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Antidiabetic potential of plants used in Cuba

García Mesa, M.

National Institute of Angiology and Vascular Surgery, 1551 Calzada del Cerro, 12000 Cerro, Havana, Cuba

milagros.mesa@infomed.sld.cu

Abstract

Diabetes mellitus is a metabolic disease that is a health problem worldwide. The high blood glucose levels for prolonged periods lead to its pathological consequences (nephropathy, retinopathy, neuropathy, dyslipidemia, healing disorders, cardiovascular diseases and the threatened diabetic foot syndrome). Besides insulin, oral hypoglycemic drugs are the most widely used medication for diabetes however, the difficulties to get a long-term glycemic control and unpleasant side effects suggest the, need for new therapeutic options. There is a lack of information about the anti-diabetic potentials of medicinal plants used in Cuba. Consequently, the current review is focused on the pharmacological evidence available in this respect to provide a scientific support for the development of new drugs in Cuba and other countries with environmental and/or cultural similarities. Twenty four species with antidiabetic potentials from 17 botanical families were identified, being Liliaceae and Lamiaceae the most represented families, with three species each, followed by Anacardiceae, Moraceae and Malvaceae with two species each. All plants are traditionally used for diabetes in Cuba or in other countries. Most evidence relays on pre-clinical pharmacological assessments, therefore, there is a need for more comprehensive research to obtain standardized products. The identified mechanisms of action (similar to those of known drugs) and active principles (sulfur compounds, polyphenols, phytosterols, anthocyanins, flavonoids and others) would help to this purpose. The possible influences of these herb preparations on patients under conventional treatments should be evaluated.

Key words: Diabetes mellitus, glucose, hypoglycemic, traditional medicine

Introduction

Diabetes mellitus (DM) is a metabolic disease classified to two main types: type-1 diabetes, a state of insulin deficiency due to severe defect in islet β-cell function, and type-2 diabetes that is characterized by a combination of resistance to action of insulin and insufficiency in insulin secretion. Both types of diabetes progressively lead to pathological complications: nephropathy, retinopathy, neuropathy, dyslipidemia, healing disorders, cardiovascular diseases and the threatened diabetic foot syndrome[1,2].

The high blood glucose levels for prolonged periods lead to its pathological consequences of DM. Hyperglycemia causes increased protein glycation and the formation of early and advanced glycation end products (AGEs) which are major factors responsible for the complications associated with diabetes. Therefore, the maintenance of glycaemia in its normal range is the goal of antidiabetic therapy[1, 2].

Besides insulin, the most widely used medication for diabetes are oral hypoglycemic drugs with different mechanisms of action including the increase of insulin secretion for pancreatic ß cells (sulfonylureas like Glibenclamide); decrease of liver glucose formation , elevation of glucose uptake by peripheral tissues (Metformin); reduction of the hydrolysis of carbohydrates by inhibition of alpha glycosidase activity (Acarbose) and increase of sensitivity to insulin (biguanides, thiazolidinedione)[1]. However, these drugs are not adequately effective in maintaining long-term glycemic control in most patients, even when used in combination related, in part, with genetic polymorphism of drug metabolizing enzymes [3]. Furthermore, the occurrence of serious complications in patients is still a problem [4] and unpleasant side effects such as severe hypoglycemia, lactic acidosis, peripheral edema and abdominal discomfort [2] therefore, searching for new antidiabetic more effective agents with fewer side effects is a scientific challenge.

Many known drugs have been primary discovered from plants [5], suggesting that they could provide opportunities for developing new products. Thus, an analysis the information about plants with this therapeutic of potential that are traditionally used in a given country is the first stage of the research strategy aimed to obtain efficacious and safe standardized herb preparations and/or purified drugs [5, 6] needed to improve diabetic patient´s quality of life.

DM is a health problem worldwide and Cuba is not an exception[7]. Though the integration of scientifically supported natural products to healthcare services is an objective of Cuban health system[8, 9], there is a lack of information about the antidiabetic potential of medicinal plants used in this country that would support a plant selection for drug development in Cuba and other countries with environmental and/or cultural similarities. Consequently, the current review focused on the results of pharmacological evaluations with validated experimental models [10] and/or controlled clinical trials that suggest the possible therapeutic utility of preparations derived from the species that will be included in the Cuban Pharmacopea [9] and others that are used in Cuba too[11-16].

