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Chapter 4

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

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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].

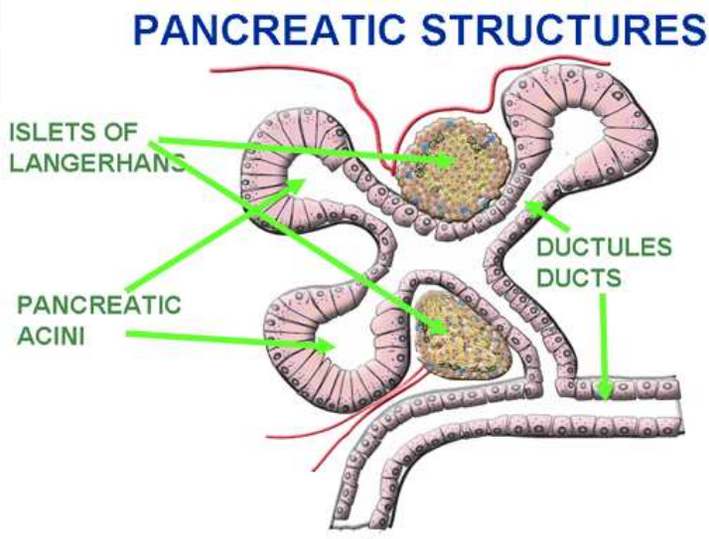


Figure 1. The structure of the pancreas which houses islets of Langerhans

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).

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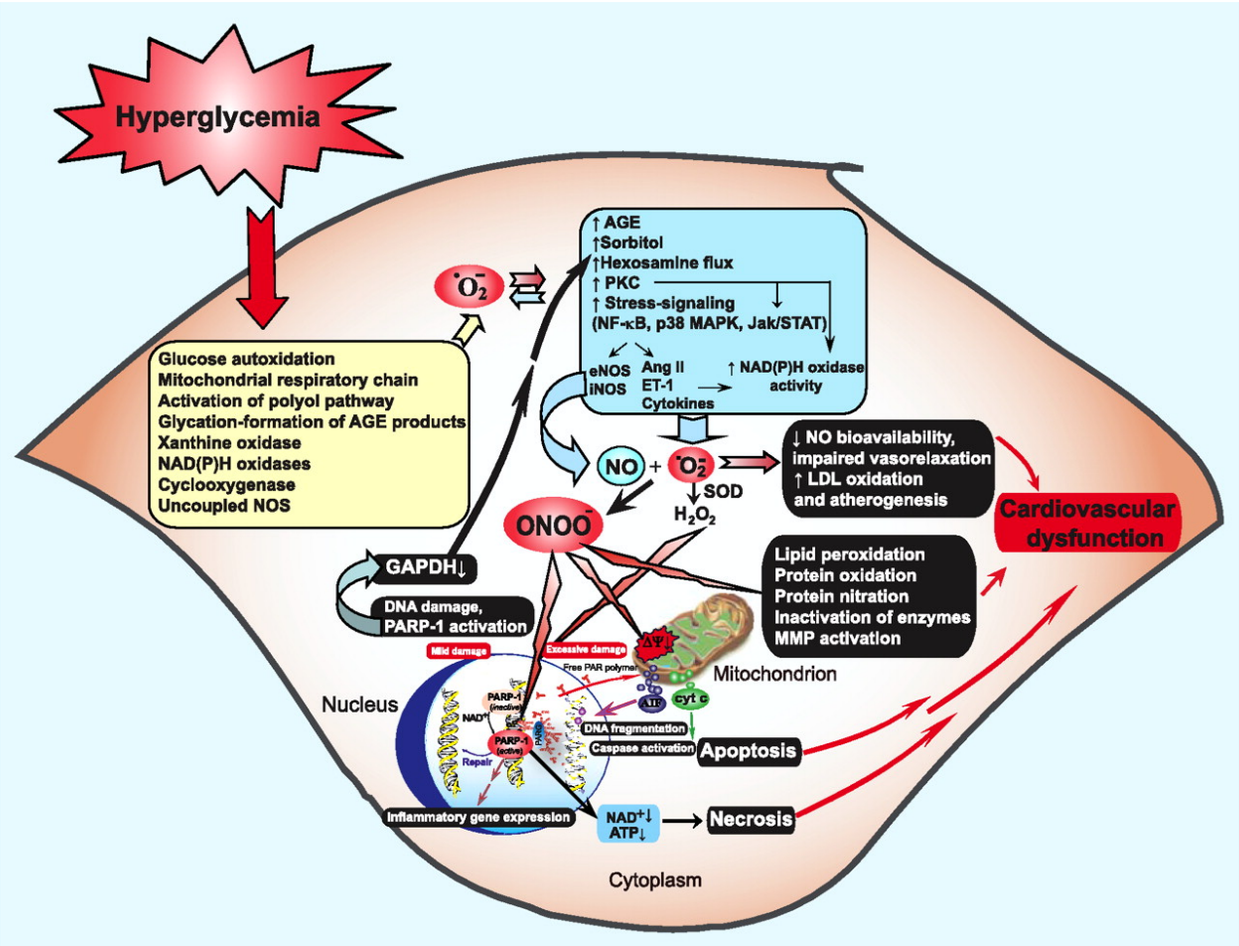


