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Antidiabetic potential of some less commonly used plants in traditional medicinal systems of India and Nigeria

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ABSTRACT

The incidence of diabetes mellitus continue to rise annually all over the world with India and Nigeria having recorded cases of 65.1 and 3.9 million respectively in 2013 and expected to increase by a large amount in 2035. Hyperglycemia is a pre-condition for the development of diabetic complications and is accompanied by an increase in the production of free radicals. The present available treatment option for diabetes like sulfonylurea, metformin and alpha-glucosidase are restricted by their limited actions, secondary failure rates, and side-effects; and unaffordable to the majority of the population. Hence, the need to screen for more medicinal plants with antidiabetic ability due to the fact that plants are; biodegradable, safe and cheap with fewer side-effects. In this review article, we have presented the current status of diabetes in India and Nigeria and the role of some less commonly used medicinal plants from both countries that have antidiabetic potential.

KEY WORDS: Antidiabetic plants, diabetes, hypoglycaemic activity, medicinal plants, oxidative stress

INTRODUCTION

The World Health Organization (WHO) defines diabetes mellitus (DM) as a degenerative and chronic disease that occurs when the pancreas does not produce enough insulin, or when the body cannot effectively use insulin [1]. It is a disorder of the metabolism of carbohydrates, fats, and lipids, which is characterized by a high fasting blood sugar [2]. It manifests as chronic hyperglycemia and leads to the development of diabetes-specific micro vascular pathology in the retina, glomerulus and peripheral nerve culminating into serious complications affecting the eyes, kidneys and arteries [3,4].

WHO statistics shows that worldwide 347 million people have diabetes and 80% of diabetic deaths occur in low and middle-income countries [1]. According to the International Diabetes Federation, India is ranked second only to China in the list of top ten countries for a number of people with diabetes. [5]. In Africa, it is estimated that about 19.8 million adults have diabetes with Nigeria and South Africa having 3.9 and 2.6 million, respectively. It is estimated that by 2035, the percentage of diabetic patients in Africa would cross an alarming figure of 58% [5].

Type 2 diabetes, is the major form of diabetes accounting for 90-95% of all diabetic cases [6] and nearly half of all patients suffering from the disease are older than 65 years of age [7]. It is a complicated and divergent disease which in addition to blood sugar control requires the management of lipid parameters, blood pressure and thrombotic factors [8].

The treatment for diabetes is both difficult and tedious; it is expensive, costly and not affordable by majority of African and Asian populations [9]. The current treatments for DM include the use of insulin and synthetic drugs such as sulfonylurea, metformin, alpha-glucosidase inhibitors and thiazolidinedione's in addition to lifestyle adjustments. These synthetic drugs are valuable but restricted by their limited action, pharmacokinetic properties, secondary failure rates and accompanying side-effects like hypoglycemia, damage to liver, lactic acidosis, diarrhea, abdominal pain, weight loss and loss of appetite [7,10-12].

Due to the problems associated with the current treatments, a large percentage of diabetics resort to alternative remedies that are purported to improve glycemic control [8]. The WHO estimated that approximately 80% of the world's population rely mainly on traditional medicines for their primary health care [13]. The screening of medicinal plants for novel bioactive compounds is, therefore, an important goal for scientists. Importantly, the plant based drugs are biodegradable, safe, and cheap, having fewer side-effects, in India, China and other ancient traditional medicinal systems in the world, medicinal plants have been the major source of treatment for DM since time immemorial [14-16].

The importance of research on medicinal plants is validated by the fact that a plethora of new drugs have been developed from plants; relevant examples include cromolyn used as bronchodilator, developed from *Ammi visnaga* (L) Lamk;

galegine, from *Galega officinalis* L, which is a model for the synthesis of metformin and other bisguanidine-type antidiabetic drugs, papaverine from *Papaver somniferum* which forms the basis of cerapramil used in the treatment of hypertension, [17]. *Artemisia annua* (Quinhaosu) gave rise to artemininin, this compound and it analogs are now used as antimalarial therapy in many countries [18]. Paclitaxel (Taxol®), the most exciting plant-derived anticancer drug discovered in recent years, is derived from several key precursors (the baccatins) in the leaves of various Taxus species; *Taxus brevifolia* [19].