Data were withdrawn from Google Scholar and PubMed data bases using the following search parameters or combinations: "the plant scientific name", "diabetes", "glucose", "medicinal plant", without applying restrictions with respect to the publication date, the type of the study or the language.

The scientific and vernacular names, botanical families and uses in Cuba of plants with antidiabetic potentials are summarized in the Table 1. Details of its pharmacological effects, proposed mechanisms of action and active principles are described as follows:

***Allium cepa* L.** (*A. cepa*)

Traditional use to treat diabetes in: Brazil [17] Cameroon [18], India [19] Morocco [20] , Nigeria [21].

A. cepa is considered a promising herb for diabetes treatment [22]. Oral administration of the bulbs in different types of preparations (freeze dried, juice or aqueous extract) induced the reduction of fasting blood glucose in experimental animals [23, 24]. Patients with type 2 DM had lower levels of glycaemia and consumption of hypoglycemic drugs after a daily intake of onion juice or natural bulbs. [25, 26]. The inhibition of insulin breakdown is the proposed mechanism of action [27]. S-allyl-cysteine sulfóxide, a compound released from the processed bulbs, could be responsible for this effect [19].

***Allium sativum* L.** (*A. sativum*)
Traditional use to treat diabetes in: USA [17], Cameroon [18], India [19] Morocco [20]
Oral administration of *A. sativum* bulb juice provoked a reduction of fasting blood glucose concentrations in rats with experimentally induced diabetes [27], [28]. In general, clinical evidence available on its antidiabetic efficacy is not consistent[29] the reduction of insulin breakdown is considered the probable mechanism of action [30]. S-allyl-cysteine sulfóxide and ajoene, two metabolites that are present in garlic processed bulbs, have been the active principles identified [19].

***Allophylus cominia* (L.) Sw.** (*A. cominia)*
Traditional use to treat diabetes in: Mexico [31]
Aqueous and chloroform extracts of *A. cominia* leaves showed Streptozotocin-induced diabetic rats, though the water preparation was the most effective to improve glucose tolerance of normal rats, while the organic one showed the best effect with diabetic animals. Fatty alcohols were identified as the major components of the last one [32].

***Aloe vera* (L.) Burm F.** (*A.Vera*)
Traditional use to treat diabetes in: Mexico, Peru and USA [17], Cameroon [18], India [19].
Decrease of fasting blood glucose and increase of insulin circulating levels were seen in genetically diabetic rats and mice with Streptozotocin-induced diabetes orally treated with non-processed *A.Vera* gel, as well as aqueous and ethanol gel extracts [33, 34]. Clinical evaluations of the effect of consuming aloe leaf juice on type 2 diabetic patients, demonstrated the reduction of fasting blood glucose concentrations and potentiation of Glibenclamide hypoglycemic effect [35, 36]. A randomized and controlled clinical trial with pre-diabetic subjects showed the beneficial effects of the intake of standardized preparations of *A vera* leaf gel on metabolic syndrome[37]. The inhibition of alpha glycosidase enzyme activity along with augmentation of insulin synthesis and secretion are considered the probable mechanisms of the effects of Aloe preparations. Phytosterols (lofenol 24-methyl-lofenol, ethyl-lofenol, cicloartanol and 24-methylen-cicloartanol), polysaccharides and glycoproteins are the active principles identified [19, 33, 34, and 38].

***Anacardium occidentale* L.** (*A. occidentale)*
Traditional use to treat diabetes in: Brazil and Jamaica [17] Cameroon [18], Nigeria [21].
Intravenous administration of *A. occidentale* stem bark N hexane extract induced a reduction of fasting blood glucose levels in Beagle dogs, in addition, oral treatment with stem bark aqueous and methanol extracts improved glucose tolerance in normal and fructose-fed diabetic rats [39]. Stigmast-4-en-3-ol and stigmast-4-en-3-one are probable plant constituents responsible for the hypoglycemic effect. [40].

