabetes mellitus [14, 15-16].

2.2. Type 2 diabetes mellitus

Type 2 diabetes mellitus is one of the most common diseases of the western world and is associated with cardiovascular disease [17]. Type 2 diabetes mellitus (formerly called NIDDM, type II or adult-onset) is characterized by insulin resistance in peripheral tissue and an insulin secretory defect of the beta cell. This is the most common form of diabetes mellitus and is highly associated with a family history of diabetes, old age, obesity and lack of exercise. It is more common in women, especially women with a history of gestational diabetes. Type 2 diabetes mellitus is characterized by derangement of carbohydrate, protein and fat metabolism [18]. Insulin resistance and hyperinsulinemia eventually lead to impaired glucose tolerance [19].

Defective beta cells become exhausted, further fuelling the cycle of glucose intolerance and hyperglycaemia. The aetiology of type 2 diabetes mellitus is multifactorial with evidence of genetic involvement [20-21]. Types of diabetes mellitus of various known aetiologies are grouped together to form the classification called "other specific types." This group includes persons with genetic defects of beta-cell function (this type of diabetes was formerly called MODY or maturity-onset diabetes in youth) or with defects of insulin action; persons with diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis; persons with dysfunction associated with other endocrinopathies (e.g., acromegaly); and persons with pancreatic dysfunction caused by drugs, chemicals or infections. Diabetic cardiomyopathy (DCM) has also been extensively reported in type 2 diabetes mellitus [22-25]. DCM is recognized as asymptomatic progressing structural and functional remodelling in the heart of diabetics, in the absence of coronary atherosclerosis and hypertension. Diabetic cardiomyopathy is a fairly common cause of heart failure in the native population with type-2 diabetes mellitus and results in high morbidity and mortality [22]. Few of the classical symptoms of DCM include marked left ventricular (LV) systolic dysfunction, dysfunction of coronary microcirculation, in relation with glycaemic levels, insulin resistance, sympathetic overdrive, endothelial dysfunction, abnormalities of the angiotensin-renin system, and remodelling/hypertrophy, diastolic dysfunction and impairment of coronary flow reserve (CFR) may be associated in DM [22-24].

3. Global impact of diabetic mellitus

Diabetes mellitus is a disease common to all parts of the world [26]. It is a common and very prevalent disease affecting the citizens of both developed and developing countries. It has been estimated that 25% of the world population is affected by this disease [27]. Currently, India has got the largest number of diabetics and is being called as diabetic capital of the world. Diabetes has significant health consequences for individuals and communities. In fact, many countries face large increases in the number of people suffering from diabetes. The World Health Organization estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000. Additionally, it has been estimated that the number will increase to over 366 million by 2030 and that large increases will occur in developing countries, especially in people aged between 45 and 64 years [28].

A large disparity in total health spending for diabetes among the top 80 most populous countries exists, varying from USD 1.3 million to USD 198.0 billion. The country with the highest total expenditure, the United States of America, will spend 52.7% of the global expenditure. India, the country with the largest population of people living with diabetes, will spend an estimated USD 2.8 billion or less than 1% of the world total. The total diabetes spending in the 18 countries in IDF's African Region will be only USD 1.2 billion, 0.3% of the global total [29]. The absolute level of health expenditure in developing countries appears to be quite low. The lowest 20 spending countries in the top 80 most populated countries will spend less than USD 50 per person per year for managing diabetes and diabetes-related complications. Expenditure at this level cannot even cover the annual wholesale cost of a generic oral agent capable of preventing acute, life-threatening hyperglycaemia [29]. Considering the health services and therapeutic treatments needed to manage diabetes and diabetes-related complications, more health care resources are required to provide adequate diabetes care in the poor countries.

