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Overview of Anti-Diabetic Medicinal Plants: The Nigerian Research Experience

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Abstract

Medicinal plants have been used since ancient times for the treatment and management of diabetic mellitus (DM) in traditional medicine systems of many cultures throughout the world. Recently, the World Health Organization (WHO) recommended the use medicinal plants for the management of DM and further encouraged the expansion of the frontiers of scientific evaluation of the hypoglycemic properties of diverse plant species. Accordingly, the hypoglycemic activity of a vast number of plant products have been evaluated and confirmed in animal models as well as in human beings. In some cases, the bioactive principles of the medical plants have been isolated and identified. In order to harness these natural resources and maximize the socioeconomic benefits derivable from Nigerian medicinal plants efforts should be geared toward research funding and deployment of Research and Development (R & D) policy framework into medicinal plants research endeavours.

Keywords: Diabetic mellitus; Bioactive principles; Medicinal plants; Nigeria

Introduction

Overview

Herbal medicines involve the integration of several therapeutic experiences and practices of indigenous systems of medicine that may span many previous generations, which often provide valuable guidelines to the selection, preparation and application of herbal formulation with a view to providing therapeutic benefits. Treatment of illness and maintenance of health/well-being using herbal medicines is the oldest and most popular form of healthcare practice known to humanity that has been practiced by all cultures in all ages throughout the history of civilization.

Medicinal plants have been used since ancient times for the treatment and management of diabetic mellitus (DM) in traditional medicine systems of many cultures throughout the world [1,2]. Currently, medicinal plants continue to play an important role in the management of DM, especially in developing countries, where many people do not have access to conventional anti-diabetic therapies [3,4]. In developed countries, the use of anti-diabetic herbal remedies has been on the decline since the introduction of insulin and synthetic oral hypoglycemic drugs during the early part of the 20th century. However, recently in the developed countries, there has been the resurgence of interest in medicinal plants that exhibit hypoglycemic property [5]. The renewed interest in herbal anti-diabetic remedies in developed countries is believed to be motivated by several factors that include: adverse reactions, high secondary failure rates and cost of conventional synthetic anti-diabetic remedies [1]. Recently, the World Health Organization (WHO) recommended the use medicinal plants for the management of DM and further encouraged the expansion of the frontiers of scientific evaluation of hypoglycemic properties of diverse plant species [6]. Consequently, current estimates showed that over 70% of the global population applies resources derived from traditional medicine for the management and alleviation of DM and its complications [5,7,8].

Ethno-pharmacological surveys indicate that more than 1,200 plants are used in traditional medicine systems following claims of their hypoglycemic properties [3,9]. The hypoglycemic activity of a large number of plant products have been evaluated and confirmed in animal models [10-13] as well as in human beings [14,15]. In some cases, the bioactive principles of the medical plants have been isolated and identified [3,11,15]. Nevertheless, the mechanisms of action of most of these anti-diabetic bioactive principles are not well defined and remain largely speculative. However, reports suggest that the array of anti-diabetic bioactive principles in medicinal plants may act in synergy to exert glycemic control [16,17] through interference with one or more processes involved in glucose metabolism and homeostasis [3,18].

The present review sought to highlight some experimentally confirmed anti-diabetic medicinal plants and their bioactive principles that have been implicated in exerting glycemic control. By extension, the outlook and regular form in which scientific investigations on some Nigerian indigenous anti-diabetic medicinal plants are designed and carried out, coupled with the obvious limitations of these research findings were also considered for review.

