

# Herbal therapy: A review of emerging pharmacological tools in the management of diabetes mellitus in Africa

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## ABSTRACT

**Background:** Diabetes mellitus is a chronic physiological glucose metabolic disorder. It has affected millions of people all over the world thereby having a significant impact on quality of life. The management of diabetes includes both nonpharmacological and conventional interventions. Drawbacks in conventional therapy have led to seeking alternative therapy in herbal medicine. Therefore, the need to review, elucidate and classify their mode of action in therapy for diabetes disease arises. **Materials and Methods:** Comprehensive literature reports were used to review all conventional agents and herbal therapy used in the management of diabetes. An online database search was conducted for medicinal plants of African origin that have been investigated for their antidiabetic therapeutic potentials. **Results:** The results showed that of the documented sixty five plants used, fourteen inhibit intestinal absorption of glucose, three exhibit insulin-mimetic properties, seventeen stimulate insulin secretion from pancreatic beta cells, twelve enhance peripheral glucose uptake, one promotes regeneration of beta-cell of islets of Langerhans, thirteen ameliorate oxidative stress and twenty induces hypoglycemic effect (mode of action is still obscure). Thirteen of these plants have a duplicate mode of actions while one of them has three modes of actions. These agents have a similar mechanism of action as the conventional drugs. **Conclusion:** In conclusion, antidiabetic activities of these plants are well established; however, the molecular modulation remains unknown. It is envisaged that the use of herbal therapy will promote good health and improve the status of diabetic patients.

**Key words:** Antidiabetic, diabetes, herbal therapy, *in vitro*, *in vivo*

## INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder caused by abnormal metabolism of carbohydrate, promoted by factors such as insulin deficiency and/or insulin resistance.<sup>[1]</sup> The prevalence of diabetes globally was estimated to be 4.0% in 1995 and is projected to rise to 5.4% (300 million) by the year 2025. In 2010, 12.1 million people were estimated to be living with diabetes in Africa, and this is projected to increase to 23.9 million by 2030.<sup>[2]</sup> Diabetes mellitus has affected several millions of people all over the world, thereby significantly impacting on the economy, health, quality of life and life expectancy of patients, as well as on the health care systems.<sup>[3]</sup>

There are two major forms of diabetes mellitus; insulin-dependent diabetes mellitus (IDDM) also known

as type I diabetes and non-insulin-dependent diabetes mellitus (NIDDM) also known as type II diabetes.<sup>[4]</sup> IDDM is caused by failure to release insulin from the  $\beta$ -cells of the islets of Langerhans in the pancreas. NIDDM is caused by insulin resistance probably due to too few insulin receptors.<sup>[5]</sup>

The major causes of IDDM include genetic predisposition, environmental factors such as nutrition, exposure to viruses and allergens and autoimmunity leading to destruction of insulin-producing pancreatic  $\beta$ -cells.<sup>[6]</sup> The major causes of NIDDM include genetic and environmental factors. IDDM requires insulin injection to prevent ketosis and other complications as well as maintenance of life.<sup>[4]</sup> The complications of IDDM and NIDDM include; retinopathy, neuropathy, angiopathy, nephropathy, infection and diabetic ketoacidosis.<sup>[4]</sup> Diabetic foot disease which is due to changes in blood vessels and nerves, often leads to ulceration and subsequent limb amputation. Skin disorders are also more common in diabetics. Bacterial (mycobacterium and anaerobic) and fungal infections are common in diabetics.<sup>[4]</sup>

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Various approaches have been used in the management of diabetes mellitus. These are nonpharmacological interventions including; diet therapy, physical activity, acupuncture and hydrotherapy and mineral supplementation.<sup>[5-7]</sup> The conventional management of diabetes mellitus includes; insulin therapy, oral glucose-lowering agents such as sulfonylurea, biguanides, alpha-glucosidase inhibitors, thiazolidinediones, and meglitinides.<sup>[8-13]</sup> Another approach which has been tried is the prevention of autoimmune attack using immunosuppressive compounds.<sup>[14-18]</sup> Transplantation of either the pancreas or preparations of islet tissues has also been tried.<sup>[17,18]</sup> Regardless of the efficiency of the above-mentioned methods used in the management of the disease, they have several drawbacks. These include; adverse side effects, cost (expensive) and inaccessible to many communities. This has led to the use of herbal therapy as an alternative method in the management of the disease.

Therefore, this review has chronicled the nonpharmacological and pharmacological interventions used in the management of diabetes mellitus and their drawbacks leading to sourcing for herbal therapy.

### Nonpharmacological interventions in the management of diabetes mellitus

#### Diet therapy

Given the heterogeneous nature of type 2 diabetes, no single dietary approach is appropriate for all patients. Meal plans and diet modifications are generally individualized by a registered dietician to meet patient needs and lifestyle. A typical conventional approach would recommend a diet composed of 60–65% carbohydrate, 25–35% fat, and 10–20% protein with limited or no alcohol consumption.<sup>[5]</sup>

#### Vegetables

Vegetables are among the numerous plant adjuncts tried on the treatment of diabetes mellitus. Bitter melon (*Momordica charantia*) and Ivy gourd (*Coccinia indica*) are hypoglycemic when administered orally. Other vegetables such as cabbage (*Brassica oleracea*) green leafy vegetables, beans, and tubers are hypoglycemic in both experimental animals and humans.<sup>[19]</sup>

#### Mineral supplementation

The treatment of diabetes requires nutritional supplementation, as these patients have a greatly increased need for many nutrients. These improve blood sugar control and prevent many major complications of diabetes. The mineral supplements include:

Chromium (Cr) is an essential element required for normal lipid and carbohydrate metabolism. Brewers yeast appears to be the richest source of GTF-chromium,

followed closely by black pepper, wheat germ, rye bread, mushrooms, prunes, wine, and beer. Most meats, fresh fruits, and cheeses are fair sources of chromium. Cereals are poorer sources, their chromium decreasing with refining and processing.<sup>[20]</sup>

Vanadium is known to play a role in the regulation of intracellular signaling and as a cofactor of enzymes essential in energy metabolism hence reduces gluconeogenesis and increases glycogen deposition.<sup>[21]</sup> A reasonable amount of supplemental vanadium is 20 µg/day. Vanadyl sulfate at a dose of 100 mg/day is effective in improving insulin sensitivity. Good sources of vanadium include seafood, mushrooms, olives, whole grain bread, carrots and vegetable oils.<sup>[22]</sup>

Magnesium (Mg) is one of the major mineral constituents of the human body. Its functions include strengthening cell membrane structure, cofactor to several enzymes like kinase, which participate in energy production processes and participation in deoxyribonucleic acid (DNA) replication.<sup>[23]</sup> A reasonable amount of supplemental magnesium is 450 mg/day.<sup>[23]</sup>

Zinc is an important trace element in diabetes. It is a cofactor for insulin. Although its real mechanisms in carbohydrate metabolism is not clear, zinc has influence in carbonic anhydrase, alkaline phosphatase, alcohol dehydrogenase, pancreatic carboxypeptidases A and B, lactate dehydrogenase, glutamate dehydrogenase, glyceraldehyde-3-phosphate dehydrogenase and maltose dehydrogenase. Zinc plays a vital role in the biosynthesis of nucleic acids, RNA polymerases, and DNA polymerases; hence its involvement in the healing processes of body tissues. Other physiological processes that require zinc include hormone metabolism, immune responses and stabilization of ribosomes and membranes.<sup>[24]</sup>