4. Diabetic mellitus and oxidative stress

Diabetes mellitus is associated with an increased risk of cardiovascular diseases mediated via oxidative stress. ROS can directly damage lipids, proteins or DNA and modulate intracellular signaling pathways, such as mitogen activated protein kinases and redox sensitive transcription factors causing changes in protein expression with irreversible oxidative modifications [30-31]. Hyperglycaemia-induced mitochondrial dysfunction and endoplasmic reticulum stress has been shown to promote reactive oxygen species (ROS) accumulation, accelerates cellular damage and significantly contributes to the diabetic complications development and progression [30, 32-33]. PA *et al.* [34] described the mechanism of cardiovascular dysfunction in diabetes mellitus (Figure 2).

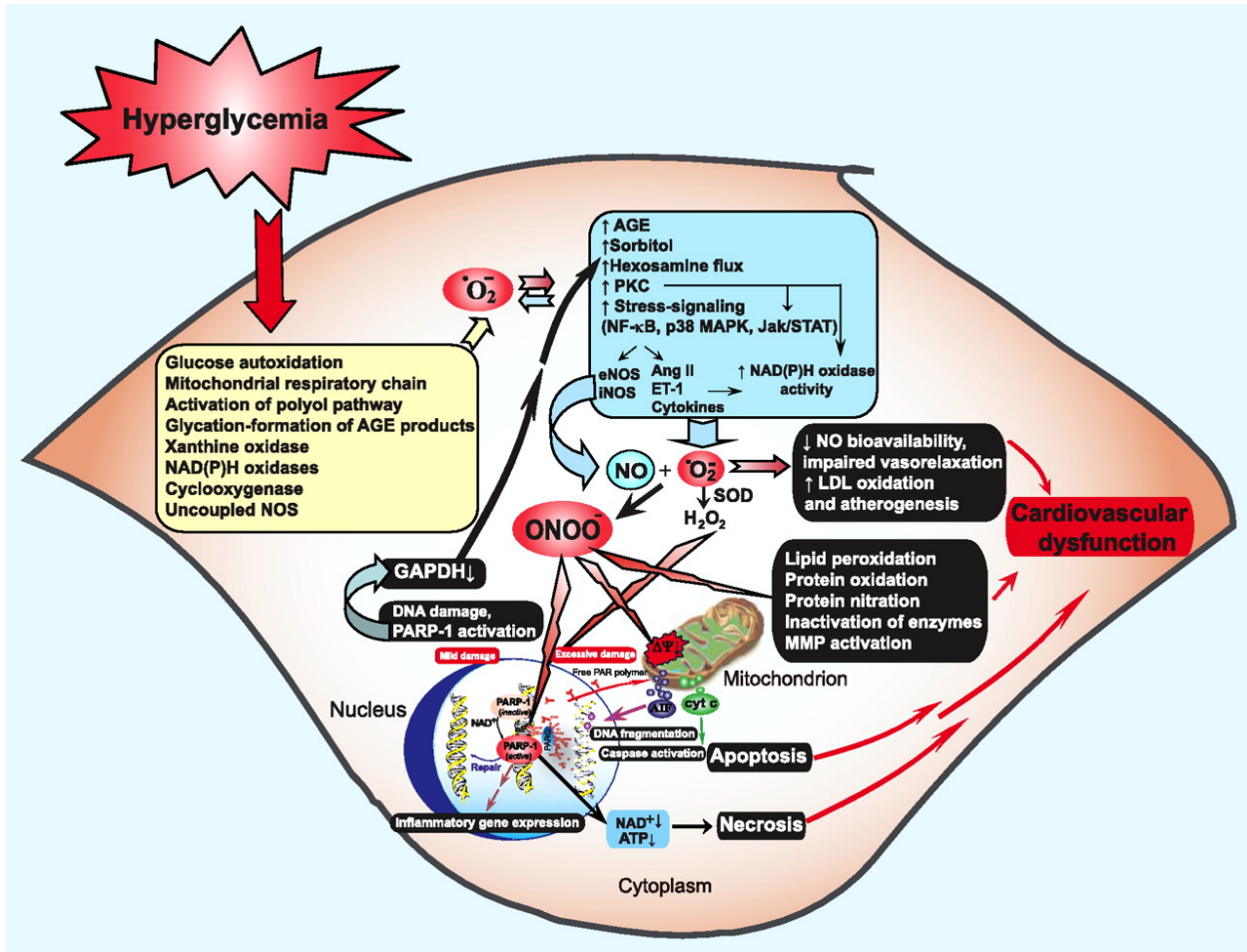


Figure 2. Mechanisms of cardiovascular dysfunction in diabetes: role of superoxide and peroxynitrite. Hyperglycaemia induces increased superoxide anion ($O_2^{\bullet-}$) production via activation of multiple pathways including xanthine and NAD(P)H oxidases, cyclooxygenase, uncoupled nitric oxide synthase (NOS), glucose autoxidation, mitochondrial respiratory chain, polyol pathway, and formation of advanced glycation end products (AGE). Hyperglycaemia-induced increased superoxide generation may also favour an increased expression of nitric oxide synthases (NOS) through the activation of NF κ B, which may increase the generation of nitric oxide (NO). Superoxide anion may quench NO, thereby reducing the efficacy of a potent endothelium-derived vasodilator system. Superoxide can also be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) and interact with NO to form a reactive oxidant peroxynitrite (ONOO⁻), which induces cell damage via lipid peroxidation, inactivation of enzymes and other proteins by oxidation and nitration, and activation of matrix metalloproteinases (MMPs) among others. This figure was adapted from [34].

Hyperglycaemia-induced oxidative stress also mediates endothelial dysfunction which plays a central role in the pathogenesis of micro- and macro-vascular diseases with resultant increase in pro-inflammatory cytokines and induction of apoptosis and impairment of nitric oxide release. Hyperglycaemia induces vascular damage probably through a single common pathway - increased intracellular oxidative stress- linking four major mechanisms, namely the polyol pathway, advanced glycation end-products (AGEs) formation, the protein kinase C (PKC)-diacylglycerol (DAG) and the hexosamine pathways [35]. However, synthetic drugs against diabetes mellitus have been reported with avalanche of side effects (Table 1) as reported by Kavishankar *et al.* [36].