Common anti-diabetic medicinal plants

It is worthwhile to note here that there is yet no effective cure for DM and available drugs and insulin therapy used for the management of the disease are associated with several undesirable side effects [19-21]. The undesirable side effects and high cost of anti-diabetic drugs led to the search for medicinal plants that exhibit hypoglycemic property, with a view to applying them for the management of DM [22,23]. Several species of medicinal plants used for the management of DM worldwide have been evaluated. Some of theplants include: *Allium cepa* (Onion), *Allium sativum* (Garlic), *Aloe vera*, *Cinnamomum cassie*,

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Coccinia indica, *Gymmema slyvestre* (Gurnar), *Momordica charantia* (Bitter Melon), *Catharanthus roseus* (Madagascar Periwinkle), *Muurrayi komingii*, *Ocimum sanctum*, *Panax ginseng*, *Trigonella foemum-graecum* (Fenugreek) *Pterocarpus marsupium* (Indian Kino) and *Syzigium cumini* [3,18,24-26]. A survey of several medicinal plant research findings showed that the polysaccharides, sterols, terpenoids, alkaloids, saponins, flavonoids, amino acids and their derivatives are the most encountered bioactive principles that exhibited glycemic control in experimental animals [18,24,27].

Onion (*Allium cepa*); Alliaceae and garlic (*Allium sativum* L.) [28-30]

Oral administration of onion (*A. cepa* L.) and garlic (*A. sativum* L.) to alloxan-induced diabetic rats for 30 days ameliorated hyperglycemia, reversed weight loss and depletion of liver glycogen. The anti-diabetic bioactive principles of *A. cepa* L. and *A. sativum* L. were *S*-methylcysteinesulfoxide (SMCS) and *S*-allylcysteinesulfoxide (SACS) respectively. The studies showed that SMCS and SACS exerted their anti-diabetic properties by stimulating insulin secretion as well as compete with insulin for insulin inactivating sites in the liver. Specifically, SACS inhibited gluconeogenesis in the liver. In addition, SACS from *A. sativum* L impeded lipid peroxidation due to its antioxidant and secretagogue actions. The capacities of *A. cepa* L. and *A. sativum* L. to alleviate DM in the experimental rats were comparable with diabetic rats treated with glibenclamide and insulin. The study also noted that SMCS and SACS caused significant increase in the biosynthesis of cholesterol from acetate in the liver, which was an indication of low capacities of allium products to protect the rats against risk factors associated with DM.

Aloe vera (Aloe barbedensis); Aspholedeceae [31,32]

A 1.0 µg of five phytosterols- lophenol, 24-methyl-lophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylene-cycloartanol from *A. vera* exhibited comparable capacities to lower blood glucose levels in Type II diabetic BKS.Cg-m+/+Lepr$^{db/J}$ (*db*/*db*) mice following 28 day treatment. The five phytosterols caused significant decrease in blood HbA_{1c} levels by 15-18%. Additionally, severe diabetic mice treated with the five phytosterols did not suffer weight loss because of rapid excretion of glucose in the urine. The findings suggested that phytosterols derived from *A. vera* gel have a long-term blood glucose lowering effect, which could be applied as agents of glycemic control in Type 2 DM. Studies showed thatphytosterols stimulate the biosynthesis and/or release of insulin as well as alter the activity of carbohydrate metabolizing enzymes.

Catharanthus roseus [L.] G. Don; Apocynaceae [33,34]

The Madagascar periwinkle (*C. roseus*), is a traditional remedy and was marketed in England as 'Vinculin' for the treatment of DM. Earlier studies showed that leaf aqueous extracts of *C. roseus* administered orally to rabbits and dogs caused hypoglycemic response. Similar studies using variety of laboratory animals and limited clinical trials gave negative or at best equivocal results. Alkaloids, notably, catharanthine (17), leurosine (18), lochnerine (19), tetrahydroalstonine (20), vindoline (21), and vindolinine (22) are the major anti-diabetic principles present in *C. roseus*. Specifically, studies showed that vincamine (23) and (-)-eburnamonine (24) caused extensive decrease in rat brain tissue glucose concentration, with concomitant increase in lactate and pyruvate concentrations as well as the lactate pyruvate ratio and increase in tissue ATP contents. *In vitro* studies showed that the quinoline derivatives, quinolate and 3-mercaptopicolinate, inhibited hepatic gluconeogenesis from lactate or alanine by inhibiting muscle cytosolic/mitochondrial phosphoenolpyruvate carboxykinase and cytosolic aspartate aminotransferase activities. Certainly the active alkaloids analogs of *C. roseus* exhibited oral hypoglycemic activity of one third capacities when compared with tolbutamide.