***Artocarpus altilis* (Park. inson) Forb. Erg** (*A. altilis)*
Traditional use to treat diabetes in: India[41]
Oral administration of *A. altilis* leaf aqueous extract was able to inhibit glucose load- induced hyperglycemia in normal rats[42]. Methanol extracts of *A. altilis* fruit inhibited alpha glucosidase activities *in vitro* at µg/mL concentration levels in concentration dependent manner[43], suggesting an antidiabetic potential.

***Bixa orellana* L.** (*B. orellana*)
Traditional use to treat diabetes in: Jamaica[17], Nigeria [44], Trinidad and Tobago [45]
Orally administered *B. orellana* seed aqueous and chloroform extracts induced the reductions of fasting glycaemia, as well as the increase of glucose tolerance and insulin circulating levels in normal beagle dogs [46] the improved insulin utilization by peripheral tissues is the proposed mechanism of hypoglycemic action [19].

***Carica papaya* L.** (*C. papaya)*
Traditional use to treat diabetes in: USA [17], Trinidad and Tobago[44], Mexico[47], Nigeria [48]. India[49]
Hypoglycemic potential *of C. papaya* leaf aqueous extract was demonstrated by lowering of fasting blood glucose levels in rats with Streptozotocin - and Aloxan.- induced diabetes that were orally treated with this product [50, 51].

***Cassia occidentalis* L.** (*C. occidentalis)*
Traditional use to treat diabetes in: Cameroon[18] India[49]
Intake of water, petroleum ether, and chloroform and ethanol *C. occidentalis* leaf extracts induced decreases of fasting blood glucose concentrations in normal and Aloxan-induced diabetic rats.

Sennosides A and B and anthraquinones have been identified as active principles of the hypoglycemic effect [52, 53].

***Cecropia peltata* L.** *(C.peltata)*
Traditional use to treat diabetes in: Mexico[54]
Oral treatment with *C. peltata* aqueous leaf extract induced the improved tolerance to pyruvate of rats with Streptozotocin-induced diabetes, while fasting blood glucose was reduced by the administration of a methanol extract to normal mice[55]. The inhibition hepatic glucose mobilization and gluconeogenesis are probable mechanisms of the hypoglycemic action. while chlorogenic acid has been identified as active principle responsible of this effect [54] .

***Ficus carica* L** *(F. carica)*
Traditional use to treat diabetes in: Morocco [56]
A decrease of glycaemia and increase of glucose uptake by increase of glucose uptake by the skeletal muscles was induced in rates with diabetes induced by Streptozotocin treated with a leaf decoction of *F. carica* [57].

***Hibiscus rosa- sinensis* L** (*H. rosa sinensis)*
Traditional use to treat diabetes in: USA[17]
In normal rats, the aqueous extract of the flower of *H. rosa sinensis* improved the tolerance to an oral glucose load. It also significantly lowered the blood glucose and Glycosylated hemoglobin without change of serum insulin levels in rats with diabetes induced by Streptozotocin. [58]. The hypoglycemic effect of ethanol extracts from the flowers of *H. Rosa sinensis* flowers were demonstrated in Streptozotocin-induced diabetic rats, while an ethanol leaf extract induced the increase of circulating insulin levels in diabetic mice [59, 60].

***Hibiscus sabdariffa* L** (*H. sabdariffa)*
Traditional use to treat diabetes in: Venezuela [15], Jordan [61]
Oral administration of the *H. sabdariffa* flower aqueous extract to rats prevented the changes of metabolic parameters (glucose, insulin triglyceride, LDL/HDL, non-enzymatic glycosylation and lipid peroxidation) and weight loss associated to Aloxan-induced diabetes [62, 63]. Anthocyanins have been identified as the possible contributors to the biological effects of *H. sabdariffa* leaf and flower preparations [62].

***Manguifera indica* L.** (*M. indica)*
Traditional use to treat diabetes in: Brazil [17] , Nigeria[21, 41], India[64] .
Hypoglycemic effects, comparable to Glibenclamide, has been shown by preparations obtained from *M. indica* when rats with Streptozotocin- induced- diabetes were treated with aqueous extracts from the stem barks or leaves of this plant; or ethanol extracts from its seed kernels [65,66].