Manganese (Mn) is a trace metal in the body. It is both an activator and a constituent of several enzymes. It is necessary for the normal activity of hydrolyases, kinases, decarboxylases, transferases, leucine aminopeptidase, alkaline phosphatase and of the enzymes of oxidative phosphorylation. Manganese metalloenzymes include pyruvate decarboxylase, arginase, glutamate synthetase, and manganese superoxide dismutase.<sup>[25]</sup>

Molybdenum (Mo) affects glucose metabolism. In the hepatocytes, molybdenum stimulates glycolysis and accelerates glycogen degradation.<sup>[26]</sup> Mo also increases insulin receptor autophosphorylation and phosphorylation of its substrate and augments glucose transport, oxidation and lipogenesis in adipocytes.<sup>[26]</sup>

Molybdate is an effective antihyperglycemic agent in diabetics with severe insulin resistance. It is associated with a substantial reduction of hyperinsulinemia and an increase in pancreatic insulin stores. The glucose-lowering effect of Mo may be partly related to attenuation of hepatic glucose production. Hence, Mo proves to be an effective blood glucose-lowering agent in severely diabetic patients.<sup>[27]</sup>

Iron is an important element, it is found in the portion of the cell involved in energy production and as a cofactor for several enzymes such as succinic dehydrogenase, catalase, and cytochromes.<sup>[28]</sup> Insulin is known to cause a rapid and marked stimulation of iron uptake by fat cells, redistributing transferrin receptors from an intracellular membrane compartment to the cell surface. Insulin is also responsible for the increased ferritin synthesis.<sup>[29]</sup> Reciprocally, iron influences insulin action. Iron interferes with insulin inhibition of glucose production by the liver. Hepatic excretion and metabolism of insulin is reduced with increasing iron stores, leading to peripheral hyperinsulinemia.<sup>[30]</sup> In fact, the initial and most common abnormality seen in iron overload conditions is liver insulin resistance. Iron overload also affects skeletal muscle, the main effector of insulin action.<sup>[31]</sup>

#### **Physical activity**

In well-controlled diabetes, physical activity improves the body's ability to use glucose and lowers the insulin requirement. Exercise should start at a low level and gradually increase to avoid adverse effects such as injury, hypoglycemia, or cardiac problems.<sup>[32]</sup>

#### **Acupuncture and hydrotherapy**

Acupuncture is the best-known alternative therapy in the United States of America for chronic pain and is used in the treatment of diabetes. Acupuncture is effective in treating not only diabetes, but also in preventing and managing complications of the diseases.<sup>[7]</sup> Acupuncture activates glucose-6-phosphatase an important enzyme in carbohydrate metabolism and affects the hypothalamus. Acupuncture acts on the pancreas to enhance insulin synthesis, increase the number of receptors on target cells, and accelerate the utilization of glucose, resulting in lowering of blood sugar. Acupuncture also has an antiobesity effect, which is the most modifiable risk factor for type 2 diabetes. The therapeutic effect of acupuncture on diabetes is not the result of its action on one single organ but on multiple systems.<sup>[7]</sup> Acupuncture can be effective in treating complications of diabetes and is promising in patients with dietary control, physical exercise, breathing exercises and massage. Although acupuncture shows some effectiveness in treating diabetes, its mechanisms are still obscure.<sup>[7]</sup>

Since hot-tub therapy can increase blood flow to skeletal muscles, it has been recommended for patients with type 2 diabetes who are unable to exercise. Hot-tub therapy decreases weight, mean plasma glucose level and mean glycosylated hemoglobin.<sup>[6,7,33]</sup> However, caution should be taken that the water is not too hot as neuropathy may prevent the patient from noticing that they are burning themselves; proper water sanitation and appropriate guidance should be considered.<sup>[6]</sup>

### **Conventional management of diabetes mellitus**

#### **Insulin therapy (exogenous insulin)**

Insulin therapy restores normoglycemia, suppressing ketogenesis, delaying or arresting diabetic complications. Insulin also stimulates the synthesis of glucokinase and moderates the degree of gluconeogenesis.<sup>[9]</sup> Weight gain, hypoglycemia, skin reactions, insulin resistance due to antibody reaction, insulin lipid dystrophy, visual disturbance and allergy are common side-effects of insulin therapy. Insulin therapy is also unavailable to many communities in developing countries due to inaccessible health facilities and socioeconomic factors.<sup>[2]</sup>

#### **Oral glucose – lowering agents**

##### **Sulfonylurea**

These include sulfonylurea such as tolbutamide and glyburide. The mode of action of sulfonylureas could be chiefly explained by inhibition of KATP channels initiating insulin secretion from the pancreatic  $\beta$ -cells. This enhances the glycolytic flux and inhibits glucose output from the liver inhibiting gluconeogenesis.<sup>[34]</sup> Thus, these drugs could be used only in patients with type 2 diabetes having functional beta cells for endogenous insulin production. A significant side effect is hypoglycemia and weight gain due to hyperinsulinemia. The weight gain is implicated as a cause of secondary drug failure.<sup>[13]</sup>

##### **Biguanides**

These reduce hepatic glucose output, fasting glucose output and fasting glucose levels by increasing hepatic insulin sensitivity. They reduce intestinal absorption of glucose. These include the drug metformin derived from a medicinal plant, *Galega officinalis*.<sup>[11]</sup> Metformin is a biguanide agent that lowers blood glucose primarily by decreasing hepatic glucose production and increases muscle glucose uptake. It also reduces plasma triglyceride and low-density lipoprotein (LDL)-cholesterol levels and reducing insulin resistance. Metformin is used as monotherapy or in combination with sulfonylureas for the management of type 2 diabetes. The side-effects include weakness, fatigue, shortness of breath, nausea, dizziness, lactic acidosis, and kidney toxicity.<sup>[11]</sup>

### *Alpha-glucosidase inhibitors*

Alpha-glucosidase inhibitors, such as acarbose (Precose) and miglitol (Glyset), are indicated as monotherapy or in combination with sulfonylureas for management of type 2 diabetes. These are inhibitors of intestinal  $\alpha$ -glycosidase.<sup>[10]</sup> These agents inhibit the breakdown of complex carbohydrates and delay the absorption of monosaccharide from the gastrointestinal tract. The major side-effects are gas, bloating and diarrhoea.<sup>[10]</sup>

### *Thiazolidinediones*

These are represented by troglitazone, rosiglitazone and pioglitazone. The thiazolidinediones are a unique drug class of “insulin sensitizers” that promote skeletal muscle glucose uptake and to a much lesser extent, in the liver.<sup>[35]</sup> Troglitazone is the first agent of this drug class to be introduced in the United States of America market and like metformin, it reduces insulin resistance. Troglitazone is beneficial in patients requiring large daily amounts of insulin (more than 30 units/day) whose diabetes is still uncontrolled. Troglitazone is also effective when used in combination with other oral agents thereby potentially delaying the need to start insulin therapy.<sup>[36]</sup>

Molecular mechanisms of action of these agents are through binding avidly to peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ). Thiazolidinediones are selective agonists of PPAR $\gamma$ . When activated by a ligand, such as a thiazolidinedione, PPAR $\gamma$  binds to the 9-*cis* retinoic acid receptor retinoid X receptor to form a heterodimer. This binds to DNA to regulate the genetic transcription and translation of a variety of proteins involved in cellular differentiation and glucose and lipid metabolism.<sup>[37]</sup>