Oral administration of dichloromethane:methanol (1:1) leaf and twig extracts of *C. roseus* at dose = 500 mg/kg to streptozotocin (STZ)-induced diabetic rats for 7 and 15 days gave 48.6 and 57.6% hypoglycemic activity, respectively. The same dose for 30 days exhibited protective effect against STZ challenge. The anti-diabetic action of *C. roseus* was as a result of inhibition of hepatic glycogen synthase, glucose 6-phosphate-dehydrogenase, succinate dehydrogenase and malate dehydrogenase activities coupled with increased mobilization of glucose following treatment of the experimental rats. Similarly, the same dose of *C. roseus* extracts ameliorated oxidative stress as exemplified by lower levels of 2-thiobarbituric acid reactive substances (TBARS) in diabetic rats following treatment.

Cinnamomum cassie (Chinese cinnamon); Lauraceae [35]

Cinnamon methylhydroxychalcone polymer (MHCP) from cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. Therefore, MHCP may be useful in the treatment of Type II DM and in the study of the pathways leading to glucose utilization in peripheral cells.

Coccinia indica; cucurbibaceae [36,37]

Orally administered pectin materials isolated from fruit extracts of *C. indica* at dose = 200 mg/100 g body weight/day caused hypoglycemia in normal rats. The study noted that pectin materials caused significant reduction in blood glucose and an increase in the liver glycogen as a result of increase in hepatic glycogen synthetase activity and corresponding reduction in phosphorylase activity. Hypoglycemic effect of ethanolic extract of *C. indica* is partly due to the repression of the key gluconeogenic enzyme (glucose-6-phosphatase), but did not affect alanine aminotransferase and aspartate amino transferase activities, in starved male rats.

Fiscus bengalensis; Moraceae [38]

Leucopelargonidin-3-0-alpha-L rhamnoside from dimethoxy ether extract of Indian Banyan tree *F. bengalensis* Linn bark at a medium effective dose = 100 mg/kg caused hypoglycemia and increased blood insulin levels in normal and moderately alloxan-induced diabetic dogs following two hours oral administration. The bioactive glycoside stimulated insulin secretion in the experimental animals. Furthermore, acute (doses = 0.2-1.8 g/kg) administration to mice and chronic (doses = 100, 250 and 500 mg/kg) daily administration to rats for a period of one month respectively did not elicit toxic effects even at the high dose of 1.8 g/kg in experimental animals.

Gymmema slyvestre (Gurnar); Asclepiadaceae [39,40]

G. sylvestre extracts at various doses caused decreased blood sugar level in STZ-induced diabetic rat models, which was comparable with the standard anti-diabetic drug-tolbutamide. Also, human experiments showed that GS4 (dose = 400 mg/day), a water-soluble extract from leaves of *G. sylvestre*, administered to patients suffering from insulin-dependent diabetes mellitus (IDDM) and placed on insulin therapy, caused the normalization of their serum lipid profiles, whereas insulin

requirements together with fasting blood glucose and glycosylated haemoglobin (HbA_{1c}) and other glycosylated plasma protein levels remained higher than that of the control subjects. Nevertheless, GS4 therapy appears to enhance endogenous insulin biosynthesis, possibly by regeneration/revitalization of the residual β-cells of IDDM individuals.

Ginseng (Panax ginseng); *Araliaceae* and Fenugreek (*Trigonella foenum-graecum* L.) [41,42]

In vivo experiments using STZ-induced diabetic rats chronically administered with food mixed with steroid saponins from the seeds of fenugreek (*T. foenum-graecum* L) (dose = 12.5 mg/300 g body weight per day) showed significantly increase in food intake as well as the motivation to eat in normal rats. it also stabilized the food consumption in diabetic rats, which resulted in a progressive weight gain in these animals, in contrast to untreated diabetic controls. Aerobic exercise in combination with ginsenosides from *P. ginseng* promote lower serum lipid, regulate lipid metabolism, promote anti-oxidation, and enhance immune activity.