***Morinda citrifolia* L.** (*M. citrifolia)*
Traditional use to treat diabetes in: Polynesia [67]
M. citrifolia juice to diabetic rats induced a reduction of fasting blood glucose concentrations, increase of circulating insulin and improvement of glucose tolerance in diabetic rats[68-70].
Furthermore, the buthanol soluble fraction of a root extract demonstrated a hypoglycemic effect in diabetic mice [71]. Moreover, this species fruit and leaf methanol extracts, as well as a commercial *M. citrifolia* juice, displayed insulin-like activities, without influence on insulin effects on cultured 3T3-L1 adipocytes *in vitro*, suggesting that an insulin-like activity could be its mechanism of action [72].

***Musa x paradisiaca* L.** (*M. paradisiaca)*
Traditional use to treat diabetes in: Nigeria [73]
The changes of blood levels of lipids, glucose and insulin, besides liver and muscle glycogen concentrations induced by Streptozotocin in rats were prevented by pretreatment with a dry filtrate of a *M. paradisiaca* root methanol extract [74].

***Ocimum basilicum* L.** (*O. basilicum)*
Traditional use to treat diabetes in: USA [17]
Reduction of glucose blood levels of Streptozotocin-induced diabetic rats was demonstrated with treatment with *O. basilicum* whole plant aqueous extract [75].

***Ocinum sanctum* L.** (*O. sanctum)*
Traditional use to treat diabetes in: USA[17], India[27, 64]
O. sanctum is considered a promising herb for

diabetes treatment [22]. Dietary supplementation with *a* leaf powder, as well as the intra-gastric administration of ethanol and water leaf extracts or chloroform, petroleum ether or ethyl acetate fractions from ethanol extracts to rats, with experimentally induced hyperglycemia were able to reduce blood glucose levels and other serum and liver metabolic changes related to diabetes [19, 27, 76]. Hypoglycemic and hypolipidemic effects were confirmed by a randomized placebo-controlled, single blind trial performed with type 2 DM [77].A one- month dietary supplement with *O. sanctum* powder leaded to a reduction of glycated protein, total cholesterol, low density lipoprotein , very low density lipoprotein and triglyceride in patients with type 2 DM[78]. Buthanol and ethyl acetate fractions of an aqueous leaf extract induced insulin secretion from rat isolated pancreas; therefore the Induction of insulin release from pancreas ß cells is the proposed mechanism of action [79].

***Psidium guajava* L.** (*P. guajava*)
Traditional use to treat diabetes in: India[49, 64], Togo[80.] .
The antidiabetic potential of different *P. guajava* preparations has been demonstrated. Lower glycaemia levels were found in normal rats and Alloxan-induced diabetic mice and rats after juice intraperitoneal injection [81]. On the other hand, *P. guajava* leaf aqueous extracts showed hypoglycemic effect in Lepr(db)/Lepr(db) diabetic mice, as well as normal and Streptozotocin-induced diabetic rats, while water and ethanol extracts from the leaves improved glucose tolerance, increased insulin circulating levels and hexokinase, phosphofructokinase and glucose-6-phosphate dehydrogenase enzymatic activities in the livers of rats with diabetes induced by Streptozotocin. Furthermore, treatment with a leaf water and acetyl acetate extract leaded to a decrease of HbA1c and fructosamine in the blood of diabetic mice and rats [82].Seed and fruit peel aqueous extracts demonstrated similar hypoglycemic effects [83-85].
A reduction of postprandial glycaemia , and fasting levels of HbA1c, total cholesterol, triglycerides and LDL-C were demonstrated in type 2 diabetic patients after daily intake of *P. guajava* aqueous leaf extract [80, 82] .
The in vitro inhibitory effect on reduced alpha glucosidase (mainly alpha amylase) activity *in vitro* suggests an acarbose-like mechanism of action for this preparation [85]. Quercetin, elagic acid, cianidine, rutin and kaempherol are possible leaf constituents responsible of the hypoglycemic effect.[86]