Although the role of natural product in new drug discovery is encouraging and has frequently resulted in development of new drugs [20], the success of drug discovery depends on evolving stringent criteria to avoid false positive drug candidates. Surfeit of information warrants proper documentation. The evaluation of the scientific efficacy of traditional systems of medicine is an area of great interest especially in developing economies where sometimes the cost of medication may be prohibitive. Excellent reviews [13,21-23] on antidiabetic plants have already been written. This current review aims to bring in focus and document the use of less commonly used antidiabetic plants on which fewer studies have been conducted. Some of these plants, albeit less researched, hold immense potential as antidiabetic therapeutic agents in India and Nigeria.

ANTIDIABETIC PLANTS USED IN NIGERIA AND INDIA

The climatic conditions in Nigeria and India support the growth and thriving of various plant species and hence the use of these plants by the poor population to ameliorate disease conditions. There are about 800 plants that may possess antidiabetic properties according to ethno botanical information [24]. Most of the current drugs available have been directly or indirectly derived from plants. An example is metformin that was derived from the plant *G. officinalis* L.

The plants with antioxidant and antidiabetic potential included in this review are *Azadirachta indica* (AI) A. Juss, *Mangifera indica* (MI) L, *Terminalia arjuna* Roxb. Ex DC, *Terminalia catappa* L, *Terminalia chebula* Retz, *Syzygium cumini* (L) Skeels, *Syzygium aromaticum* (L) Merr. and L.M. Perry, *Vernonia amygdalina* (VA) Delile and *Xylopia aethiopica* (XA) (Dunal) A. Rich.

The general botanical data, taxonomic data, distribution in the world, experimental design, compounds isolated, mechanism of action, the antidiabetic and antioxidant capability of the plants are presented below:

Mangifera indica L. (Common Name: Mango)

Mango in an important species of the family anacardiaceae and the genus *Mangifera*, it is native to South East Asia from where it spread all over the world, it is the most popular fruit in the tropical and subtropical regions of the world. It is the national fruit of India, Pakistan, Philippines and the national tree of Bangladesh [25].

The plant is widely grown in Nigeria, where in addition to the fruit consumption it is used for the treatment and management of diabetes [26]. The peel and pulp of the plant contain carotenoids, and polyphenols such as quercetin, kaempferol, gallic acid, caffeic acid, catechins, tannins, mangiferin, leucocyanidin, epiatechin, quercetin and chromogenic acid [27]. Phenolics have scavenging activity on free radicals mainly due to the presence of hydroxyl groups. Recently, Mohan *et al.* [28] isolated a compound 1, 2, 3, 4, 6-penta-O-gallolyl-β-D-glucose from the methanolic extract fraction of mango that is a potent inhibitor of 11-β-hydroxysteriod hydrogenase enzyme and ameliorates high fat diet (HFD) induced diabetes in C57BL/6 mice.

Mangiferin (1, 3, 6, 7-tetrahydroxy-xanthone-C2-β-D-glucoside) a bioactive compound isolated from MI possesses a wide range of pharmacological actions including being anticancer [29,30], antibacterial [31], anti HIV [32], antioxidants [33], and antidiabetic [34,35].

The administration of mangiferin at a dose of 10 and 20 mg/Kg body weight (i.p.) in type 1 and 2 diabetic rats for 30 days showed significant antidiabetic, hypo-lipidemic, alpha amylase and alpha-glucosidase inhibitory effect [36]. This glucoside has also been shown by Li *et al.* [37] to improve renal function of diabetic nephropathy in rats and its inhibitory effect on overexpression of transforming growth factor-β1, advanced glycation end and extracellular matrix accumulation, Polyol pathway activation, reactive oxygen species (ROS) generation and mesangial cells proliferation. Miura *et al.* [38] demonstrated that the mangiferin exerts its antidiabetic activity by decreasing the insulin resistance.

The ethanolic extracts of MI showed significant free radical scavenging activity and have cytoprotective (anti-apoptotic) effect; the leaves and fruits extract reduce the absorption of glucose in type 2 diabetes and stimulate glycogenesis in liver causing reduction in blood glucose level [39].

Vernonia amygdalina Delile (Asteraceae)

VA is a perennial shrub-like plant with green leaves growing up to 1.3-3 m high that is native to Africa, widely grown in Nigeria and West Africa. It is reported to contain phytochemicals useful in the treatment and management of certain diseases. It has been introduced into India and is now being cultivated in parts of central and eastern India [40].