The potential role of the thiazolidinediones in reducing hepatic lipid content in non-alcoholic steatohepatitis is still under investigation. The thiazolidinediones do not increase insulin secretion. On the contrary, thiazolidinediones reduce insulin levels acutely, which may be a consequence of improved insulin sensitivity and/or reduced circulating fatty acids (as fatty acids stimulate insulin secretion). In the longer term, thiazolidinediones arrest the decline in  $\beta$ -cell function that occurs in type 2 diabetes, perhaps by protecting the  $\beta$ -cell from lipotoxicity. The thiazolidinediones are of no use in type 1 diabetes or in the occasional lean insulin-deficient (but insulin-sensitive) patient with type 2 diabetes.<sup>[37]</sup>

In addition to promoting adipogenesis and fatty acid uptake, thiazolidinediones improve insulin sensitivity by altering hormone production by adipocytes. Adipocytes secrete a number of important hormones, referred to as “adipokines,” including leptin, adiponectin, resistin and tumor necrosis factor- $\alpha$ .<sup>[38,39]</sup> The disadvantage of these

drugs is that they are expensive oral agents. These drugs decrease plasma triglyceride levels, but such decrease may be associated with weight gain and an increase in LDL – cholesterol levels.<sup>[40]</sup> Hepatotoxicity is a concern requiring monthly monitoring of liver function every month for the first 8 months of treatment and every other month for 4 months thereafter.<sup>[35]</sup>

### *Meglitinides*

One of the meglitinides is repaglinide. Repaglinide is an insulin secretagogue, the first of the meglitinide class. It is a member of the carbamoyl methyl benzoic acid family (glinides) introduced in early 1998. It is structurally different from the traditional sulfonylureas, but shows chemical resemblance to the nonsulfonylurea moiety of the glibenclamide molecule.<sup>[12]</sup> Nateglinide, the newest member of the class has recently become available. The meglitinides stimulate the release of insulin from the pancreatic  $\beta$ -cells. However, this action is mediated through a different binding site on the “sulfonylurea receptor” of the  $\beta$ -cells and the drugs have somewhat different characteristics when compared with sulfonylureas. In contrast to glibenclamide, meglitinides do not stimulate calcium-dependent exocytosis.<sup>[12]</sup> Unlike commonly used sulfonylureas, the meglitinides have a very quick onset of action and a short half-life. Repaglinide is a suitable option for patients with severe sulfa allergy who are not candidates for sulfonylurea therapy. The drug is used as monotherapy or in combination with metformin. The major side effects are weight gain, gastrointestinal disturbances and hypoglycaemia.<sup>[41]</sup>

## **Advancements in diabetes management**

### *Prevention of autoimmune attack*

There are several attempts made to control autoimmune attack on the  $\beta$ -cells and there are several on-going diabetes prevention trials worldwide. In general, it is preferable to start a specific immuno-modulatory treatment while substantial  $\beta$ -cells mass remains; that's during the prediabetic phase.<sup>[14,42]</sup> The vitamin B-complex nicotinamide is currently undergoing a multicentre trial in Europe. Nicotinamide is thought to protect against damage acting as an antioxidant and thus inhibits the deleterious effects of free radicals. It also inhibits the enzyme Poly (ADP-ribose) polymerase, thereby saving the cellular stores of nicotinamide adenosine diphosphate. Furthermore, it stimulates islet cell proliferation.<sup>[16]</sup> Another interesting immunosuppressive compound, which has shown encouraging results in newly diagnosed patients, is cyclosporine A, which acts by inhibiting T-helper lymphocyte function.<sup>[43]</sup> Unfortunately cyclosporin A must be given early and it has potentially serious side effects, including a toxic action on the  $\beta$ -cell itself.<sup>[16]</sup> Newer immunosuppressive drugs, such as FK-506/Transpl, are

under investigation, and some of these side effects may be avoided. Moreover, Bacillus Calmette-Guerin, a nonspecific immunostimulant, has been shown to induce extended remission in newly diagnosed patients by unknown mechanism.<sup>[15]</sup>

### Transplantation

Transplanting technology of either the pancreas or preparations of islet tissues is limited by the problem of obtaining donor tissue and preventing immune rejection of the graft.<sup>[17]</sup> Nevertheless, transplanting is as yet the only available treatment that can lead to insulin independence. Human allograft transplantation cannot be used on a large scale in clinical practice. After whole pancreas transplantation the graft survival after 1-year is 85–90%. Islet transplants are much more vulnerable. Many of them fail within few weeks or months after engraftment and most islet transplants.<sup>[17]</sup> The reasons for these functional failures are largely unknown, although insufficient numbers of islets, engraftment difficulties, chronic rejection and recurrence of autoimmune disease have been suggested to be contributing factors. Moreover, hyperglycemia in the recipient after transplantation deteriorates islet graft survival and function.<sup>[18]</sup>

One of the major obstacles for clinical islet transplantation is a lack of donors. Therefore, it is important to optimize the number of  $\beta$ -cells harvested from each donor, stimulate the growth and/or differentiation of  $\beta$ -cells or to genetically manipulate insulin-producing cell lines for transplantation.<sup>[17]</sup> The differentiated  $\beta$ -cells have the ability to proliferate at a low pace. The proliferation rate can be affected in many ways, for example, by growth stimulating hormones like growth hormone and prolactin. Also, the size and composition of the graft and the blood glucose level in the recipient are of crucial importance for  $\beta$ -cell replication.<sup>[17]</sup>

### Herbal management

The drawbacks of conventional therapy though effective, have led to seeking alternative therapy in herbal medicine. Many pharmaceutical drugs are derived from plants that were first used in traditional systems of medicine, and according to WHO, about 25% of medicines are plant-derived.<sup>[44]</sup> Traditional knowledge has proven a useful tool in the search for new plant-based medicines. Less than a quarter of the estimated 250,000 medicinal plant species have been investigated for hypoglycemic activity.<sup>[45]</sup> Moreover, only a small number of these have received a scientific medicinal evaluation to establish their efficacy. Examples of plants that have been documented for diabetic therapy in Africa have been reviewed and discussed subsequently.

## METHODOLOGY

This review was carried out using comprehensive and systematic literature reports on the use of traditional and conventional therapy in the management of diabetes and emergence of herbal therapy. Empirical searches were conducted using Google Scholar (<http://www.scholar.google.com>), and Science Direct (<http://www.science.direct.com>), PubMed and Medline for medicinal plants of African origin that have been studied and investigated for their antidiabetic therapeutic potentials both *in vivo* and *in vitro*. In addition to these databases, the University of Fort Hare's online database was also used. Some articles were found through tracking citations from other publications or by directly accessing the journals' website. The keyword combinations for the search were antidiabetic, antihyperglycemia, hypoglycemia, mode of action, medicinal plant, and Africa. Following the search, the antidiabetic plants were categorized and presented based on their mode of actions and parts of Africa they are used including East, West, North and Southern Africa.