Figure 2. Mechanisms of cardiovascular dysfunction in diabetes: role of superoxide and peroxynitrite. Hyperglycaemia induces increased superoxide anion (O2•–) production via activation of multiple pathways including xanthine and NAD(P)H oxidases, cyclooxygenase, uncoupled nitric oxide synthase (NOS), 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 NFκB, 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 sulfonylurea 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

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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 ß-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
Mangifera indica	Anacardiaceae
Senna occidentalis	Fabaceae
Euphorbia convuludiodes	Euphobiaceae
Khaya senegalensis	Meliaceae
Acacia nilotica	Mimosaceae
Vernonia amygdalina	Asreraceae
Fiscus thonnigii	Moraceae
Angeissus leiocarpus	Combretaceae
Gossypium hirsutum	Malvaceae
Vitillarta paradoxa	Sapotaceae
Anacardium occidentalis	Anacardiaceae
Anana senegalensis	Anonaceae
Psidium guajava	Myrtaceae
Moringa oleifera	Mringaceae
Azadirachata indica	Meliaceae
Alluvium cepa	Liliaceae
Ctrus medica	Rutaceae
Parkta filicoidea	Mimosaceae
Allium sativum	Liliaceae
Balanites aegyptiaca	Zygophyliaceae
Bauhinia reticulate Casalpiniaceae	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, marsupsin, pterosupin, pterostilbene, salacinol, swerchirin, trigonelline, berberine, harmane, norharmane, 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 convuludiodes, Acacia nilotica, Vernonia amygdalina,Cassia goratensis,Cassia arereh, Calotropis procera, Senna occidentalis, Alluvium cepa, Ipomoea batatas, Vitex gekowskii,Ctrus medica, Parkta filicoidea, Allium sativum, Anacardium occidentalis, Azadirachata indica,Vitillarta paradoxa, Gossypium hirsutum,

Lawsonia inermis, Moringa oleifera, Psidium guajava, Bauhinia reticulate, 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 hypoglyceamic 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 ($p < 0.0.5\%$) 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 *Allum 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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References

[1] Kameswara Rao B, Rajasekhar MD, Sreelatha A, and Apparao C. Treatment of diabetes mellitus: Plant drugs vs oral hypoglycemic agents and insulin. In Recent Progress in Medicinal Plants, 14, pp. 279-296, Biopharmaceuticals Studium Press, Houson, TX, USA; 2006.

[2] Shin HJ, Kim JH, Yi JH, Han SW, Kim HJ. Polyuria with the Concurrent manifestation of Central Diabetes Insipidus (CDI) & Type 2 Diabetes Mellitus (DM). Electrolyte & Blood Pressure 2012; 10(1):26-30.

[3] Smolek MK, Notaroberto NF, Jaramillo AG, Pradillo LR. Intervention with vitamins in patients with nonproliferative diabetic retinopathy: a pilot study. Clinical Ophthalmology 2013; 7:1451-1458.

[4] Lidén MK. Prevention and protection in diabetic nephropathy. Lakartidningen 2013; 110(21):1025-1027.

[5] Westerberg DP (2013). Diabetic ketoacidosis: evaluation and treatment. American Family Physician. 87(5):337-346

[6] Liu J, Wang S, Feng L, Ma D, Fu Q, Song Y, Jia X, Ma S. Hypoglycemic and antioxidant activities of paeonol and its beneficial effect on diabetic encephalopathy in streptozotocin-induced diabetic rats. Journal of Medical Foods 2013; 16(7):577-586.