Agent	Mechanism	Site of action	Advantages	Side effects
Sulphonylureas	Stimulating insulin production by inhibiting the K-ATP channel	Pancreatic beta cells	Effective and inexpensive	Hypoglycaemia and weight gain.
Metformin	Decreases insulin resistance	Liver	Weight loss Does not cause hypoglycaemia	Nausea and diarrhoea. Hypoglycaemia occurs when combined with sulphonylurea or insulin
Thiazolidinediones	Reduce insulin resistance by activating PPAR- γ	GI tract	Low risk	Increased liver enzymes, weight gain, oedema, mild anaemia
α -glucosidase inhibitors	Reduces intestinal glucose absorption	Fat, muscle	Decreases postprandial plasma triglyceride levels	Diarrhoea, abdominal pain, flatulence; Serum levels of transaminases increases at doses

Adapted from Kavishankar *et al.* [36].

Table 1. Synthetic drugs and their side effects

5. Drug-induced diabetic mellitus and their mechanisms of action

The most common drugs that are currently being used for the experimental induction of diabetes are alloxan and streptozotocin (STZ). Streptozotocin (STZ) is a synthetic antineoplastic agent that is classified as an anti-tumour antibiotic and is chemically related to other nitrosureas used in cancer chemotherapy [37]. Intra-venous injection of 60mg/kg dose of streptozotocin in adult Wistar rats, makes pancreas swell and at last causes degeneration in Langerhans islet beta cells and induces experimental diabetes mellitus in 2-4 days [37]. Both alloxan and STZ have been extensively documented for the induction of diabetes via free radical generation and depletion of antioxidant defense system [38-40]. STZ has been reported to significantly decrease the activity of erythrocytes antioxidative enzymes catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) [38-39]. Several drugs, with pharmacological properties including theophylline, aspirin, isoniazid and nalidixic acid can cause transient hyperglycaemia in over dosage, but only streptozotocin, alloxan and the rodenticide vacor are likely to cause permanent diabetes. Alloxan and the product of its reduction, dialuric acid, establish a redox cycle with the formation of superoxide radicals that undergo dismutation to produce hydrogen peroxide via Fenton reaction [41]. Similarly, the