### Plants used in the management of diabetes mellitus in Africa

#### Green tea (*Camellia sinensis*)

Green tea (leaves of *Camellia sinensis*, Theaceae) is a popular beverage in Kenya and East Asia, and also used as a herbal remedy in Europe and North America. Green tea is considered to be antiinflammatory, antioxidative, antimutagenic, and anticarcinogenic and can prevent cardiac disorders. Epidemiologically, it has been suggested that green tea consumption prevents type 2 diabetes.<sup>[46]</sup> Green tea extract contains polyphenols like catechin, epicatechin, epigallocatechin, and their gallates, tannin, and caffeine. Furthermore, the polyphenols in green tea extract have epigallo-catechin-3-gallate as the main constituent with anti-diabetic activity.<sup>[47]</sup> The extract also has pyrroloquinoline quinone, a newly discovered vitamin.<sup>[48]</sup> Some constituent components enhance the basal and insulin-stimulated glucose uptake, inhibit intestinal glucose uptake by inhibiting the sodium-dependent glucose transporter in the intestinal epithelial cells, and reduce serum glucose level in alloxan-diabetic rats.<sup>[49]</sup> Controversially, caffeine acutely lowers insulin sensitivity in humans.<sup>[50]</sup>

#### Onion (*Allium cepa*) and garlic (*Allium sativum*)

Onion (*A. cepa*) and garlic (*A. sativum*) contains active hypoglycemic constituents. Garlic (*A. sativum*) also contains hypoglycemic organic sulfur compounds.<sup>[51]</sup> Volatile oils in raw onion and garlic cloves lower fasting glucose concentration in both diabetic animals and human subjects. The active components are believed to be sulfur-containing compounds such as allyl propyl disulfide in onions and

diallyl disulfide (allicin) in garlic. These active ingredients lower glucose levels by competing with insulin (which is also a disulfide) for insulin-inactivating sites in the liver, resulting in an increase of free insulin. Onion extracts reduce blood sugar levels in a dose-dependent manner. A typical dosage of *A. cepa* is one 400 mg capsule daily while the general dosage of garlic is 4 g fresh garlic or 8 mg of the essential oil.<sup>[52]</sup>

#### ***Panax ginseng (Panax quinquefolius)***

*Panax ginseng* (*P. quinquefolius*) is widely used in Chinese medicine for over 2000 years. The root of ginseng has been used for over 2000 years in the Far East for its health promoting properties. It is also used in Northern Africa, especially in Egypt.<sup>[53]</sup> Of the several species of ginseng, *P. ginseng* (Asian ginseng) and *P. quinquefolius* (American ginseng) are commonly used. Constituents of all ginseng species include ginsenosides, polysaccharides, peptides, polyacetylenic alcohol, and fatty acids. Most pharmacological actions of ginseng are attributed to ginsenosides, a family of steroids named steroidal saponins.<sup>[54]</sup> The chemical composition of ginseng products and potency may vary with the plant extract derivative, the age of the root, the location where grown, the season when harvested, and the methods of drying. Both Asian and American ginseng has significant hypoglycemic action. The blood lowering effect appears to be attributed to ginsenoside Rb-2 and more specifically to panaxans I, J, K and L. But whether these constituents have a similar effect on type 2 diabetes is yet unknown.<sup>[55]</sup> The ginseng's mechanisms of action are thought to be: Slowing the digestion of food, decreasing the rate of carbohydrate absorption into portal hepatic circulation; ginseng may affect glucose transport, which is mediated by nitric oxide (NO); and lastly, ginseng may modulate NO-mediated insulin secretion and NO stimulates glucose-dependent secretion of insulin. However, the side-effects of ginseng are nervousness and excitation. The recommended daily ginseng dosage is 1–3 g of the crude root, or 200–600 mg of a standardized extract.<sup>[56]</sup>

#### ***Bitter Gourd (Momordica charantia)***

Bitter Gourd (*M. charantia*), also known as balsam pear is a tropical vegetable widely cultivated in parts of Asia, Africa, and South America, which has been extensively used in folk medicine as a remedy for diabetes.<sup>[57]</sup> The active, hypoglycemic constituents include charantin, obtained from an alcohol extract of the fruit, and a polypeptide called p-insulin (plant insulin or polypeptide-p) isolated from the fruit and seeds of the plant. The p-insulin consists of 166 residues containing 17 amino acids and has a molecular weight of 11,000. It is structurally and pharmacologically comparable to bovine insulin, and is composed of two polypeptide chains with disulfide bonds. p-insulin has an

onset of action similar to bovine insulin (30–60 min) and a peak hypoglycemic effect after 4 h in type I diabetics, compared with 2–3 h for regular insulin. Although the precise mechanism of action remains to be fully elucidated, *M. charantia* stimulates insulin release or possibly glycogen synthesis in the liver.<sup>[57]</sup> In addition, the plant is believed to contain several anti-diabetic principles. The hypoglycemic effects of this plant appears to be due to extra-pancreatic activity, including increased glucose utilization by the liver;<sup>[58]</sup> decreased glucose synthesis by depression of key gluconeogenic enzymes like glucose-6-phosphatase and fructose-1,6-biphosphatase; and enhancement of glucose oxidation through the shunt pathway via activation of glucose-6-phosphate dehydrogenase.<sup>[59]</sup> Interestingly, these herbs on an individual basis are reported to possess a variety of healthful properties, including blood glucose regulating, immunomodulation, liver detoxifying, and anti-inflammatory properties. These properties are significant to the diabetic as autoimmune processes are believed to play a role in the destruction of  $\beta$ -cells, and inflammation mediated by free radicals is also characteristic of the diabetic condition.<sup>[60]</sup>

The recommended dose of bitter melon depends on the form it is being consumed. Dosage for tincture ranges from 5 mL 2–3 times daily to as high as 50 ml/day. However, bitter melon juice is very difficult to make palatable since, as the name implies, it is quite bitter. To avoid the bitter taste, the Indians and Chinese crush the herbs and form tablets. In Central America, it is prepared as an extract or decoction.<sup>[60]</sup> Dosage of capsulized dried powder range from 3 to 15 g daily. That is quite a large dose so to avoid the necessity of taking so many capsules; a standardized extract may be used at dosages of 100–200 mg 3 times daily.<sup>[60]</sup>

#### ***Ackee fruit (Blighia sapida)***

Ackee is the National fruit of Jamaica and was imported from West Africa in the 18<sup>th</sup> century. It is a tall, leafy tree (up to 12 m) that produces clusters of fruits widely used for human consumption and for industrial purposes. The fruit is yellow in color and shaped like an oblong capsule that contains three cream-colored arils. The arils may be consumed safely when the fruit becomes red and opens under the light of the sun. It is then commonly boiled in water or milk and eaten alone or in meat or fish dishes. It is also consumed raw in some African countries. Ackee fruit contains hypoglycin, a natural toxin. It exists as a cyclic amino acid, hypoglycin A (HG-A), and its gamma-glutamyl derivative, HG-B. When the fruit is consumed unripe, it produces an acute toxic effect within 2–3 h with symptoms including nausea, vomiting, headache, and drowsiness. Coma and death may occur within 12 h in severe cases. The most toxic is HG-A, which is found in the unripe arils. HG-A is a water-soluble liver toxin that produces

hypoglycemia through the inhibition of gluconeogenesis, secondary to the limitation of cofactors (CoA and carnitine) that are essential for the oxidation of long-chain fatty acids.<sup>[61]</sup> The concentration of HG-A in the unripe ackee is 20 times greater than in the mature fruit. However the level of concentration of the toxin lowers rapidly after its exposure to the sun. The seeds contain HG-B and are always poisonous. An important factor seems to be the nutritional status of the person consuming ackee since diagnosed patients often present chronic malnutrition and vitamin deficiencies. When ingested unripe, ackee produces vomiting and fatal cases of poisoning.<sup>[61]</sup>

#### ***Khat (Catha edulis)***

*Catha edulis* popularly called khat is an evergreen shrub of the tropics. The fresh leaf is traditionally chewed by some people in East Africa and the Arabian Peninsula to attain a state of euphoria and stimulation. Since the leaf rapidly loses its effect upon wilting, the chewing habit has remained endemic to the areas where the plant is cultivated.<sup>[62]</sup>

In South Africa, the plant has found its way to the country due to influence of availability of this plant through improved road networks, and the availability of air transport, and the habit has spread considerably in those regions and countries where the plant does not.<sup>[62]</sup> Although it has been reported that there is moderate *in vitro* antidiabetic property of *C. edulis*,<sup>[63]</sup> there is no published scientific article substantiating this claim in animal models.