[7] Bell DS. Diabetes: a cardiac condition manifesting as hyperglycemia. Endocrine Practice 2008; 14(7):924-932.

[8] Yoshimura M, Anzawa R, Mochizuki S. Cardiac metabolism in diabetes mellitus. Current Pharmaceutical Design 2008; 14(25):2521-2526.

[9] Andreozzi F, Gastaldelli A, Mannino GC, Sciacqua A, Succurro E, Arturi F, Folli F, Perticone F. Increased carotid intima-media thickness in the physiologic range is associated with impaired postprandial glucose metabolism, insulin resistance and beta cell dysfunction. Atherosclerosis 2013; 229(2):277-281.

[10] Simopoulos AP. Dietary omega-3 Fatty Acid deficiency and high fructose intake in the development of metabolic syndrome, brain metabolic abnormalities, and non-alcoholic Fatty liver disease. Nutrients 2013; 5(8):2901-2923.

[11] Li H, Yu X. Emerging Role of JNK in Insulin Resistance. Current Diabetes Reviews 2013; Sep;9(5):422-428.

[12] Li Y, Zhang H, Jiang C, Xu M, Pang Y, Feng J, Xiang X, Kong W, Xu G, Li Y, Wang X. Hyperhomocysteinemia promotes insulin resistance by inducing endoplasmic reticulum stress in adipose tissue. J Biological Chemimstry 2013; 288(14):9583-92.

[13] Sutradhar SR, Ali L, Khan AK, Siddiqui NI, Sarker CB, Rahman S, Huq MH, Debnath CR. Ketosis resistance in under thirty diabetic subjects. Mymensingh Medical Journal 2004; 13(2):134-137.

[14] Chhabra P, Brayman KL. Stem cell therapy to cure type 1 diabetes: from hype to hope. Stem Cells Translational Medicine 2013; 2(5):328-336.

[15] Ting C, Bansal V, Batal I, Mounayar M, Chabtini L, El Akiki G, Azzi J. Impairment of immune systems in diabetes. Advances in Experimental Medicine & Biology 2012; 771:62-75.

[16] Thompson JA, Perry D, Brusko TM. Autologous regulatory T cells for the treatment of type 1 diabetes. Current Diabetes Reports 2012; 12(5):623-32.

[17] Psallas M, Manes C. Incretins in type 2 diabetes mellitus: cardiovascular and antiatherogenic effects beyond glucose lowering. Hippokratia Medical Journal 2012; 16(2):100-105.

[18] Pathak R, Pathak A (2012). Study of life style habits on risk of type 2 diabetes. International Journal of Applied & Basic Medical Research 2012; 2(2):92-96.

[19] Santaguida L, Balion C, Hunt D. Diagnosis, prognosis, and treatment of impaired Satyavati GV, Tandon N, Sharma M (1989). Indigenous Plant Drugs For Diabetes Melli-

tus 2008. [updated 1989 October; Available from: http://www.rssdi.org/1989_october/article1.pdf

[20] Ramirez-Garcia SA, Cabrera-Pivaral CE, Huacuja-Ruiz L, Flores-Alvarado LJ, Pérez-García G, González-Rico JL, López-Velázquez A, Topete-González, LR,Rosales-Góme RC, Candelario-Mejía G, Villa-Ruano N. [Implications in primary health care of medical genetics and genomic in type 2 diabetes mellitus]. Review in Medical Institute & Sociology 2013; 51(3):e6-e26.

[21] Morgan AR. Determining genetic risk factors for pediatric type 2 diabetes. Current Diabetes Reports 2012; 12(1):88-92.

[22] Muhammad Z, Hashmi A. Frequency of diabetic cardiomyopathy among type-2 diabetics presenting as heart failure. Journal of College of Physicians & Surgeons- Pakistan 2013; 23(8):538-542.

[23] Patil MB, Burji NP. Echocardiographic evaluation of diastolic dysfunction in asymptomatic type 2 diabetes mellitus. Journal of Association of Physicians- India 2012; 60:23-26.

[24] Shrestha NR, Sharma SK, Karki P, Shrestha NK, Acharya P. Echocardiographic evaluation of diastolic function in asymptomatic type 2 diabetes. Journal of Nepal Medical Association 2009;Jan-Mar;48(173):20-23.