Momordica cymbalaria (Bitter Melon); Cucurbiteae [43,44]

Oral and intra-peritoneal administration of aqueous fruit extracts of *M. charantia* to normal rats lowered the glycemic response without altering the insulin response. Also, aqueous extract and the residue after alkaline chloroform extraction reduced hyperglycemia in diabetic mice after 1 hour. The recovered plant matters by acid water wash of the chloroform extract following alkaline water wash engendered a slower hypoglycemic effect. These findings suggested that orally administered *M. charantia* extracts lower glucose concentrations independently of intestinal glucose absorption and involved an extra-pancreatic effect.

In another study, *M. cymbalaria* fruit powder caused reduction in blood sugar concentrations in alloxan-induced diabetic rats following 15 days treatment. Elevated serum cholesterol and triglycerides levels were lowered with significant improvement in hepatic glycogen level in treated diabetic rats. The study showed the anti-diabetic and hypolipidemic properties of *M. cymbalaria* fruit powder.

Muurrayi komingii (Cury leaf); *Rutaceae* [11,12]

A single oral administration of aqueous leaf extracts of *M. koenigii* (doses = 200, 300 and 400 mg/kg) lowered blood glucose level in normal and alloxan-induced diabetic rabbits. The reduction on blood glucose levels in normal and mild diabetic rabbits corresponded to 14.68% and 27.96% following 4 hours of oral administration of 300 mg/kg of the leaf extract. Likewise, 300 mg/kg of the leaf extract caused a marked improvement in glucose tolerance by 46.25% in sub-diabetic and 38.5% in mild diabetic rabbits at 2 hours post prandial test. The study suggested that the aqueous leaf extracts of *M. koenigii* may be prescribed as adjunct to dietary therapy and treatment of DM. *Aegle marmelos* possess anti-diabetic and hypolipidemic effects in diabetic rats.

Ocimum sanctum (Holy basil); Lamiaceae [45]

Alcoholic leaf extract *O. sanctum* ameliorates hyperglycemia in normal-glucose fed hyperglycemic and streptozotocin-induced diabetic rats by potentiating the action of exogenous insulin in the rats. The anti-diabetic action of alcoholic leaf extract *O. sanctum* was comparable with that of the standard anti-diabetic drug-tolbutamide.

Allium cepa, Allium sativum, Aloe vera, Cajanus cajan, Coccinia indica, Caesalpinia bonducella, Ficus bengalenesis, Gymnema sylvestre, Momordica charantia, Ocimum sanctum, Pterocarpus marsupium, Swertia chirayita, Syzigium cumini, Tinospora cordifolia and Trigonella foenum-graecum [3]

All the above named plants stimulate insulin release from isolated pancreatic Islets cells by virtue of their phytochemical contents, especially the saponins and glycosides fractions.

Polygala senega; Polygalaceae [18]

The triterpenoid glycoside-Senegin-II and saponins are the main anti-diabetic components of *P. senega* (L.). Study showed that n-butanol extract of *P. senega rhizomes* (SN) (dose = 5.0 mg/kg) caused reduction in the blood glucose of normal and KK-Ay mice following 4 hours intra-peritoneal administration. However, STZ-induced diabetic mice did not experience significant change in the blood glucose following the administration of SN. The study proposed that the hypoglycemic effect of SN occurs without altering plasma insulin concentration.

Syzigium cumini (Eugenia janbolaria); *Mytaceae* [46]

At the dose levels of 200 and 400 mg/kg, ethyl acetate and methanol extracts of *S. cumini* (Myrtaceae) seed exhibited significant anti-inflammatory activity in carrageenan induced paw edema in Wistar rats. This anti-inflammatory activity of the plant extract could be of therapeutic benefit by ameliorating increased inflammatory response associated with DM.