#### ***Fenugreek (Trigonella foenum graecum)***

*Trigonella foenum graecum* has been used as a remedy for diabetes, particularly in India and Africa. The active principal is in the defatted portion of the seed, which contains the alkaloid trigonelline, nicotinic acid and coumarin. Administration of the defatted seed (1.5–2.0 g/kg daily) reduces fasting and postprandial blood levels of glucose, glycagon, somatostatin, insulin, total cholesterol, and triglycerides and increased high-density lipoprotein-cholesterol levels.<sup>[60]</sup> Human studies have confirmed the glucose and lipid-lowering effects. The fiber constitutes potential mechanisms of fenugreek's beneficial effect in diabetic patients. Dosages of the fiber range from 10 to 100 g daily in divided dosages. The major side-effect is that the urine may have a maple syrup smell after fenugreek consumption.<sup>[60]</sup>

#### ***Gurmar (Gymnema sylvestre)***

*Gymnema sylvestre*, a plant native in the tropical forests of Africa and India, has long been used as a treatment for diabetes. It is postulated that *G. sylvestre* enhances the production of endogenous insulin. A typical dosage of *G. sylvestre* extract is 400–600 mg/day. One of its side-effects may be a reduction or loss of the taste sensation

of sweetness and bitterness although this occurs only if the plant is directly exposed to the tongue.<sup>[60]</sup>

#### ***Bitter leaf (Vernonia amygdalina)***

*Vernonia amygdalina* commonly known as bitter leaf is a small tree growing up to 3 m high. It occurs wild in most countries of tropical Africa. In South Africa, the plant is found in KwaZulu Natal, Mpumalanga, Eastern and Northern Cape Provinces. It is probably the most used plant in the genus *Vernonia*. The common and documented medicinal uses include treatment of malaria, venereal diseases, wounds, hepatitis, and diabetes. The leaves may be consumed either as a vegetable or aqueous extracts as tonics for the treatment of various illnesses. It has been reported that chloroform extract of the plant has hypoglycemic activity in both normoglycemic and alloxan-induced hyperglycemic rats. Ebong *et al.*,<sup>[64]</sup> also reported the anti-diabetic efficacy of combined ethanolic extracts of *Azadirachta indica* (neem) and *V. amygdalina* in rats. Also *V. amygdalina* extract alone shows hypoglycemic activity in diabetic rats.<sup>[65]</sup>

#### ***Aloe vera***

The dried sap (fluid) of *A. vera* is a traditional remedy used for diabetes in the Arabian peninsula and Africa. *A. vera* juice is prepared from *A. vera* gel, a mucilaginous preparation obtained from the leaves of the plant. Oral administration of the juice reduces fasting blood glucose and triglyceride levels in type 2 diabetic patients with or without combination of a conventional antidiabetic agent. The amount used is one tablespoon of *A. vera* juice with no significant adverse effects reported.<sup>[60]</sup>

#### ***Marula (Sclerocarya birrea)***

*Sclerocarya birrea* commonly known as marula is one of the most highly valued indigenous trees in southern Africa. It grows up to 15 m high with gray fissured bark, stout branchlets, and pale foliage. The leaves are compound, pinnate and the flowers greenish-white or reddish. The fruits are yellow and closely resemble the mango fruits. The pulp of the fruit is delicious, and the large nut is also edible. In Africa, the tree is commonly found in savannah regions, and its geographical distribution stretches from Gambia in the west across to Nigeria and Cameroon, in Central Africa, and to Ethiopia and Sudan in the east. In South Africa, the plant is commonly found in the Northern Province.<sup>[62]</sup> The Zulu people use the bark decoction to treat diarrhea, dysentery, fevers, stomach ailments, ulcers and bacterial-related diseases. Traditional Zulu healers wash in bark decoctions before treating patients with gangrenous rectitis and also administer the decoction to the patient.<sup>[62]</sup> Dimo *et al.*<sup>[66]</sup> has shown that a methanol/methylene chloride (1:1) extract of the plant reduces blood glucose and increases plasma insulin levels in diabetic rats.

The extract also prevents body weight loss and reduces plasma cholesterol, while the triglyceride and urea levels normalized with controls. It has also been reported that an aqueous stem-bark extract of the plant has hypoglycemic effect in normal and streptozotocin (STZ) treated diabetic rats.<sup>[67]</sup> These observations thus lend confidence to the folkloric use of the plant in the management and/or control of adult-onset diabetes in some African communities.

#### *Wild cucumber (Momordica foetida)*

*Momordica foetida* is a perennial climbing herb with tendrils and popularly known as Wild cucumber. It is commonly found in Gabon, Malawi, Ghana, Sudan, and Tanzania. The flowers are cream, often with a reddish or orange center, having the male and female flowers on the same plant. The characteristic fruit is bright orange with prickles, and the plant has a strong unpleasant smell. The herb is used to treat a number of ailments including hypertension, diabetes mellitus, fever and symptoms of malaria.<sup>[62]</sup> In diabetes management, the information is still obscure. An isolate from the plant, fetidin, has shown the exhibit hypoglycaemic effect in normal and not in diabetic rats.<sup>[68]</sup> Moreover, the mechanism of action of the plant has not been elucidated. These are classical examples of plants used in traditional medicine in the management of diabetes in Africa with different cultural background. Other plants used in East, West, North or Southern Africa are outlined in Tables 1-4.

These antidiabetic plants have been reported in different parts of the Africa for the treatment of diabetes with different therapeutic targets.<sup>[128]</sup> Some have been investigated in STZ and alloxan induced diabetic rats at different dosages to evaluate their antidiabetic potentials. The majority of these plants displayed hypoglycemic effect. Some of the mechanisms of action reported are related to inhibition of mitochondrial function, stimulation of glycolysis, activation of adenosine mono-phosphate kinase (AMPK) pathway, suppression of adipogenesis, uptake of glucose and induction of LDL. Also, some plants with anti-diabetic properties have also been reported to inhibit carbohydrate digestive enzymes such as  $\alpha$ -glucosidase and  $\alpha$ -amylase.<sup>[129]</sup> Antioxidant properties and modification of insulin structure or insulin receptor sensitivity, as well as up-regulation of glucose transporter of some plants, have been reported in several studies.<sup>[130]</sup>

In this review, it has been noted that there are several possible mechanisms through which these herbs can act to control the blood glucose level.<sup>[130]</sup> The mechanisms of action can be related, generally, to the ability of the plant in question (or its active principle) to lower plasma glucose level by interfering with one or more of the processes involved in glucose homeostasis.<sup>[8,130,131]</sup>

In a nutshell, the reported mechanisms whereby medicinal plants act as anti-diabetic therapies can be summarized as follows:

**Table 1: Some of the plants that are documented to be used in Southern Africa to manage diabetes mellitus**

Scientific name	Parts of the plant used	Mechanisms of actions	Type (class) of herb	Region commonly used	References
<i>Artemisia afra</i> (Asteraceae)	Leaf	Induces hypoglycemic effect; ameliorates oxidative stress	G, F	South Africa	[62,69]
<i>Aloe vera</i> (L.) Burm (Asphodelaceae)	Whole plant	Ameliorates oxidative stress	F	South Africa	[70,71]
<i>Aloe arborescens</i> (Asphodelaceae)	Leaf	Inhibits glucokinase and G6Pase activities	A	South Africa	[72]
<i>Artemisia roxburghiana</i> (Asteraceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	South Africa	[73]
<i>Allium sativum</i> (Alliaceae)	Garlic gloves	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	South Africa	[74]
<i>Allium cepa</i> (Alliaceae)	Bulbs	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	South Africa	[75]
<i>Brachylaena discolor</i> (Asteraceae)	Leaves, roots and stems	Stimulates glucose utilization in adipocytes	D	South Africa	[63]
<i>Cissampelos capensis</i> (Menispermaceae)	Leaves	Induces hypoglycemic effect	G	South Africa	[63]
<i>Salvia coccinia</i> (Lamiaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	South Africa	[73]
<i>Monstera deliciosa</i> (Araceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	South Africa	[73]
<i>Abies pindrow</i> (Pinaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	South Africa	[73]
<i>Catharanthus roseus</i> (Apocynaceae)	Juice leaf	Stimulates insulin release from $\beta$ -cells of Langerhans	C	South Africa	[76-78]

Contd...