VA is rich in amino acids, minerals and vitamins [41]. The decoction from the leaves is often used in the African traditional treatment for the management of diabetes, malaria, infertility, and sexually transmitted diseases [42-47]. The plant is said to have antimalarial compounds like alkaloids, tannins, and saponins [48] and also anticancer properties [49]. In comparison to other plants, VA accounted for 9.2% of medicinal plants used as an alternative medicine in central Nigeria [50]. In Nigeria, a dosage form of freeze-dried aqueous leaf extract of this plant has been developed and formulated, which is suitable for therapeutic use in the management of DM. Mostly in Nigeria, the decoction

from the leaf is often used in combination with that of other plants by traditional healers and medical practitioners to treat diabetes, fever and gastrointestinal problems [51].

The ethanolic extracts of the plant has a strong bioactive compound that has blood sugar lowering action in rats and can serve as an effective antioxidant [52], Ong *et al*. [53] showed that VA has anti-hyperglycemic effect on streptozotocin (STZ)-induced diabetic rat model and this effect is mediated through the inhibition of key hepatic G6pase, which causes an increase in expression and translocation of GLUT4 in skeletal muscles. The combined leaf extract of A. *indica* (AI) and VA ameliorates hyperglycemia and hepatic oxidative stress in diabetic rats [54] and the methanolic extract of VA has the ability to mitigate cycasin-induced oxidative damage in colonic tissues [55].

The composite decoctions of VA, *Gongronema latifolium* (Benth) and *Occimum gratissimum* (Linn) reduced the postprandial blood glucose concentrations of diabetic subjects [56]. Two flavonoids and terpenoids: Vernolide and edotides have been isolated from the VA plant. Octahydrovernodalin is the most important bitter principle in the plant [57]. Ong *et al*. [58] also isolated four main polyphenols in the ethanolic extract namely dicaffeoyl-quinic acid, chlorogenic acid, 1,5-dicaffeoyl-quinic acid and luteolin-7-O-glucosidase. Dicaffeoyl-quinic acid is the most abundant in the plant. The administration of 400 mg/Kg body weight of VA extract is found to exert most effective anti-hyperglycemic activity [59].

The two major glucose transporters that regulate glucose uptake into the tissues are GLUT1 (non-insulin responsive) and GLUT4 (insulin-responsive). While G6pase is one of the rate-limiting gluconeogenic enzymes that regulate, the synthesis of glucose and results has shown strong suppression of G6pase activity by extracts of VA [60]. VA extract was found also to protect pancreatic β-cells and the polyphenols present are responsible for this action especially dicaffeoyl-quinic acid.

Most of the traditional uses of the plant have been systematically and scientifically validated and the study of oxidative stress in diabetic rats showed that the aqueous extracts of VA decrease the levels of serum malondialdehyde an indication of the antioxidant property of the plant [60].

Xylopia aethiopica (Dunal) A. Rich

XA, also known as the African pepper or Ethiopian pepper, belongs to the family annonaceae and the genus *Xylopia*. It is a tropical, slim, tall and aromatic tree that grows up to 15-30 m. It is found in the west, central and southern Africa in humid forest zones, native to Nigeria, Ghana, Kenya, Ethiopia, Senegal and Uganda.

XA is a common ethno medicine in West Africa where it is used in the treatment of rheumatism and arthritis, cough, stomachache, bronchitis, biliousness and dysentery [61]. The fruit and vegetable have many medicinal properties and contains phytochemicals, vitamins and minerals. Phytochemicals like flavonoids are potentially anti-allergic, anti-carcinogenic, anti-viral and antioxidants, the ethanolic extract of XA was found to increase steroid hormone [62], the aqueous extract was also shown to have anti-amylase and anti-lipase activity with antioxidant potentials [63].

A poly-herbal formulation sold in Nigeria containing the following: *Stachytarpheta angustifolia, Alstonia congensis, and* XA in the ratio 3:2:1 was found to have hypoglycemic and hyperlipidemic activities [64].