Trigonella foemum-graecum (Fenugreek) [47]

T. foenum-graecum (Fenugreek) seeds fraction (dose = 0·5 g/kg body weight) significantly exerted glycemic control in normal, Type I or Type II diabetic rats. The soluble dietary fibre (SDF) fraction controlled elevation of blood glucose after oral ingestion of sucrose in normal and Type II diabetic rats. Intestinal disaccharides activity and glucose absorption were sufficiently suppressed, whereas gastrointestinal motility increased following treatment of the rats with SDF fraction. Daily oral administration of SDF to Type II diabetic rats for 28 days caused decreased serum glucose level but increased liver glycogen content with enhanced total antioxidant status. Serum insulin and insulin secretion were not affected by the SDF fraction. Overall, *T. foenum-graecum* seed extracts enhanced glucose transport in 3T3-L1 adipocytes as well as increased insulin sensitivity. Therefore, SDF fraction of *T. foenum-graecum* seeds exerted anti-diabetic effects through inhibition of carbohydrate digestion and absorption, and enhancement of peripheral insulin action. The anti-diabetic bioactive principles and possible mechanism of action of these medicinal plants are summarized in Table 1.

Nigerian medicinal plants with confirmed anti-diabetic activity

DM is rapidly emerging as a major public health problem in Nigeria. Close to a decade ago, the prevalence rate of Type II DM, according to the International Diabetes Foundation/WHO reports, was estimated to be over 3.4% of 24 million Nigerian DM sufferers between the ages of 20-79 years and with projected estimate of 3.9% rise in 2025 [48,49]. Furthermore, death rates arising from DM and related complications in other sub-Saharan African countries range from 21 to 49 per 100 000 persons, compared with 18 in the USA and 6 per 100 000 persons in the UK [50].

A number of Nigerian indigenous and naturalized medicinal plants used and recommended by traditional healers and herbalists