***Salvia officinalis* L.** (*S. officinalis)*
Traditional use to treat diabetes in: Brazil, USA [17], Morocco[56]
Aqueous and ethanol extracts from the leaves of *S. officinalis* inhibited alpha glucosidase activity *in vitro*. Caffeic, rosmaric and cumaric acids seem to be active principles responsible for this effect [87]. Moreover, post-prandial blood glucose concentrations, as well as Intestinal sucrase and maltase activities were reduced while expression of *Insulin* and *Glut-4* genes was enhanced in rats with diabetes induced by Alloxan, thus suggesting that up regulation of *Insulin* and *Glut-4* genes expression and inhibition of α-glucosidase activities are the two mechanisms that play a considerable role in *S. officinale* hypoglycemic action [88].

***Solanun americanum* Mill.** (*S. americanum)*
Traditional use to treat diabetes in: USA [17]
The hypoglycemic effect of *S. americanum* methanol leaf extracts has been demonstrated with alloxanized mice and rats, as well as with normal and glucose –induced hyperglycemic rats [89, 90].

***Tamarindus indica* L** *(T. indica)*
Traditional use to treat diabetes in: India[64]
Decreased fasting blood glucose levels, besides lower liver and muscle glycogen contents, as well as inhibition of hepatic and renal glucose 6 phosphate dehydrogenase, aspartate and alanin transaminase activities were shown in rats with Streptozotocin- induced diabetes treated with *T. indica* aqueous seed extract[91]. Inhibition of insulinase activity is the proposed mechanism of *T indica* hypoglycemic activity[30.] Flavonoids seem to be the active compounds[64].

***Tecoma stans* Linn.** (*T. stans)*
Traditional use to treat diabetes in: Mexico and USA[17], India [49]
T. stans hydro-alcohol leaf extract showed

hypoglycemic action in normal and dexamethasone-induced hyperglycemic mice [92]. Furthermore, lower hyperglycemic peak without change of fasting blood glucose was observed in normal and Streptozotocin-induced diabetic rats. Inhibition of intestinal alpha glucosidase activity is the probable mechanism of hypoglycemic action [93] while the tecomine-1 and 2 alkaloids are the possible active principles [94].

Zingiber officinale **Roscoe** (*Z. officinale)*

Traditional use to treat diabetes in: USA [17], Morocco [56], India[64]

Rats with diabetes induced by Streptozotocin showed reduced glucose concentrations in liver and pancreas after oral administration of *Z. officinale* rhizome hydro-alcohol extract [95]. Moreover, a rhizome juice inhibited serotonin-induced hyperglycemia and hyperinsulinemia in normal rats and induced a reduction of fasting blood glucose concentrations, increase of circulating insulin levels and improvement of glucose tolerance on Streptozotocin diabetic rats [96] On the other hand, hyperglycemia, lipid peroxidation and renal lesions characteristic of diabetes induced by Streptozotocin were prevented in rats treated with a *Z. officinale* rhizome dried powder [96]. Increment of insulin secretion is considered the mechanism of anti-hyperglycemic action, while gingerols are the probable active principles of the pharmacological effect [95].

Discussion

This study has shown that 24 edible and/or medicinal plants, commonly used in Cuba, have hypoglycemic potentials. They belong to 17 botanical families, being Liliaceae and Lamiaceae represented by three species each, followed by Anacardiaceae, Moraceae and Malvaceae, each one represented by two, suggesting that other species from these families should be considered for the screening of the antidiabetic potentials of plants.

Interestingly, only five (A. *cominia, A. occidentale, O. sanctum , S. americanum and T. stans.)* are considered useful for traditional treatment of diabetes in Cuba, but they are used for this purpose in other countries. However, current communication technics allow knowledge globalization, including traditional medicine.