Syzygium aromaticum (Linn.) Merrill and Perry (Myrtaceae) (Common Name: Cloves)

S. aromaticum (clove) belongs to the family myrtaceae and the genus *Syzygium*. Native to Indonesia, this plant can grow to a height of 8-12 m, it is an aromatic flower bud commonly used in Africa, Asia and other parts of the world for the preparation of different spicy dishes. In Nigeria most traditional medical practitioners use the fruits and cloves by boiling in water and the decoction is administered to patients for the treatment of cough, chest congestion and catarrh and the compound eugenol present in this plant is responsible for the aroma and has antioxidative and antimycotic ability [65].

A triterpenoid compound extracted from the clove plant named oleanolic acid has potent diuretic/saluretic, anti-hyperlipidemic, antioxidant and hypoglycemic effects [66], Ngubane *et al*. [67] showed that oleonolic acid exhibited anti-hyperglycemic effect in STZ-induced diabetic rats by the attenuation of the activities of glycogenic enzymes and the compound eugenol present in this plant is responsible for the aroma and has antioxidative and antimycotic ability. The oil from the extract of this plant protects experimental animals from hepato-nephrotoxicity and oxidative stress due to aflatoxins [68].

Clove bud powder (CBP) possesses high phenolic content, free radical scavenging activity and metal chelating and reducing properties, the major phenolic compounds found are Kaempferol, isoquercitrin, gallic acid, ellagic acid, and caffeic acid [69]. Dietary supplementation of CBP in type 2 diabetic rats showed anti-hyperglycemic, hepatoprotective, hypolipidemic and antioxidant activities, by suppressing oxidative stress and delaying carbohydrate digestion [70].

Oleanolic acid (3 β-hydroxy-olea-12-en-28-oic acid) and maslinic acid have been reported to modulate the activity of the intestinal glucose transporters and carbohydrate hydrolyzing enzymes thus reducing postprandial hyperglycaemia and that the ethanolic extract of this plant suppresses elevated blood glucose levels in type 2 diabetic KK-A^y mice [70].

Free and bound phenolic extract of clove bud was found to inhibit carbohydrate hydrolyzing enzymes; alpha-amylase and alpha-glucosidase in a dose-dependent manner (200-800 μg/ml) [71]. Decreasing the postprandial hyperglycemia peak is very crucial in the treatment of diabetes; there is a strong correlation between the phenolic content of clove and the enzyme inhibitory

activities and with a strong antioxidant property which is the mechanism and the basis for its anti-diabetic action [71].

Azadirachta indica A. Juss (Common Name: Neem)

AI A. Juss is a member of the Meliacea family and the genus Azadirachta. It is a fast-growing tree that can reach up to 15-20 m and can sometimes reach 40 m. The plant is native to India and adapted to sub-arid and sub-humid tropical climates. It is widely grown in India, Pakistan, Indonesia, Sri Lanka, Caribbean, Nigeria, South and Central America. It is called "Dogonyaro" in Nigeria and grown all over the country, especially in the northern region. The plant has been used in the Indian Ayurveda traditional medicine for over 2000 years for the healing of various diseases and ailments [72].

The composite leaf extract of AI and VA at 500 mg/Kg body weight ameliorates hypoglycemia and hepatic oxidative stress in STZ-induced diabetic rats [54]. AI leaves glucosamine an active component of neem leaves is responsible for immunostimulatory activity in albino mice [73].

The chloroform extract of AI administered on murine diabetic model for 21 days significantly reduced the fasting blood sugar and islet regeneration and protection properties [74]. The administration of 500 mg/kg body weight of AI leaf extract and AI bark extract was effective in improving the antioxidant status in cardiac and skeletal muscles [75]. Khosla *et al*. [76] showed that azadirachtin and nimbin are the active ingredients in AI and they have the ability to regenerate the pancreatic beta cell. Recently Tiwari *et al*. [77] showed that the administration of the composite extract of *Aegle marmelos*, AI, *Murraya koengii*, *Occimum sanctum*, and *S. cumini* at 100 mg/Kg body weight caused a significant reduction in the blood sugar level, total cholesterol, triglyceride, low-density lipoproteins and an increase in the level of high-density lipoproteins.

Syzygium cumini (L.) Skeels

This plant belongs to the family myrtaceae and the genus *Syzygium*; it is an evergreen tropical plant native to South East Asia and widely grown in Africa. The fruit of the plant is widely used in cooking as spice and condiments to add flavor to foods.