Plant and family	Plant part used	Bioactive principles	Mechanism of action	References
Allium cepa (Onion); Alliaceae	Onion bulbs.	• S-methyl cysteine sulphoxide. • S-allylcysteinesulphoxide.	• Stimulate insulin secretion. • Compete with insulin for insulin inactivating sites in the liver.	[28,29]
Allium sativum (Garlic); Alliaceae.	Garlic gloves	• S-methyl cysteine sulphoxide. Precursor of allicin and garlic oil.	• Stimulate insulin secretion. • Inhibit glucose production by the liver	[28,30]
Aloe vera (Aloe barbedensis); Aspholedeceae	Leaf, pulp and gel.	• Phytosterols.	• Stimulate synthesis and/or release of insulin • Alter the activity of carbohydrate metabolizing enzymes.	[31,32]
Catharanthus roseus; Apocynaceae	Fresh leaf juice.	• Alkaloids: catharanthine, leurosine and vindolinine. • Taninins.	• Increase hepatic utilization of glucose. • Suppress activities of gluconeogenic enzymes.	[33,34]
Cinnamomum cassie (Chinese cinnamon); Lauraceae	Bark.	• Cinnamaldehyde. • Cinnamic alcohol. • Methyl hydroxyl chaconne polymer.	• Enhance insulin action. • Increase glucose uptake and glycogen synthesis.	[35]
Coccinia indica; Cucurbitaceae	Leaves.	• Beta sitosterol. • Pectin	• Suppress glucose-6-phosphatase. • Stimulate glycogen synthase activity and reduction of phosphorylase activity.	[36,37]
Fiscus bengalensis; Moraceae	Leaves and bark.	• Lecoperlargonin derivative.	• Increase insulin secretion. • Inhibit insulinase activity.	[38]
Gymmema slyvestre (Gurnar); Asclepiadaceae	Leaves.	• Gymnenosides and gymnemic acid (from saponin fraction). • Trilepene glycosides.	• Stimulate insulin secretion from rat Islets. • Decrease the activity of gluconeogenic enzymes. • Induce β-cell regeneration.	[39,40]
Ginseng *(Panax ginseng); Araliaceae* Fenugreek *(Trigonella foenumgraecum* L.)	Roots and leaves.	• Polysaccharides. • Ginsenosides (steroidal saponins).	• Slow absorption and digestion of carbohydrates. • Affect NO mediated glucose transport.	[41,42]
Momordica cymbalaria (Bitter Melon); Cucurbiteae	Fruit pulp, seeds, leaves and whole plant.	• Charantin (a peptide). • Insulin-like polypeptide P (vegetable insulin).	• Stimulate insulin secretion. • Suppress the activity of gluconeogenic enzymes. • Increase β-cells in diabetic rats.	[43,44]
Muurrayi komingii(Cury leaf); *Rutaceae.* Aegle *marmelos Corr.* (Rutaceae)	Leaves.	• Carbazole alkaloids. • Copolin-α-glucose.	• Stimulate insulin secretion. • Increase glycogenesis and decrease glycogenolysis and gluconeogenesis.	[11,12]
Ocimum sanctum (Holy basil); Lamiaceae	Leaves.	• Pectins.	• Stimulate insulin secretion.	[45]
Allium cepa,Allium sativum,Aloe vera, Cajanus cajan, Coccinia indica, Caesalpinia bonducella, Ficus bengalenesis, Gymnema sylvestre, Momordica charantia, Ocimum sanctum, Pterocarpus marsupium, Swertia chirayita, Syzigium cumini, Tinospora cordifolia and Trigonella foenumgraecum	Whole plant	• Saponins and glycosides	• Hypoglycemic and anti-hyperglycemic activity. • Stimulate insulin release from isolated pancreatic Islets.	[3]
Polygala senega; Polygalaceae	Rhizomes	• Triterpenoid glycoside-Senegin-II • saponins	• Decrease hepatic glucose output. • Increase insulin sensitivity.	[18]
Pterocarpus marsupium; Falcaceae	Bark.	• Epicatechin and catechin (tannins). • Pterostibene (flavonoid),	• Prevent beta cell damage in rats. • Regenerate functional pancreatic β-cells. • Enhance insulin secretion.	[3]
Syzigium cumini (Eugenia janbolaria); Mytaceae	Seeds, leaves and fruit pulp.	• Mycaminose.	• Stimulate kinases involved in peripheral utilization of glucose.	[46]
Trigonella foemum-graecum (Fenugreek); Falcaceae	Seeds.	• Alkaloids- trigoneline; nicotinic acid and coumarins. • 4-hydroxy isoleucine. • Galaclomannan.	• Slow digestion and absorption of carbohydrates. • Increase glucose-induced insulin secretion. • Enhancement of peripheral insulin action.	[47]

Table 1: Some common anti-diabetic bioactive principles of medicinal plants.

for the treatment of DM have been investigated for their anti-diabetic properties using animal models. Most of the studies on medicinal plants with anti-diabetic potentials have been conducted in several Nigerian Research Institutes and Universities [17,26,49,51-54]. Almost all of these scientific investigations were carried out using chemically induced diabetic rats. A few other studies have also been conducted using *in vitro* cell culture-based bioassays [55].

The names of some Nigerian indigenous anti-diabetic medicinal plants investigated, design of the experiment and outcomes of the investigations are summarized in Table 2.