[25] Galderisi M. Diastolic dysfunction and diabetic cardiomyopathy: evaluation by Doppler echocardiography. Jornal of American College of Cardiology 2006; Oct 17;48(8): 1548-1551.

[26] Adebola PO, Grierson DS and Afolayan AJ. An ethnobotanical study of plants used for the treatment of diabetes in the Eastern Cape Province, South Africa. African Journal of Biotechnology 20055; 4(12): 1458-1460.

[27] Erasto P, Adebola PO, Grierson DS and Afolayan AJ. An ethnobotanical study of plants used for the treatment of diabetes in the Eastern Cape Province, South Africa. African Journal of Biotechnology 2005; 4(12): 1458-1460.

[28] Wild SH, Roglic G, Sicree R, Green A, King H. Global Burden of Diabetes Mellitus in the Year 2000. Available from http://www3.who.int/whosis/menu.cfm?

[29] Ping Zhang, Xinzhi Zhang, Jonathan Brown, Dorte Vistisen, Richard Sicree, Jonathan Shaw, Gregory Nichols. Global healthcare expenditure on diabetes for 2010 and 2030. Diabetes research and clinical practice 2010; 78: 293-301.

[30] Diogo CV, Suski JM, Lebiedzinska M, Karkucinska-Wieckowska A, Wojtala A, Pronicki M, Duszynski J, Pinton P, Portincasa P, Oliveira PJ, Wieckowski MR. Cardiac mitochondrial dysfunction during hyperglycemia--the role of oxidative stress and p66Shc signaling. International Journal of Biochemistry & Cell Biology 2013; Jan; 45(1):114-122.

[31] Yang H, Jin X, Kei Lam CW, Yan SK. Oxidative stress and diabetes mellitus. Clinical Chemistry & Laboratory Medicine 2011; 49(11):1773-1782.

[32] Folli F, Corradi D, Fanti P, Davalli A, Paez A, Giaccari A, Perego C, Muscogiuri G. The role of oxidative stress in the pathogenesis of type 2 diabetes mellitus micro- and macrovascular complications: avenues for a mechanistic-based therapeutic approach. Current Diabetes Reviews 2011; 7(5):313-324.

[33] Madonna R, De Caterina R. Cellular and molecular mechanisms of vascular injury in diabetes-part I: pathways of vascular disease in diabetes. Vascular Pharmacology 2011; 54(3-6):68-74.

[34] Patel DK, Prasad SK, Kumar R, Hemalatha S. Asian Pacific Journal of Tropical. An overview on antidiabetic medicinal plants having insulin mimetic property. Asian Pacific Journal of Tropical Biomedicine 2012; 320-330.

[35] Bonnefont-Rousselot D, Beaudeux JL, Thérond P, Peynet J, Legrand A, Delattre J. [Diabetes mellitus, oxidative stress and advanced glycation endproducts]. Annales Pharmaceutiques Francaises 2004; 62(3):147-157.

[36] Kavishankar GB, Lakshmidevi N, Mahadeva Murthy S, Prakash HS, Niranjana SR. Diabetes and medicinal plants-A review. International Journal of Pharmaceutical & Biomedical Sciences 2011; 2(3), 65-80.

[37] Akbarzadeh A, Norouzian D, Mehrabi MR, Jamshidi SH, Farhangi A, Verdi A. Allah, Mofidian SMA and Rad B. Lame. Induction of diabetes by streptozotocin in rats. Indian Journal of Clinical Biochemistry 2007; 22 (2) 60-64.

[38] Ali MM, Agha FG. Amelioration of streptozotocin-induced diabetes mellitus, oxidative stress and dyslipidemia in rats by tomato extract lycopene. Scandinavian Journal of Clinical Laboratory Investigation 2009; 69(3):371-379.

[39] Kade IJ, Ogunbolude Y, Kamdem JP, Rocha JB. Influence of gallic acid on oxidative stress-linked streptozotocin-induced pancreatic dysfunction in diabetic rats. Journal of Basic & Clinical Physiology & Pharmacology 2013; 26:1-11.

[40] Lenzen S. "The Mechanisms of Alloxan- and Streptozotocin-induced Diabetes". Diabetologia 2008; 51 (2): 216–226.

[41] Szkudelski T. The mechanism of alloxan and streptozotocin action in β cells of the rat pancreas. Physiological Research 2001; 50(6):537-546.