S. cumini is well-known for its antidiabetic properties; gallic acid, rutin and chlorogenic acid are the main phenolic present in this plant and the extracts of all parts of the plant is used in traditional medicine [78]. Aqueous extract is found to improve endothelial dysfunction, antioxidant, anti-inflammatory and anti-thrombic properties of adenosine deamine activity in erythrocytes [78].

A dose of 400 mg/kg body weight of aqueous seed extract of *S. cumini* has hypoglycemic, insulin sensitizing and hypo-lipidemic activity in HFD-STZ induced rats due to an increase in peroxisome proliferator-activated receptor $(PPAR)_{y}$ and $PPAR_{\alpha}$ protein expression [79]. The active fraction of *S. cumini* was found to regenerate pancreatic islets and insulin secretion in STZ-induced diabetic mice [80]. Sharma *et al*. [81] demonstrated that the aqueous extract of *S. cumini* seed when given orally to mice at a dose of 250 mg/kg body weight for 21 days effected and repaired the liver damage associated with alloxan diabetes. The extract of this plant inhibits alpha-glucosidase and alpha-amylase, which are the two enzymes responsible for the metabolism of carbohydrate, and this limits the postprandial glucose and consequently controlling diabetes [82]. The seed extract is found to act as a chemo-protective agent against *in vivo* oxidative stress and genomic damage [83].

Terminalia catappa. L.

This plant belongs to the family Combretacea and to the genus Terminalia found growing in the warmer parts of India, Asia, Africa and Australia. The tree is primarily used as an ornamental and as a shade tree; the seeds are edible like almonds. The extracts of the bark and leaves are reported to have anticancer and aphrodisiac capability [84], antioxidant and anti-inflammatory [85] and anti-malarial [86]. This may be as a result of high contents of tannins in the plant making them a good source of antioxidants [87]. Kinoshita *et al*. [88] isolated chebulagic acid and corilagin from the 50% ethanol extract of the plant with a strong free radical scavenging activity and these compounds are found to have hepato-protective and antioxidant actions, by suppressing the generation of ROS followed by the inhibition of apoptosis.

Terminalia arjuna (Roxb) Wight and Arn

This is a plant belonging to the family Combretaceae and genus Terminalia commonly called arjuna. It is a large tree found throughout the South Asia region, and it is an exotic tree in India, it can grow up to a height of 25-30 m. The bark and fruits of this plant is used in traditional Indian medicine as an anti-dysentric, anti-pyretic, astringent, cardiotonic, lithotriptic, anticoagulant, hypolipidemic and anti-microbial, the large amount of flavonoids is responsible for the antioxidant and anti-microbial properties [89]. The bark contains arjunine a lactone, arjunetin, essential oils and reducing sugars. The methanolic extract exhibited analgesic activity and acute anti-inflammatory activity [90]. The extracts of this plant have the presence of alkaloids, triterpenoids, tannins and flavonoids. Gallic acid, apigenin, luteolin, quercetin, epicatechin, ellagic acid and 1-O-galloyl glucose are some of the compounds that have been isolated from this plant [91].

A dose of 250 and 500 mg/kg body weight of *T. arjuna* extract was found to have reno-protective and antioxidant ability in isolated perfused kidneys [92]. The leaf extracts when administered at a dose of 100 and 200 mg/kg body weight orally to STZ-induced diabetic rats was found to significantly normalize blood glucose level and this is due to its antioxidant role [93]. Due to the presence of tannins, saponin, and flavonoids, the bark extract exhibited antidiabetic activity by enhancing the peripheral utilization of glucose by correcting the impaired liver and kidney glycolysis and by limiting gluconeogenic formation, an action similar to that of insulin [94]. Perveen *et al*. [95] showed that

Table 1: Summary of the selected plant species with their active component and their therapeutic effects