Plant and family	Plant part used	Study design	Experimental findings	References
Aloe arborescens; Asphodelaceae	AE of leaf gel	Normal and alloxan-induced diabetic rats; 21 day treatment.	• Decrease FBG in diabetic rats. • Restore plasma insulin and TAG levels. • Increase glucokinase activity.	[56]
Brachylaena discolor; Astaraceae	DCM:MeOH (1:1) extracts of roots, leaves and stem	*In vitro* bioassay using cultured Chang liver, 3T3-L1 adipose and C2C12 muscle cells.	• Increase glucose utilization in 3T3-L1 adipocytes, Chang liver and muscle cells.	[55]
Cissampelos capensis; Menispermaceae	AE of leaves	*In vitro* bioassay using cultured Chang liver, 3T3-L1 adipose and C2C12 muscle cells.	• Decrease FBG level. • No toxic effects.	[55]
Clauseria anisata(Wild) Hook; Rutaceae	Root extract.	Normal and STZ rats.	• Cause dose dependent reduction in FBG levels.	[57]
Harpagophylum procumbens DC; Pedaliaceae	AE of roots	Normal and STZ rats.	• Cause dose dependent reduction in FBG levels.	[58]
Hypoxis hemerocallidea(African Potato); Hypoxydaeae	MeOH extract of corm and AE of roots.	Normal and STZ rats (AT).	• Cause dose dependent reduction in FBG levels. • Less effective than glibenclamide.	[59,60]
Momordica balsamina L.*;* Cucurbitaceae	AE of stem and flower.	*In vitro* bioassay using cultured Chang liver, 3T3-L1 adipose and C2C12 muscle cells.	• Increase glucose utilization in 3T3-L1 adipocytes, Chang liver and muscle cells.	[55]
Sclerocarya birrea [(A. Rich) Hochst]; Anacardiaceae	AE of stem bark.	Normal and STZ rats (AT).	• Decrease FBG levels. • Increase plasma insulin level.	[61]
Sclerocarya birrea [(A. Rich) Hochst]; Anacardiaceae	AE of stem bark.	Normal and STZ rats (AT and for 21 days treatment).	• Decrease FBG levels. • No effect on plasma insulin level. • Increase hepatic glycogen synthesis (AT). • Decrease plasma urea and creatinine levels. • Increase glomerular filtrate rate.	[26]
Sclerocarya birrea [(A. Rich) Hochst]; Anacardiaceae	DCM:MeOH (1:1) extracts of stem bark and roots.	*In vitro* bioassay using cultured Chang liver, 3T3-L1 adipose and C2C12 muscle cells.	• Increase glucose utilization in the liver and muscle. • Toxic to the hepatocytes.	[55]
Securridaca langepedunculat; Polygalaceae	Root-bark extract.	Normal and STZ rats.	• Decrease FBG levels in normal and STZ rats.	[52]
Vernonia amygdalina; Compositae	AE of stem	Normal and STZ rats.	• Increase glucose uptake.	[58]
Vernonia amygdalina; Compositae	AE of leaves.	Glucose uptake in rats fed with high fat diet for 8 weeks.	• Normalize insulin levels. • Increase glucose uptake in muscle and adipose tissue. • Decrease intestinal glucose uptake.	[62]
Gongronema latifolium; Ascepiadaceae	AE of leaves.	Normal and STZ rats (for 28 days treatment).	• Decrease FBG levels and increase hepatic glycogen.	[51,63]
Azadirachta indica; Meliaceae	AE of leaves.	Normal and STZ rats (AT).	• Decrease FBG levels.	[64]
Vinca major L.*;* Apocynaceae	DCM:MeOH (1:1) extracts of roots and leaves.	*In vitro* bioassay using cultured Chang liver, 3T3-L1 adipose and C2C12 muscle cells.	• Increase glucose utilization in liver. • Cytotoxic.	[55]

AE = aqueous extract; FBG = fasting blood glucose; TAG = triacylglycerol; MeOH = methanol; CH_2Cl_2 = methylene chloride; STZ = streptozotocin; DCM = dichloromethane; AT = acute treatment

Table 2: Nigerian indigenous anti-diabetic medicinal plants.

***Brachylaena discolor*; Astaraceae, *Cissampelos capensis*, *Momordica balsamina* L.; Cucurbitaceae, *Sclerocarya birrea* and *Vinca major* [55]**