[42] Etuk EU, Bello SO, Isezuo SA, Mohammed. Ethnobotanical Survey of Medicinal Plants used for the Treatment of Diabetes Mellitus in the North Western Region of Nigeria. Asian Journal of Experimental Biology &. Sciences 2010; (1):55-59.

[43] Naik RG. Hypoglygemig Plants-Abstracts On Clinical Trials. [updated 1989 October;]. Available from: ttp://www.rssdi.org/1989_october/abstract.pdf.

[44] Herrera AA, Aguilar S L, Garc BH, Nicasio TP, Tortoriello J. Clinical trial of *Cecropia obtusifolia* and *Marrubium vulgare* leaf extracts on blood glucose and serum lipids in type 2 diabetics. Phytomedicine 2004; 11:561–566.

[45] Mohamed B, Abderrahim Z, Hassane M, Abdelhafid T, Abdelkhaleq L. Medicinal plants with potential antidiabetic activity – A review of ten years of herbal medicine research (1990-2000). International Journal of Diabetes Metabolism 2006; 14:1-25.

[46] Eddouks M, Maghrani M, Lemhadri A, Ouahidi ML, Jouad H. Ethnopharmacological survey of medicinal plants used for the treatment of diabetes mellitus, hypertension and cardiac diseases in the south-east region of Morocco. Journal of Ethnopharmacology 2002;.82:97-103

[47] Pulok KM, Kuntal M, Kakali M, Peter JH. Leads from Indian medicinal plantswith hypoglycemic potentials. Journal of Ethnopharmacology 2006; 106:1–28.

[48] Esmaeili MA, Yazdanparast R. Hypoglycaemic effect of *Teucrium polium*: studies with rat pancreatic islets. Journal of Ethnopharmacology 2004; 95:27-30.

[49] Miura T, Itoh C, Iwamoto N, Aato M, Kawai M, Park SR, Suziki I. Hypoglycemic activity of the fruit of the *Momordica charantia* in Type 2 diabetic mice. Journal of Nutrition Science & Vitaminology (Tokyo). 2001; 47:340-4.

[50] Kim MJ, Ryu GR, Chung JS, Sim SS, Min DS, Rhie DJ, Yoon SH, Hahn SJ, Kim MS, Jo YH.. Protective effects of epicatechin against the toxic effects of streptozocin on rat pancreatic islets: in vivo and in vitro. Pancreas 2003; 26:292-299.

[51] Gholap S, Kar A. Hypoglycaemic effects of some plant extracts are possibly mediated through inhibition in corticosteroid concentration. Pharmazie 2004; 59:876-878.

[52] Heidari R, Zareae S, Heidarizadeh M. Extraction, Purification, and Inhibitory Effect of Alpha-Amylase Inhibitor from Wheat (*Triticum aestivum* Var. *Zarrin)*. Pakistan Journal of Nutrition 2005; 4:101-105.

[53] Hideaki K, Taka-aki M, Yoshihisa N, Dan K, Munehide M, Yoshimitsu Y. Oxidative Stress and the JNK Pathway in Diabetes. Current Diabetes Reviews 2005; 65-72.

[54] Goycheva V, Gadjeva BP (2006). Oxidative stress and its complications in diabetes mellitus. Trakia Journal of Sciences 2006; 4:1-8.

[55] Pérez-Matute P, Zulet MA, Martínez JA. Reactive species and diabetes: counteracting oxidative stress to improve health. Current Opinion in Pharmacology 2009; 9:771-779.

[56] Dembinska-Kiec A, Mykkänen O, Kiec-Wilk B, Mykkänen H (2008). Antioxidant Diogo CV, Suski JM, Lebiedzinska M, Karkucinska-Wieckowska A, Wojtala A, Pronicki M, Duszynski J, Pinton P, Portincasa P, Oliveira PJ, Wieckowski MR. Cardiac mitochondrial dysfunction during hyperglycemia--the role of oxidative stress and p66Shc signaling. International Journal of Biochemistry & Cell Biology 2013; 45(1):114-22.

[57] Crespy V, Williamson G (2004). A review of the health effects of green tea catechins in in vivo animal models. J Nutr, 134:3431S–3440S.

[58] Uma MM, Sudarsanam D. Phytomedicine for Diabetes mellitus: An overview. Research in Pharmacy 2011; 1(4): 28-37.