Plant species name	Used component	Property/effect	References
MI L.	1, 2, 3, 4, 6-penta-O-gallolyl-β-D-glucose	Inhibits 11-β-hydroxysteriod hydrogenase enzyme. antidiabetic	[23]
	Mangiferin (1, 3, 6, 7-tetrahydroxy-xanthone-C2-β-D-glucoside)	Improve renal function of diabetic nephropathy in rats. Decrease insulin resistance	[29,30,32,33]
VA Delile	Ethanolic extracts	Lowers blood sugar	[48]
	Dicaffeoyl-quinic acid	Protect pancreatic β cells	[55]
XA (Dunal) A. Rich.	Aqueous extract	Anti-amylase, anti-lipase activity with antioxidant potentials	[58]
S. aromaticum (Linn.) Merrill and Perry	Oleanolic acid	Anti-hyperlipidemic, antioxidant and hypoglycaemic	[6]
	Oleanolic acid and maslinic	reducing postprandial hyper-glycaemia	[65]
AI A. Juss	Chloroform extract	Reduced fasting blood sugar, islet regeneration	[70]
	Azadirachtin and Nimbin	Regeneration of pancreatic beta cells	[72]
S. cumini (L.) Skeels	Aqueous seed extract	Hypoglycaemic, insulin sensitising and hypo-lipidemic activity in HFD-STZ induced rats. Repaired liver damage associated with alloxan diabetes	[74,76]
T. catappa. L	Chebulagic acid and Corilagin	Antioxidants	[83]
T. arjuna (Roxb)	Leaf extracts	Normalise blood glucose levels	[88]
Wight and Arn	Ethanolic extracts	Inhibit oxidation and lipid degradation	[91]
T. chebula Retz	Methanolic extracts	Plant inhibits lipid peroxide formation and scavenge hydroxyl and superoxide radical	[94]

MI: *Mangifera indica*, VA: *Vernonia amygdalina*, XA: *Xylopia aethiopica*, AI: *Azadirachta indica, S. aromaticum: Syzygium aromaticum, S. cumini: Syzygium cumini, T. catappa: Terminalia catappa, T. arjun: Terminalia arjuna , T. chebula: Terminalia chebula*, HFD: High fat diet, STZ: Streptozotocin

the antioxidant activity of *T. arjuna* bark extract is due to the rich concentration of tannins, triterpenoid and saponins like arjunic acid, arjunolic acid, arjungenin, arjunglycosides, gallic acid, ellagic acid, oligomeric proanthocyanidins, and that the antidiabetic activity is due to the stimulation of β-cells of the pancreatic islets. The administration of *T. arjuna* ethanolic extracts at a dose of 250 mg/kg body weight per oral was found to reverse diabetic condition by inhibiting oxidation and degradation of lipids [96], and due to the fact that *T arjuna* extract has the ability to reduce postprandial hyperglycemia an important cardiovascular risk factor in type 2 diabetic patients, it has got a promising anti-hyperglycaemic and hypo-lipidemic effects in type 2 diabetics [97].

Terminalia chebula Retz. (Combretaceae)

This plant belongs to the family combretaceae, and the genus *Terminalia* found growing in the Sub-Himalayan tracts. It is a tall tree plant rising to about 15-25 m. It is a revered plant in India and has been extensively used in the Ayurveda, Unani and Homeopathic medicine. It has a beneficial effect on digestive diseases, urinary diseases, diabetes, skin, heart, irregular fevers, constipation, ulcers, vomiting, colic pain and hemorrhoids [98]. Phyto-constituents present in this plants is hydrolysable tannins like gallic acid, chebulagic acid, punicalagin, chebulamin, corilagin, neochebulini acid, ellagic acid, casuarinas and 2,3,6-tri-O-galloyl-β-D-glucose, 1,6-di-O-galloyl-D-glucose and terchebulin. The methanolic extracts from the plant inhibits lipid peroxide formation and scavenge hydroxyl and superoxide radicals [99]. The methanolic extract of *T chebula* has antioxidant, anti-inflammatory and anticancer ability and the phenolic derivatives, hydrolysable tannins and oleanane type triterpenoids are the active principles [100]. Chebulagic acid from *T. chebula* at 100 mg/kg body weight significantly reduced postprandial blood glucose levels of Sprague-Dawley rats when compared to the control group.

CONCLUSION

The present review presents the current scientific literature with respect to the antidiabetic and antioxidant potential of *AI*, *MI*, *T. arjuna*, *T. catappa*, *T. chebula*, *S. cumini*, *S. aromaticum*, VA *and* XA; summarize in Table 1. These plants are not the most popular when it comes to their use as antidiabetic plants used in traditional medicine, but yet they are widely used in some traditional medicinal system in India and Nigeria. It is hoped that further studies on these plants will target the isolation, purification and characterization of the bioactive compounds, which may lead to the discovery of potent antidiabetic drugs for the management and treatment of diabetes.

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