For instance, the use of *Morinda citrifolia* products as medicinal remedies is a Polynesian tradition that has gained popularity among Cuban population during this century due to the propaganda about its beneficial properties, leading to its inclusion in a list of interesting plants [9], thus suggesting that *A. cominia* (L.) (evaluated in Cuba), that has been, *A. altilis, C. papaya , C. occidentale , C. peltata , F. carica, H. rosa sinensis , H. sabdariffa , S. americanum and T. stans. that has been receive similar attention.*

Most information available relays on pre-clinical assays and the need for more comprehensive research to develop standardized, efficacious and safe products is evident. The identified mechanisms of action (similar to those of known drugs) and active principles (sulfur compounds, polyphenols, phytosterols, anthocyanins, flavonoids and others) would help to this purpose.

The possible influences of herb preparations with antidiabetic potentials on patients under hypoglycemic treatments should be evaluated and physicians should be alerted about the importance of advising their patients for a rational use of medicinal plants.

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Scientific name (Family)	**Common Name**	**Oral uses in [11-16]**
Allium cepa L. (*Liliaceae*)	Cebolla	Food, inflammation, pain, intestinal parasites, fever, bronchial asthma, l gastric disorders, diuretic.
Allium sativum L. (*Liliaceae*)	Ajo	Spice, cold, pain and circulatory disorders.
Allophylus cominia (L.) Sw (*Sapindaceae*)	Palo de caja	Diabetes, anemia, intestinal disorders and tuberculosis
Aloe vera (Linn.) Burm F. (*Liliaceae*)	Sábila	Hepatitis, gastric ulcers, colagogue, diabeteshemorrhoids, bronchial asthma, pneumonia
Anacardium occidentale L. (*Anacardiaceae*)	Marañón	Fruit, diabetes, hypercholesterolemia, cold, hemmoptysis, stomach ulcer,dysentery
Artocarpus altilis (Parkinson) Forberg (Moraceae)	Arbol del pan	Food
Bixa orellana L. (*Bixaceae*)	Bija	Spice, bronchial asthma, diuretic
Carica papaya L. (*Caricaceae*)	Fruta bomba	Fruit, giardiasis, menstruation
Cassia occidentale L. (*Cesalpinaceae*)	Yerba hedionda, Platanillo	Diuretic, hepatic and gastric disorder
Cecropia peltata L. (Moraceae)	Yagruma	Bronchial asthma, dyspnea, cough
Ficus carica L. (Moraceae)	Higo	Fruit, diabetes, renal and bile stones, cough low blood pressure, hematuria, laxative, bronchial asthma
Hibiscus rosa sinensis L. (Malvaceae)	Mar Pacífico	Cold, respiratory diseases
Hibiascus sabdariffa L. (Malvaceae)	Flor de Jamaica, Serení	Diuretic, hypolipidemic
Manguifera indica L. (*Anacardaceae*)	Mango	Fruit, bronchitis, bronchial asthma
Morinda citrifolia L (Rubiaceae)	Noni	Diabetes, hypertension
Musa x paradisiaca L. (Musaceae)	Plátano macho	Food, bronchial asthma, cancer
Ocimum basilicum L. (Lamiaceae)	Albahaca blanca	Spice, spasmolytic, emetic, diuretic, remedy against cold, diarrhea, cancer , high blood pressure
Ocinum sanctum L. (Lamiaceae)	Albahaca morada	Diabetes, fever, headache, cold stomachache
Psidium guajava L. (Myrtaceae)	Guayaba	Fruit, diarrhea.
Salvia officinalis (Lamiaceae)	Salvia	Headache, cold, inflammation, fever, dyspnea , tonic remedy
Solanun americanum Mill. = *Solanum nigrum* var.*americanum* (Mill.) Schulz (Solanaceae)	Yerba mora	Diabetes, cancer, fever, gastritis, intestinal parasites
Tamarindus indica L. (Cesalpinaceae)	Tamarindo	Fruit, hepatic disorders, hemorrhage, diuretic
Tecoma stans Linn. (Bignoniaceae)	Saúco amarillo	Diabetes, stomach ulcer
Zingiber officinale Roscoe (Zingibareaceae)	Jengibre o Ajengibre	Spice, anti-vomiting, anti-rheumatic, aphrodisiac, immune-stimulant, tonic, anti-diarrheic, cough reliever

Table 1 Plants with antidiabetic potentials used in Cuba

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