**Table 1: Contd...**

Scientific name	Parts of the plant used	Mechanisms of actions	Type (class) of herb	Region commonly used	References
<i>Clausena anisata</i> (Rutaceae)	Root	Induces hypoglycemic effect	G	South Africa	[79]
<i>Ficus lutea</i> (Moraceae)	Leaves	Acts as $\alpha$ -amylase inhibitor in the gut	A	South Africa	[80]
<i>Ginkgo biloba</i> (Ginkgoaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	South Africa	[81]
<i>Gymnema sylvestre</i> (Asclepiadaceae)	Leaves	Inhibit carbohydrate absorption in the gut	A	South Africa	[82]
<i>Gynura procumbens</i> (Asteraceae)	Leaves	Lowers intestinal absorption of glucose; increase hepatic insulin sensitivity	A, D	South Africa	[83,84]
<i>Harpagophytum procumbens</i> (Pedaliaceae)	Root	Induces hypoglycemic effect	G	South Africa	[85]
<i>Hypoxis hemerocallidea</i> (Hypoxidaceae)	Tuber	Induces hypoglycemic effect	G	South Africa	[86]
<i>Leonotis leonurus</i> (Lamiaceae)	Leaf	Induces hypoglycemic effect	G	South Africa	[87]
<i>Momordia foetida</i> (Cucurbitaceae)	Whole plant	Induce hypoglycemic effect	G	South Africa	[68]
<i>Nelumbo nucifera</i> (Nymphaeaceae)	Rhizomes	Improves glucose uptake into the cells	D	South Africa	[88]
<i>Olea europaea</i> (Oleaceae)	Leaves	Regulate GLUT4 translocation	D	South Africa	[89]
<i>Opuntia streptacantha</i> L. (Cactaceae)	Fruits, stems	Stimulates insulin release from $\beta$ -cells of Langerhans	C	South Africa	[90]
<i>Psidium guajava</i> (Myrtaceae)	Leaves, roots	Increases glucose utilization in the liver and the muscles	A, D	South Africa	[63]
<i>Sclerocarya birrea</i> (Anacardiaceae)	Stem bark	Increases glucose utilization in the liver and the muscles	A, D	South Africa	[63,91,92]
<i>Solanum lycocarpum</i> (Solanaceae)	Fruits	Induces hypoglycemic effect	G	South Africa	[92]
<i>Strychnos henningsii</i> (Loganiaceae)	Leaves and bark	Induces hypoglycemic effect; ameliorates oxidative stress	G, F	South Africa	[93]
<i>Sutherlandia frutescens</i> (Fabaceae)	Plant shoot	Decreases intestinal glucose uptake; increases glucose uptake in muscle and adipose tissue; ameliorates oxidative stress	A, D, F	South Africa	[94]
<i>Syzygium cordatum</i> (Myrtaceae)	Leaves	Induces hypoglycemic effect; stimulates hepatic glycogenesis	A	South Africa	[95]
<i>Vernonia amygdalina</i> (Asteraceae)	Leaves	Induces hypoglycemic effect; ameliorates oxidative stress	G	South Africa	[63,65,66]
<i>Vinca major</i> (Myrtaceae)	Leaves, roots and stems	Increases glucose utilization in the liver and the muscles	C	South Africa	[64]

The herbs have been classified into type A, type B, type C, type D, type E, type F and type G herbs. G6Pase: Glucose 6 phosphatase

- Stimulation of insulin synthesis and/or secretion from pancreatic beta-cells
- Regeneration/revitalization of damaged pancreatic beta cells
- Improvement of insulin sensitivity (enhancement of glucose uptake by fat and muscle cells)
- Mimicking the action of insulin (acting like insulin)
- Slowing down the absorption of carbohydrates from the gut and altering glucose metabolizing enzymes
- Ameliorating oxidative stress.

Therefore, in this review, different medicinal plants used in Africa for management of diabetes have been classified based on their modes of action [Figure 1] including; inhibiting intestinal absorption of glucose and altering glucose metabolizing enzymes (type A herbs); having insulin mimetic properties (type B herbs); potentiating glucose-induced insulin release (type C herbs); enhance peripheral glucose

uptake (type D herbs); promote regeneration of  $\beta$ -cell of islets of Langerhans (type E herbs); and ameliorating oxidative stress (type F herbs). Some of the plants have been shown to induce hypoglycemic effect, but the mode of action still remains obscure, hence, they have been classified as type G herbs [Tables 1-4].

It is noted that, of the documented 65 plants used in treatment of diabetes in Africa as listed in Tables 1-4, 14 inhibit intestinal absorption of glucose and altering glucose metabolizing enzymes, three exhibit insulin-mimetic properties, seventeen stimulate insulin secretion from pancreatic beta cells, twelve enhance peripheral glucose uptake, one promotes regeneration of beta-cell of islets of Langerhans, 13 ameliorate oxidative stress and twenty induce hypoglycemic effect (mode of action is still obscure). Of these plants, thirteen of them have been identified to have duplicate mode of actions while one of them has three modes of actions.