reactive oxygen species results in simultaneous massive increase in cytosolic calcium concentration causes rapid destruction of B cells. In the same vein, streptozotocin enters the B cell via a glucose transporter (GLUT2) and causes alkylation of DNA. DNA damage induces activation of poly ADP-ribosylation, a process that is more important for the diabetogenicity of streptozotocin than DNA damage itself. More so, Poly ADP-ribosylation leads to depletion of cellular NAD⁺ and ATP [41]. Enhanced ATP dephosphorylation after streptozotocin treatment supplies a substrate for xanthine oxidase resulting in the formation of superoxide radicals. Also, streptozotocin liberates toxic amounts of nitric oxide that inhibits aconitase activity and participates in DNA damage [41].

6. Some scientifically validated antidiabetic plants

Recently, Etuk *et al.* [42] reported that the following medicinal plants have been validated scientifically as potent antidiabetic plants: *Acacia arabica* (Lam.) Muhl. ex Willd. (Family:

Mimosaceae), *Aegle marmelos* (L.) Correa ex Roxb. (Family: Rutaceae), *Allium cepa* L. (Family: Liliaceae), *Allium sativum* L. (Family: Alliaceae), *Aloe vera* (L.) Burm.f. (Family: Aloaceae), *Anthemis mobilis* Linn. (Family: Compositae), *Areca catechu* L. (Family: Arecaceae), *Artemisia pallens* Wall. ex DC. (Family: Compositae), *Annona squamosa* L. (Family: Annonaceae), *Andrographis paniculata* Nees (Family: Acanthaceae), *Aerva lanata* (L.) Juss. ex Schult. (Family: Amaranthaceae), *Asteracantha longifolia* Nees (Family: Acanthaceae), *Azadirachta indica* A. Juss. (Family: Meliaceae), *Biophytum sensitivum* (L.) DC. (Family: Oxalidaceae), *Bombax ceiba* L. (Family: Bombacaceae), *Beta vulgaris*

L. (Family: Chenopodiaceae), *Brassica juncea* (L.) Czern. (Family: Brassicaceae), *Barleria lupulina* Lindl. (Family: Acanthaceae), *Boerhavia diffusa* L. (Family: Nyctaginaceae), *Brickellia veronicaefolia* A. Gray (Family: Asteraceae), *Cassia auriculata* L. (Family: Leguminosae), *Caesalpinia bonducella* (L.) Roxb. (Family: Cesalpinaceae), *Capparis decidua* (Forsk.) Edgew. (Family: Capparidaceae) *Cajanus cajan* (L.) Millsp. (Family: Fabaceae), *Citrullus colocynthis* (L.) Schrad. (Family: Cucurbitaceae), *Coccinia indica* Wight & Arn. (Family: Cucurbitaceae), *Casearia esculenta* Roxb. (Family: Flacourtiaceae), *Catharanthus roseus* (L) G. Don. (Family: Apocynaceae), *Camellia sinensis* Kuntze (Family: Theaceae), *Coriandrum sativum* L. (Family: Apiaceae).