[59] Grover JK, Yadav S, Vats V. Medicinal plants of India with anti-diabetic potential. Journal of Ethnopharmacology 2002; 81:81-100.

[60] Edwin J, Siddaheswar BJ, Dharam CJ. Diabetes and Herbal Medicines. Iranian Journal of Pharmacology & Therapeutics 2008; 7: 97-106.

[61] Akinkugbe OO, Yakubu AM, Johnson TO, Mabadaje AFB, Kaine WN, Ikeme AA, Akinyanju OO, Oli JM, Kuti JA, and Akintoye CO. Non communicable diseases in Nigeria. Spectrum Books Limited, Ibadan, 1992; pp. 2-47.

[62] Bakari AG, Onyemekwue GC, Sani BG, Hassan SS, Aliyu TM. Prevalence of diabetes mellitus in suburban Northern Nigeria; Results of public screening survey. Diabetes International 1990; 9:59-60.

[63] Aderibigbe AO, Emudianughe TS, Lawal BA. Antihyperglycaemic effect of *Mangifera indica* in rat. Phytotherapy Research 1999; 13(6):504-507.

[64] Aderibigbe AO, Emudianughe TS, Lawal BA. Evaluation of the antidiabetic action of Mangifera indica in mice. Phytotherapy Research 2001; 15(5):456-458.

[65] Ojewole JA. Antinociceptive, antiinflamatory and antidiabetic properties of Hypoxis hemerocallidea (hypoxidaceae) corm [African potato] aqueous extracts in mice and rats. Journal of Ethnopharmacology 2006; 103: 126-134

[66] Atangwho IJ, Ebong PE, Eyong EU, Asmawi MZ, Ahmad M. Synergistic antidiabetic activity of Vernonia amygdalina and Azadirachta indica: biochemical effectsand possible mechanism. Journal of Ethnopharmacology 2012; 141(3):878-887.

[67] Farombi EO, Owoeye O. Antioxidative and chemopreventive properties of Vernonia amygdalina and Garcinia biflavonoid. International Journal of Environment Research and Public Health 2011; 8(6):2533-2555.

[68] Etuk EU, Mohammed BJ. Informant consensus selection method: A reliability assessment on medicinal plants used in north western Nigeria for the treatment of diabetes mellitus. African Journal of Pharmacy and Pharmacology 2009; 3(10):496-500.

[69] Mukhtar HM, Ansari SH, Ali M, Naved T, Bhat ZA. Effect of water extract of *Psidium guajava* leaves on alloxan-induced diabetic rats. Pharmazie 2004; 59(9):734-735.

[70] Huang CS, Yin MC, Chiu LC. Antihyperglycemic and antioxidative potential of Psidium guajava fruit in streptozotocin-induced diabetic rats. Food and Chemical Toxicology 2011; 49(9):2189-2195.

[71] Campos KE, Diniz YS, Cataneo AC, Faine LA, Alves MJ, Novelli EL. Hypoglycaemic and antioxidant effects of onion, Allium cepa: dietary onion addition, antioxidant ac-

tivity and hypoglycaemic effects on diabetic rats. International Journal of Food Science and Nutrition 2003; 54(3):241-246.

[72] El-Demerdash FM, Yousef MI, El-Naga NI. Biochemical study on the hypoglycemic effects of onion and garlic in alloxan-induced diabetic rats. Food and Chemical Toxicology 2005; 43(1):57-63.

[73] Li F, Li Q, Gao D, Peng Y. The optimal extraction parameters and anti-diabetic activity of flavonoids from *Ipomoea batatas* leaf. African Journal of Traditional Complementary and Alternative Medicine 2009; 6(2):195-202.

[74] Niwa A, Tajiri T, Higashino H. *Ipomoea batatas* and *Agarics blazei* ameliorate diabetic disorders with therapeutic antioxidant potential in streptozotocin-induced diabetic rats. Journal of Clinical Biochemistry and Nutrition 2011; 48(3):194-202.

[75] Gbolade AA. Inventory of antidiabetic plants in selected districts of Lagos State, Nigeria. Journal of Ethnopharmacology 2009; 121:135-139.

[76] Saidu AN, Akanya HO, Dauda BEN, and Ogbadoyi EO. Antibacterial and comparative hypoglycemic effect of Anacardium occidentale leaves. International Research Journal of Biochemistry and Bioinformatics 2012; 2(1): 006-010.

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