**Table 2: Some of the plants that are documented to be used in West Africa to manage diabetes mellitus**

Scientific name	Parts of the plant used	Mechanisms of actions	Type (class) of herb	Region commonly used	References
<i>Aloe vera</i> (L.) Burm (Asphodelaceae)	Whole plant	Ameliorates oxidative stress	F	West Africa	[70,71]
<i>Artemisia roxburghiana</i> (Asteraceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	West Africa	[73]
<i>Achyranthes aspera</i> L. (Amaranthaceae)	Whole plant	Ameliorates oxidative stress	F	West Africa	[96]
<i>Azadirachta indica</i> (Meliaceae)	Roots	Promotes regeneration of $\beta$ -cells and stimulates insulin release from the $\beta$ -cells	C, E	West Africa	[97,98]
<i>Allium sativum</i> (Alliaceae)	Garlic gloves	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	West Africa	[74]
<i>Allium cepa</i> (Alliaceae)	Bulbs	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	West Africa	[75]
<i>Abroma augusta</i> (Sterculiaceae)	Leaves	Ameliorates oxidative stress	F	West Africa	[99]
<i>Salvia coccinia</i> (Lamiaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	West Africa	[73]
<i>Monstera deliciosa</i> (Araceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	West Africa	[73]
<i>Abies pindrow</i> (Pinaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	West Africa	[73]
<i>Camellia sinensis</i> (Theaceae)	Leaves	Inhibits rate-limiting gluconeogenic enzymes, PEPCK and G6Pase	A	West Africa	[76]
<i>Catharanthus roseus</i> (Apocynaceae)	Juice leaf	Stimulates insulin release from $\beta$ -cells of Langerhans	C	West Africa	[76-78]
<i>Cinnamomum cassia</i> (Lauraceae)	Bark	Stimulates insulin release from $\beta$ -cells of Langerhans	C	West Africa	[100]
<i>Garcinia kola</i> Heckel (Clusiaceae)	Stem bark	Inhibit carbohydrate absorption in the gut	F	West Africa	[101]
<i>Ginkgo biloba</i> (Ginkgoaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	West Africa	[81]
<i>Gongronema latifolium</i> (Asclepiadaceae)	Whole plant	Activates hepatic hexokinase and decreases the activities of glucokinase; ameliorates oxidative stress	A, F	Nigeria	[102,103]
<i>Gymnema sylvestre</i> (Asclepiadaceae)	Leaves	Inhibit carbohydrate absorption in the gut	A	West Africa	[82]
<i>Gynura procumbens</i> (Asteraceae)	Leaves	Lowers intestinal absorption of glucose; Increase hepatic insulin sensitivity	A, D	West Africa	[83,84]
<i>Irvingia gabonensis</i> (Irvingiaceae)	Tuber	Exerts hypolipidaemic effects to alleviate hyperglycaemia; ameliorates oxidative stress	F	Nigeria	[104]
<i>Juniperus communis</i> (Cupressaceae)	Whole plant	Potentiates glucose induced insulin secretion; potentiates peripheral glucose utilization	C, D	West Africa	[105]
<i>Loranthus begwensis</i> (Loranthaceae)	Whole plants	Induces hypoglycemic effect	G	Nigeria	[106]
<i>Mangifera indica</i> (Anacardiaceae)	Leaves	Reduce the intestinal absorption of glucose	A	Nigeria	[107]
<i>Ocimum canum</i> (Lamiaceae)	Whole plant	Enhances insulin release from $\beta$ -cells of pancreas	C	Ghana	[108]
<i>Olea europaea</i> (Oleaceae)	Leaves	Regulate GLUT4 translocation	D	West Africa	[89]
<i>Opuntia streptacantha</i> L. (Cactaceae)	Fruits, stems	Stimulates insulin release from $\beta$ -cells of Langerhans	C	Africa	[90]
<i>Opuntia megacantha</i> (Cactaceae)	Fruits, stems	Inhibit carbohydrate absorption in the gut	A	West Africa	[109]
<i>Pycnanthus angolensis</i> (Myristicaceae)	Leaves, stems	Induces hypoglycemic effect	G	West Africa	[110]
<i>Sclerocarya birrea</i> (Anacardiaceae)	Stem bark	Increases glucose utilization in the liver and the muscles	A, D	Gambia, Nigeria and Cameroon	[63,91,92]
<i>Tetrapleura tetraptera</i> (Fabaceae)	Fruit	Induces hypoglycemic effect	G	West Africa	[111]

The herbs have been classified into type A, type B, type C, type D, type E, type F and type G herbs. G6Pase: Glucose 6 phosphatase; PEPCK: Phosphoenolpyruvate carboxykinase

**Table 3: Some of the plants that are documented to be used in East Africa to manage diabetes mellitus**

Scientific name	Parts of the plant used	Mechanisms of actions	Type (class) of herb	Region commonly used	References
<i>Aloe vera</i> (L.) Burm (Asphodelaceae)	Whole plant	Ameliorates oxidative stress	F	East Africa	[70,71]
<i>Artemisia roxburghiana</i> (Asteraceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[73]
<i>Aspilia pluriseta</i> (Compositae)	Roots	Induces hypoglycemic effect	G	Kenya	[112]
<i>Allium sativum</i> (Alliaceae)	Garlic gloves	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	East Africa	[74]
<i>Allium cepa</i> (Alliaceae)	Bulbs	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	East Africa	[75]
<i>Caesalpinia volkensii</i> (Caesalpinaceae)	Leaves	Induces hypoglycemic effect	G	Kenya	[113]
<i>Salvia coccinia</i> (Lamiaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[73]
<i>Monstera deliciosa</i> (Araceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[73]
<i>Abies pindrow</i> (Pinaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[73]
<i>Camellia sinensis</i> (Theaceae)	Leaves	Inhibits rate-limiting gluconeogenic enzymes, PEPCK and G6Pase	A	West and East Africa	[76]
<i>Catha edulis</i> (Celastraceae)	Leaves	Induces hypoglycemic effect	G	East Africa	[63]
<i>Catharanthus roseus</i> (Apocynaceae)	Juice leaf	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[76-78]
<i>Cinnamomum zeylanicum</i> (Lauraceae)	Bark	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[100]
<i>Olea europaea</i> (Oleaceae)	Leaves	Potentiate glucose-induced insulin release; increase peripheral uptake of glucose	C, D	East Africa	[89]
<i>Cogniauxia podoleana</i> Baillon (Cucurbitaceae)	Leaves	Induces hypoglycemic effect	G	Democratic Republic of Congo	[114]
<i>Erythrina abyssinica</i> (Fabaceae)	Stem bark	Induces hypoglycemic effect	G	Kenya	[115]
<i>Ficus sycomorus</i> (Moraceae)	Stem bark	Induces hypoglycemic effect	G	Kenya	[80,116]
<i>Ginkgo biloba</i> (Ginkgoaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[81]
<i>Gymnema sylvestre</i> (Asclepiadaceae)	Leaves	Inhibit carbohydrate absorption in the gut	A	East Africa	[82]
<i>Gynura procumbens</i> (Asteraceae)	Leaves	Lowers intestinal absorption of glucose; Increase hepatic insulin sensitivity	A, D	East Africa	[83,84]
<i>Kleinia squarrosa</i> (Asteraceae)	Stem bark	Induces hypoglycemic effect	G	Kenya	[117]
<i>Maesa lanceolata</i> (Myrsinaceae)	Fresh fruit	Ameliorates oxidative stress	F	East Africa	[118]
<i>Olea europaea</i> (Oleaceae)	Leaves	Regulate GLUT4 translocation	D	East Africa	[89]
<i>Opuntia robusta</i> (Cactaceae)	Fruits	Ameliorates oxidative stress	F	East Africa	[119]
<i>Opuntia streptacantha</i> L. (Cactaceae)	Fruits, stems	Stimulates insulin release from $\beta$ -cells of Langerhans	C	East Africa	[90]
<i>Pycnanthus angolensis</i> (Myristicaceae)	Leaves, stems	Induces hypoglycemic effect	G	East Africa	[110]
<i>Solanum lycocarpum</i> (Solanaceae)	Fruits	Induces hypoglycemic effect	G	Kenya	[92]
<i>Strychnos henningsii</i> (Loganiaceae)	Leaves and bark	Induces hypoglycemic effect; ameliorates oxidative stress	G, F	East Africa	[93]
<i>Tetrapleura tetraptera</i> (Fabaceae)	Fruit	Induces hypoglycemic effect	G	East Africa	[111]

The herbs have been classified into type A, type B, type C, type D, type E, type F and type G herbs. G6Pase: Glucose 6 phosphatase; PEPCK: Phosphoenolpyruvate carboxykinase

## CONCLUSION

It can be concluded on the basis of the above mentioned reviews that the majority of anti-diabetic medicinal

plants exert their blood glucose lowering effect through stimulation of insulin release from pancreatic beta-cells or through alteration of some hepatic enzymes involved in glucose metabolism and decreasing intestinal glucose