7. Antidiabetic plants in clinical trials

The following antidiabetic plants are currently under clinical trials viz:

Allium cepa L., *Clerodendron phlomoides* Linn., *Cinnamomum tamala* (Buch.-Ham.) T. Nees & Eberm., *Coccinia indica* Wight & Arn., *Enicostemma littorale* Blume, *Ficus bengalensis* L., *Momordica charantia* L., *Pterocarpus marsupium* Roxb., *Cyamopsis tetragonolobus* (L.) Taub., *Cephalandra indica* Naud., *Casearia esculenta* Roxb., *Cannabis indica* (Lam.) E. Small & Cronq., and *Syzygium cumini* L. when subjected to clinical trials, showed promising hypoglycaemic effects [43]. Other potent antidiabetic

plants in this category include *Cecropia obtusifolia*, *Marrubium vulgare*, *Asteracantha longifolia* Nees L., *Panax quinquefolius* L, *Gymnema Sylvestre*, *Phyllanthus amarus*, *Opuntia streptacantha* Lem. They were found to produce beneficial effects on carbohydrate and lipid metabolisms when administered as an adjunct on patients with type 2 diabetes [44]. These plants have been reported to improve glucose tolerance in healthy human subjects and diabetic patients, caused significant reduction in blood glucose, glycosylated haemoglobin and glycosylated plasma proteins comparable to an oral hypoglycaemic drug [45].

8. General mechanism (s) of action of medicinal plants with antidiabetic property

Different mechanisms of action of medicinal plants with anti-diabetic have been extensively described. These include inhibition of renal glucose reabsorption [46], stimulation of insulin secretion from beta cells of islets or/and inhibition of insulin degradative processes, reduction in insulin resistance [47] regenerating and/or repairing pancreatic beta cells with increasing the size and number of cells in the islets of Langerhans [45]. Stimulation of insulin secretion [48] and stimulation of glycogenesis and hepaticglycolysis [49] with antidiabetic plants is well established. Also, protective effect on the destruction of the beta cells and improvement in digestion along with reduction in blood sugar urea has been documented [50]. Prevention of pathological conversion of starch to glucose, and inhibition of β -galactocidase, α -glucocidase and alpha-amylase with concomitant capacity to lower cortisol has also been reported [51-52]. Antioxidant activity of antidiabetic plant against oxidative stress which is involved in pancreatic β -cell dysfunction has been reported as one of the mechanisms of action of anti-diabetic plants [53]. Similarly, some plant families reported for antidiabetic activity are shown below (Table 2).

9. Antioxidant activity of medicinal plants with antidiabetic activity

One of the major pathogenic mechanisms of diabetes mellitus include generation of oxidative stress, increase generation of free radicals and an impaired antioxidant defence system with concomitant imbalance of the oxidant/antioxidant status [54]. Inhibition of this cascade of oxidative processes has been reported to prevent the onset and development of diabetic complications [55]. Antidiabetic plants have been documented to scavenge free radicals, quench electronically excited compounds, reduce hydroperoxide formation, and attenuate production of reactive oxygen species (ROS) through modulation of several enzymes including xanthine oxidase, cyclooxygenase, lipoxygenase, microsomal monooxygenase, NADH oxidase and mitochondrial succinoxidase [56]. More so, plant phytonutrients such as polyphenols are known to enhance the endogenous antioxidative system, improve oxidant antioxidant balance, prevent oxidative damage, decrease lipid peroxidation, increase plasma total antioxidant capacity and induce antioxidant enzymes including superoxide dismutase, catalase and glutathione peroxidase [57].

Botanical	Family
<i>Mangifera indica</i>	Anacardiaceae
<i>Senna occidentalis</i>	Fabaceae
<i>Euphorbia convulsioides</i>	Euphorbiaceae
<i>Khaya senegalensis</i>	Meliaceae
<i>Acacia nilotica</i>	Mimosaceae
<i>Vernonia amygdalina</i>	Asreraceae
<i>Fiscus thonnigii</i>	Moraceae
<i>Angeissus leiocarpus</i>	Combretaceae
<i>Gossypium hirsutum</i>	Malvaceae
<i>Vitillarta paradoxa</i>	Sapotaceae
<i>Anacardium occidentale</i>	Anacardiaceae
<i>Anana senegalensis</i>	Anonaceae
<i>Psidium guajava</i>	Myrtaceae
<i>Moringa oleifera</i>	Mringaceae
<i>Azadirachata indica</i>	Meliaceae
<i>Alluvium cepa</i>	Liliaceae
<i>Ctrus medica</i>	Rutaceae
<i>Parkta filicoidea</i>	Mimosaceae
<i>Allium sativum</i>	Liliaceae
<i>Balanites aegyptiaca</i>	Zygophylliaceae
<i>Bauhinia reticulate</i>	Casalpiniaceae