Optimized screening and scoring methods for traditional anti-diabetic plants using Chang liver, 3T3-L1 adipose and C2C12 muscle cells, were measured for glucose utilization in all the three cell lines, toxicity in hepatocytes and myocytes *in vitro*. Cold dichloromethane (DCM): methanol (MeOH) (1:1) extract of *B. discolor* gave the best overall results, with all plant parts exhibiting high activity scores and negligible toxicity. The outcome of the study showed a high likelihood of identifying drug candidates from the crude extract of *B. discolor*, among other plants investigated. The organic leaf extract of *C. capensis* were unable to stimulate glucose utilization in at least one of the cell lines, whereas aqueous extract of *C. capensis* showed absence of *in vitro* toxicity. *M. balsamina* extracts were active in myocytes and stimulated glucose utilization in hepatocytes. However, *in vitro* toxicity results for *M. balsamina* and *V. major* extracts raised concerns for chronic use. Organic extracts *of M. balsamina* were active in hepatocytes, whereas all extracts (organic and aqueous) were active in myocytes.

The organic root extract of *S. birrea* were unable to stimulate glucose utilization in at least one of the cell lines. In another study, dichloromethane: methanol (1:1) extract of *S. birrea* bark engendered decreased blood glucose and increased plasma insulin levels in STZ-induced diabetic rats *in vivo*. Unfortunately, methanolic and aqueous bark extracts of *S. birrea* exhibited high LD_{50} values. The total activity scores of all the plant extracts investigated ranged between 0 and +6, of which only the organic leaf extract of *V. major* scored the maximum of +6. Additionally, organic leaf extracts of *V. major* strongly stimulated glucose utilization in all three cell types but with high toxicity score probably due to its alkaloids content.

***Gongronema latifolium;* Ascepiadaceae [51,64]**

Ethanolic leaf extract of *G. latifolium* has antihyperglycemic potency, which is thought to be mediated through the activation of hepatic hexokinase (HK), phosphofructokinase (PFK) and glucose-6-phosphate dehydrogenase (G6PDH) and inhibition of glucokinase (GK) activity in the liver. The findings of the study, as in the case of numerous indigenous Nigerian research exercises on anti-diabetic

medicinal plants, fell short in establishing the molecular structure of the bioactive compound(s) and its/their mechanism of action.

Prospects of Nigerian medicinal plants/research experience

There has been an increasing demand for herbal medicine by consumers in both developed and developing countries, as well as renewed interest in prospecting for medicinal plants by multinational pharmaceutical companies. Interestingly, the outcomes of many of these research exercises on anti-diabetic properties of Nigerian indigenous medicinal plants (Table 2) portrayed these plants to be of immense therapeutic value and economic importance, which could extend beyond local boundaries of healthcare systems and national markets. Unfortunately, one major limitation in advancing the goals of most research exercises is the preponderance of inability or/and failure of research bodies to identify the hypoglycemic bioactive principles of the herbal matter and elucidate their therapeutic mechanism, as exemplified in the summary of research findings presented in Table 2. These impediments are largely due to the absence of state-of-the-art scientific infrastructure and poor research funding in most institutions.

In attempt to carry out research exercise within the limits of paucity of available funds, approaches to experimental design are often too simplistic and consideration to underlying critical issues are ignored and taken for granted. In most cases, experiments are stalled in their preliminary stage and other requisite experimentations, within the concept and scope of the research exercise, to achieve a rewarding research findings are abandoned. Additionally, these challenges are further compounded when most of the useful experimental results and findings are poorly publicized because they end up in scientific journals of low internet visibility and of low or no impact factor. This communication blackout further hinders the prospects of advancing the course of medicinal plant research by other interested researchers. These setbacks have continued to be the bane of efforts in advancing the frontiers herbal medicine research in Nigeria.

From our experience, scientific evaluations of anti-diabetic potentials of medicinal plants in most Nigerian Research Institutes and Universities appear to be carried out without collaborative agenda among concerned scientists and other stakeholders. In order to extend the frontiers of research into Nigerian indigenous anti-diabetic medicinal plants and to achieve a more rewarding outcome in this regard, incentivized research exercise involving inter-institutional collaborative work should be established.

Conclusion

Efforts should be geared toward research funding and deployment of Research and Development (R & D) policy framework into medicinal plants research endeavours so as to harness these natural resources and maximize the socioeconomic benefits derivable from Nigerian medicinal plants.

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