**Table 4: Some of the plants that are documented to be used in North Africa to manage diabetes mellitus**

Scientific name	Parts of the plant used	Mechanisms of actions	Type (class) of herb	Region commonly used	References
<i>Aloe vera</i> (L.) Burm (Asphodelaceae)	Whole plant	Ameliorates oxidative stress	F	North Africa	[70,71]
<i>Artemisia roxburghiana</i> (Asteraceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	North Africa	[73]
<i>Allium sativum</i> (Alliaceae)	Garlic gloves	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	North Africa	[74]
<i>Allium cepa</i> (Alliaceae)	Bulbs	Possess insulin mimetic properties; regulates GLUT4 translocation	B, D	North Africa	[75]
<i>Psacalium decompositum</i> (Asteraceae)	Roots	Induces hypoglycemic effect	G	North Africa	[120]
<i>Salvia coccinia</i> (Lamiaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	North Africa	[73]
<i>Monstera deliciosa</i> (Araceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	North Africa	[73]
<i>Abies pindrow</i> (Pinaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	North Africa	[73]
<i>Catharanthus roseus</i> (Apocynaceae)	Juice leaf	Stimulates insulin release from $\beta$ -cells of Langerhans	C	North Africa	[76-78]
<i>Coriandrum sativum</i> (Apiaceae)	Seeds	Possess insulin like activity; potentiates insulin releasing	B, C	North Africa	[121]
<i>Eruca sativa</i> (Cruciferae)	Seeds	Ameliorates oxidative stress	F	Egypt	[122]
<i>Foeniculum vulgare</i> (Apiaceae)	Whole plant	Inhibit carbohydrate absorption in the gut	F	Morocco	[123]
<i>Ginkgo biloba</i> (Ginkgoaceae)	Whole plant	Stimulates insulin release from $\beta$ -cells of Langerhans	C	North Africa	[81]
<i>Gymnema sylvestre</i> (Asclepiadaceae)	Leaves	Inhibit carbohydrate absorption in the gut	A	North Africa	[82]
<i>Gynura procumbens</i> (Asteraceae)	Leaves	Lowers intestinal absorption of glucose; Increase hepatic insulin sensitivity	A, D	North Africa	[83,84]
<i>Olea europaea</i> (Oleaceae)	Leaves	Regulate GLUT4 translocation	D	North Africa	[89]
<i>Opuntia streptacantha</i> L. (Cactaceae)	Fruits, stems	Stimulates insulin release from $\beta$ -cells of Langerhans	C	North Africa	[90]
<i>Opuntia megacantha</i> (Cactaceae)	Fruits, stems	Inhibit carbohydrate absorption in the gut	A	North Africa	[109]
<i>Panax ginseng</i> (Araliaceae)	Leaves	Potentiates AMP phosphorylation in liver and muscle. Improves insulin sensitivity associated with insulin resistance	A, C	Egypt	[124]
<i>Urtica dioica</i> (Fabaceae)	Leaves	Induces hypoglycemic effect; stimulates insulin release from $\beta$ -cells of Langerhans	C	Algeria, Morocco	[125,126]
<i>Zizyphus spina-christi</i> (Rhamnaceae)	Leaves	Potentiates glucose utilization in the cells; activates liver phosphorylase and G6Pase enzymes	A, D	Egypt	[127]

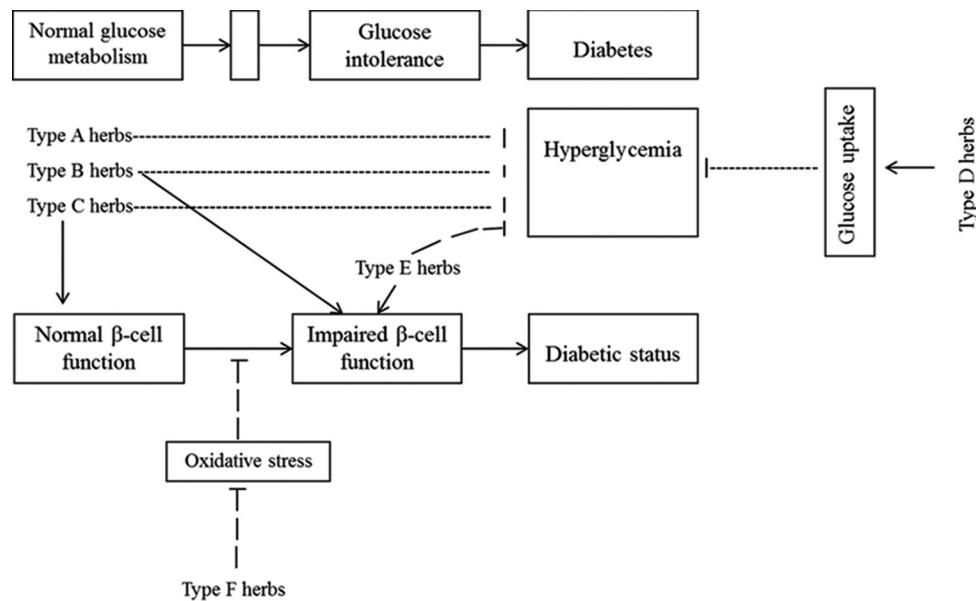
The herbs have been classified into type A, type B, type C, type D, type E, type F and type G herbs. AMP: Activated protein kinase

absorption. Another point of note in the above-mentioned reviews is that a given plant and/or its product may exert its blood glucose lowering effect through a combination of more than one mechanism.<sup>[131-133]</sup> These plants also have a similar mode of action as the conventional drugs used in the management of diabetes mellitus hence due to their advantages and accessibility; herbal therapy has surpassed conventional therapy. Moreover, traditional knowledge has proven a useful tool in the search for new plant-based medicines.

A review of literature suggests that most researchers utilize strategies that are more or less similar to one another to study medicinal plants with alleged anti-diabetic potential. That is, candidate plants are collected, extracted and screened for hypoglycemic activity using either *in vitro* or *in vivo* bioassay techniques. Then, active compounds are

isolated and identified from plants through fractionation guided bioassays. Then blood glucose lowering mechanism of action of the crude plant extract and/or active ingredients is investigated. Therefore, these studies have led to findings which are still obscure. Therefore, while the metabolic activities of these plants are well established, the molecular mechanism underlying their biological activities remains unknown.

There is a need to use molecular tools to determine genes that act as molecular signatures to be involved in the diagnosis of the disease, monitor the herbal therapeutic progress and determine the effectiveness of the bioactive compounds in efficient manner. It is vital to embrace computational biology tools to study the identified compounds in relation to existing anti-diabetic drugs in order to improve potency and efficacy of bioactive



**Figure 1:** Mechanisms underlying plants used in traditional medicine in the management of diabetes mellitus. Some inhibit intestinal absorption of glucose and alter glucose metabolizing enzymes (type A herbs); have insulin mimetic properties (type B herbs); potentiates glucose-induced insulin release (type C herbs); enhances peripheral glucose uptake (type D herbs); promotes regeneration of  $\beta$ -cell of islets of Langerhans (type E herbs); and ameliorates oxidative stress (type F herbs)

compounds, hence develop novel drugs for diabetes management. Considering the rich cultural traditions of plant use and the high prevalence of diabetes mellitus in Africa, more investigations should be encouraged in order to validate the anti-diabetic activity of the identified plants as claimed by the traditional healers.

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## AUTHOR'S CONTRIBUTIONS

CMK carried out the study and wrote the manuscript; AJA contributed to conception of the review and supervised the manuscript writing. All authors have read and approved the final manuscript.

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