Adapted from Etuk et al., 2010

Table 2. Some plant families reported for antidiabetic activity

10. Plant phytochemicals associated with antidiabetic activity

Photochemicals or phytonutrients are chemical compounds that occur naturally in plants that have protective or disease preventive properties [58]. Each type of fruit or vegetable may contain hundreds of phytochemicals. They have been reported to show multiple beneficial effects in combating diabetes and diabetes related complications [58]. The widest known

groups of phytochemicals are the alkaloids, terpenes, and phenolics. Plant constituents such as polysaccharides, peptides, alkaloids, glycopeptides, triterpenoids, amino acids, steroids, xanthone, flavonoids, lipids, phenolics, coumarins, iridoids, alkyl disulphides, inorganic ions and guanidines are reported to have antidiabetic activities [49, 59]. More interestingly, the following phytochemicals are reported to have antidiabetic activity, aminoacids like hypoglycin A and hypoglycin B, alkaloids like catharanthine, leurosine, lochnerine, arecoline and vindoline, pinitol, epicatechin, S-methyl cysteine sulphoxide, S-allyl cysteine sulphoxide, andrographolide, allicin (thio-2-propene-1- sulfinic acid S-allyl ester), shamimin, beta vulgarosides I–IV, glycoside of leucopelargonidin and leucodelphinidin, mangiferin, marsupin, pterosupin, pterostilbene, salacinol, swerchirin, trigonelline, berberine, harmaine, norharmaine, pinoline, quercetin, chlorogenic acid, hesperidin, naringin, epigallocatechin gallate, charantin, galactonmannan, lactucain C, kaempferol glucosides, caffeoyl glucoside, bakuchiol, swerchirin, thysanolactone, bellidifolin and kolaviron have been documented for potential phytonutrients [60].

11. Plant phytochemicals associated with insulinomimetic activity

They stimulate Beta cell rejuvenation, regeneration and stimulation increase insulin level, Irneccerepatoser insulin secretion and reduction of insulin binding on the insulin [34]. Some of the plant phytochemicals associated with insulinomimetic activity include the following: *Abies pindrow* Pinaceae, *Acacia arabica* (Leguminosae), *Agrimony eupatoria* (Rosaceae), *Aloe barbadensis* (Liliaceae), *Annona squamosa* (Annonaceae), *Averrhoa bilimbi* (Oxalidaceae), *Bixa orellana* (Bixaceae), *Boerhaavia diffusa* (Nyctaginaceae), *Camellia sinensis* (Theaceae), *Capsicum frutescens* (Solanaceae), *Cinnamomum zeylanicum* (Lauraceae), *Clausena anisata* (Rutaceae), *Eucalyptus globulus* (Myrtaceae), *Ficus religiosa* (Moraceae), *Hibiscus rosa* (Malvaceae), *Helicteres isora* (Sterculiaceae), *Ipomoea batata* (Convolvulaceae) *Juniperus communis* (Pinaceae), *Olea europia* (Oleaceae), *Swertia chirayata* (Gentianaeae), *Scoparia dulcis* (Scrophulariaceae), *Tinospora crispa* (Menispermaceae) *Urtifca dioica* (Urticaceae), *Vinca rosea* (Apocynaceae), *Zingiber officinale* (Zingiberaceae).

12. Some selected medicinal plants with antidiabetic potentials in Nigeria

In Nigeria, two plants, *Mangifera indica* and *Vernonia amygdalina* have been ranked highest for their antidiabetic property. Diabetes mellitus is known to affect 3% on average of adult Nigerians [61] and the prevalence in northern Nigerian is put at 1.6% [62]. Some of the selected medicinal plants with antidiabetic potentials in Nigeria are listed below.

Mangifera indica, *Angeissus leiocarpus*, *Fiscus thonnigii*, *Khaya senegalensis*, *Euphorbia convuluides*, *Acacia nilotica*, *Vernonia amygdalina*, *Cassia goratensis*, *Cassia arereh*, *Calotropis procera*, *Senna occidentalis*, *Alluovium cepa*, *Ipomoea batatas*, *Vitex gekowskii*, *Ctrus medica*, *Parkta filicoidea*, *Allium sativum*, *Anacardium occidentale*, *Azadirachata indica*, *Vitillarta paradoxa*, *Gossypium hirsutum*,

Lawsonia inermis, *Moringa oleifera*, *Psidium guajava*, *Bauhinia reticulata*, *Balanites aegyptiaca*, *Lannea kerstingii*, *Daucus carota*, *Zizyphus spina*, *Anana senegalensis*, *Eugenia caryophyllata*, *Blighia sapida*.

The leaves of *Mangifera indica* are used as an antidiabetic agent in Nigerian folk medicine. The hypoglycemic activity of *Mangifera indica* has been reported in both rats and mice [63-64]. Aqueous extract of the leaves of *Mangifera indica* were found to possess hypoglycaemic activity against glucose-induced hyperglycaemia but not with normoglycaemic or STZ-induced diabetic rats and mice respectively [63-64]. The hypoglycaemic effect of this plant was thought to be by reduction of intestinal absorption of glucose. Antihyperglycaemic activity of aqueous stem bark extract of *Mangifera indica* was also reported by Ojewole [65]. The extract from the stem bark of *Mangifera indica* administered intraperitoneally in streptozotocin induced diabetics rats produced a significant reduction in blood glucose level in rats Ojewole [65].

In Nigeria, the leaves of *Vernonia amygdalina* Del. (VA) and *Azadirachta indica* A. Juss (AI) have been used traditionally as a remedy against diabetes mellitus [66]. Atangwho et al. [66] reported that significant antidiabetic effect of the combination therapy was achieved when VA and AI were combined. The mechanism of action of the combination therapy was proposed as attenuation of oxidative stress, insulin mimetic action and β -cell regeneration. The presence of flavonoids such as luteolin, luteolin 7-O- β -glucuronoside, and luteolin 7-O- β -glucoside has been shown to be responsible for the antioxidant activity of *Vernonia amygdalina* [67]. The presence of these flavonoids could therefore contribute significantly to the antidiabetic property of *Vernonia amygdalina*.

Etuk and Mohammed [68] reported that 200 mg/kg of *V. amygdalina*, *C. procera*, *C. goratensis* and *M. indica* aqueous extracts produced a significant ($p < 0.05$) reduction in the blood glucose levels of the rats in alloxan-induced diabetic mellitus. In the same vein, *A. leicarpus*, *C. arereh* and *G. hirsutum* extracts produced a non-significant reduction ($p > 0.05$) in blood glucose levels in rats after treatment. Similarly, aqueous extracts of *M. Oleifera*, *S. occidentalis* and *K. senegalensis* were found to produce a minimal effect (about 4% reduction) on the alloxan-induced hyperglycemia in rats (Etuk and Mohammed, 2009). In summary, Etuk and Mohammed (2009) reported that 200mg/kg body weight of *Vernonia amygdalina* (67%), *Calotropis procera* (59%), *Cassia gorotensis* (53%) and *Magnifera indica* (35%) extracts produced a significant ($p < 0.05$) reduction in blood glucose levels in diabetic rats while *Angeissus leiocarpus* (30%), *Cassia arereh* (19%), *Gossypium hirsutum* (17%), *Khaya senegalensis* (4%), *Senna occidentalis* (4%) and *Moringa oleifera* (4%) produced a nonsignificant ($p < 0.05$) effect.

Previous study showed that aqueous leaves extract of *Psidium guajava* (PG) at 250 mg/kg showed statistically significant hypoglycaemic activity on alloxan-induced diabetic rats [69]. A 4-week supplementation of PG (125 and 250 mg/kg) in streptozotocin (STZ)-induced diabetic rats was shown to protect pancreatic tissues, including islet β -cells, against lipid peroxidation and DNA strand breaks induced by STZ, thereby reducing the loss of insulin-positive β -cells and insulin secretion [70]. More so, PG was found to markedly inhibited pancreatic nuclear factor-kappa B protein expression induced by STZ and restored the activities of antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase [70].

1 ml *Allium cepa* solution (0.4 g *A. cepa*/rat) has been shown to increase the fasting serum high-density lipoprotein levels and caused reduction of hyperglycaemia in streptozotocin (STZ) diabetic rats [71]. The hypoglycaemic and hypolipidaemic activities of *A. cepa* were associated with antioxidant activity via decrease superoxide dismutase (SOD) activity while no increased lipid hydroperoxide and lipoperoxide concentrations in diabetic rats treated with *A. cepa* [71]. In another experiment, onion juices exerted antioxidant and antihyperglycemic effects on alloxan-induced diabetes and consequently ameliorated liver and renal damage associated with alloxan toxicity [72].

Flavonoids from *Ipomoea batatas* leaf (FIBL) was reported to have anti-diabetic activity on alloxan-induced diabetic mice [73]. FIBL treatment (50, 100, and 150 mg/ kg body weight) for 28 days resulted in a significant decrease in the concentration of fasting blood glucose (FBG), total cholesterol (TC) and triglyceride (TG) in diabetes mellitus mice [73]. Also, FIBL significantly increased body weight (bw) and serum high-density lipoprotein cholesterol (HDL-c) level [73]. Stress and inflammation-related p38 mitogen-activated protein kinase activity and tumour necrosis factor- α production of diabetic rats were significantly depressed by *Ipomoea batatas* administration [74]. Similarly, histological examination also revealed improvement of pancreatic β -cells mass after treatments with *Ipomoea batatas* [74]. *Blighia sapida* has also been reported to have several ethnomedicinal uses of which various preparations and extracts have been made for the treatment of diseases such as dysentery, epilepsy, yellow fever and diabetes [75]. Saidu *et al.* [76] recently reported that *Anacardium occidentale* leaves at 300mg/kg body weight showed significant hypoglycaemic activity in alloxan-induced diabetic rats comparable to the standard drug-metformin.

13. Conclusion

Diabetes mellitus is a metabolic disorder in the endocrine system. It is known to be a dreadful disease that is found in all parts of the world with a serious threat to the health of mankind. Diabetes mellitus affect most of the people of both developed and developing countries. There are lots of synthetic drugs that have been used to control and to treat diabetic patients with partial recovery from this dreaded disease. Alternative to these synthetic agents, plants provide a potential source of hypoglycemic drugs and are widely used in several traditional systems of medicine to prevent diabetes. Several medicinal plants have been investigated for their beneficial use in different types of diabetes. Several phytonutrients have been identified from medicinal plants and this presents an exciting opportunity for the development of new types of therapeutics for diabetes mellitus. Most abundant phytonutrients present in medicinal plants are the alkaloids, terpenes, and phenolics. Phytomedicine has been used since ancient time in many parts of the world where access to modern medicine is limited. Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drugs continues because the existing synthetic drugs have several limitations as shown in table 1. The treatment of diabetes with synthetic drugs in the developing countries is expensive due to poverty and lack of access to Medicare. Hence, phytotherapy has significant role to play in

the developing countries compared to synthetic drugs because it is safe, less expensive and available as a gift of nature.

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