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Hypoglycemic and Antihyperglycemic Activities of Nine Medicinal Herbs Used as Antidiabetic in the Region of Lubumbashi (DR Congo)

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The aim of this study was to assess the hypoglycemic and antihyperglycemic activities of nine plants used as antidiabetic treatments in Lubumbashi and its surroundings. Those are *Albizia adianthifolia*, *Azanza garckeana*, *Cassia occidentalis*, *Cassia sieberiana*, *Erythrina abyssinica*, *Gladiolus klattianus*, *Rauvolfia caffra*, *Strychnos spinosa*, and *Vitex madiensis*. Aqueous extracts, obtained by decoction and maceration, were administered (500 mg/kg) *per os* to guinea pigs (*Cavia porcellus*), both in glucose baseline conditions and in oral glucose tolerance test (OGTT) conditions (glucose, 2 g/kg; follow-up over 210 min). For OGTT experiments, area under the curve of blood glucose levels, maximum glucose concentration (Cmax), and time to reach Cmax (Tmax) were used to compare test groups with the control conditions (glucose group). In hypoglycemic tests, only three species induced significant ($p < 0.001$) lowering of normal glycemia: *A. adianthifolia* (33% reduction), *C. occidentalis* (32%), and *V. madiensis* (43%); in the same conditions, the positive control glibenclamide (6 mg/kg) induced a blood glucose lowering of 55%. In OGTT conditions, all tested herbs were active, with the highest inhibition of glycemia increases for *V. madiensis* (62%) and *A. adianthifolia* (57%), compared with the hyperglycemic inhibition rate of glibenclamide (50%). Oral glucose tolerance test conditions appear as essential to detect the extracts most interesting for clinical use. These data support the use of studied plants for diabetes treatment in traditional Congolese medicine and indicate a good knowledge of tradipraticians in the field. Copyright © 2017 John Wiley & Sons, Ltd.

Keywords: antihyperglycemic; hypoglycemic; diabetes; herbal medicines; traditional African medicine; Lubumbashi.

INTRODUCTION

Longtime considered as a developed-countries disease, type 2 diabetes has, in only a few years, become a major public health problem with an alarming and growing prevalence, especially in developing countries (Hossain *et al*., 2007). In the Democratic Republic of Congo, during the last decade, the prevalence of diabetes tripled to reach, in 2015, 1.8 million diabetic patients with an estimated 1.2 million undiagnosed patients (International Diabetes Federation, 2015). In DR Congo and other developing countries, access to modern healthcare systems remains quite limited (Deaton and Tortora, 2015). Consequently, an important proportion of patients mainly access ancestral healing resources to solve their primary care needs (WHO, 2013), either through traditional healers or family-inherited knowledge (Kahumba *et al*., 2015). Treatments are mostly based on herbal medicines, more rarely on drugs originating from animals or minerals; it is estimated that about 70% of people use herbal products for their everyday health problems (Busia, 2005). Given the emerging importance of diabetes and this wide use of herbal medicines, a survey was undertaken over 49 tradipraticians of the Lubumbashi region to inventory herbs alleged to be effective in controlling diabetes (Bakari *et al*., 2016). The present study aims to assess the antihyperglycemic and hypoglycemic effects of nine plant species highly cited in our survey (Table 1).

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MATERIAL AND METHODS

Plant material. The nine plants species were harvested in November 2011 in two areas around the Lubumbashi town (Kashamata; 11°44′49.7″S; 27°31′15″E; 1210 m; and Katuba; 11°44′45.0″S; l27°26′35.5″E; 1216 m) and in Kipushi (11°45′46.3″S; 27°14′57.7″E; 1200 m): *Albizia adianthifolia* (stem bark; Kashamata), *Azanza garckeana* (leaves; Katuba), *Cassia occidentalis* (root; Kipushi), *Cassia sieberiana* (leaves; Kashama), *Erythrina abyssinica* (root; Kashamata), *Gladiolus klattianus* (bulb; Kalebuka), *Rauvolfia caffra* (root), *Strychnos spinosa*

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Table 1. Ethnobotanical data on selected plants

Botanical name	Local name	Part used	Voucher reference number[a]	Treated diseases	Extraction yield (%)	References
Albizia adianthifolia (Schumach.) W. Wight (Fabaceae)	Kasikeaze (Tshokwe), Kapeta nzovu (Bemba, Luba)	Leaves and stem bark	512	Diabetes; syphilis; aphrodisiac; hiccup	2.9[b]	Data from our survey
Azanza garckeana (F. Hoffm.) Excell & Hillc. (Malvaceae)	Muti ya makamashi (Swahili)	Leaves	180	Diabetes; epilepsy; edema	3.2[b]	Data from our survey
Cassia occidentalis L. (Fabaceae)	Lukunda bajanyi (Tshiluba), Mbaw-mbaw (Kikongo)	Root or whole plant	1098	Constipation; diabetes; verminosis	2.8[b,d]	Data from our survey and Katemo *et al*. (2012)
Cassia sieberiana DC (Fabaceae)	Mugunga (Hemba) Mununga nunsi (Bemba, Lamba)	Leaves	172	Diabetes; lactation induction; verminosis	3.2[b]	Data from our survey and Waterman *et al*. (2010)
Erythrina abyssinica Lam. ex DC (Fabaceae)	Kinsungu (Tabwa), Isungwa (Hemba), Katshiyitshiyi (Luba)	Root bark	174	Diabetes; hernia; sinusitis	2.6[b]	Data from our survey
Gladiolus klattianus Hutch. (Iridaceae)	Kitala (Bemba), Kitokatoka (Luba)	Bulb	306	Diabetes; gonorrhea	2.2[c]	Data from our survey
Rauvolfia caffra Sond. (Apocynaceae)	Mutalala (Bemba)	Leaves and stem	6046	Diabetes; malaria; tuberculosis, antibacterial	2.4[b]	Data from our survey and Clarkson *et al*. (2004)
Strychnos spinosa Lam. (Strychnanceae)	Sansa (Bemba), Kisongole (Luba)	Root bark	519	Abdominal pain; diabetes; dysentery; gonorrhea	2.7[b]	Data from our survey and Maroyi (2011)
Vitex madiensis Oliv. (Verbenaceae)	Mufutu (Luba), Mufute Kinka (Bemba)	Leaves, roots	1247	Diabetes; asthma; anemia; diarrhea	3.1[b,e]	Data from our survey, Disengomoka *et al*. (1983)

[a]Voucher specimens were deposited in the Kipopo-INERA herbarium, DR Congo.
[b]Water extract (decoction; 50 g of powder for 100 mL of water; boiling for 15 min); % m/m.
[c]Water extract (maceration; 50 g of powder for 150 mL of water; room temperature for 24 h); % m/m.
[d]Extract of roots.
[e]Extract of leaves.

(Kashamata), and *Vitex madiensis* (leaves; Kashamata). The collected plants were authenticated by Dr Jean Lejoly, Université Libre de Bruxelles (Belgium), and voucher specimens were deposited at the herbarium of Kipopo-INERA/DR Congo (Table 1).

Preparation of extracts. The plant organs were dried in the shade at room temperature and coarsely ground using a manual stainless steel grinder. Fifty grams of each plant powder were treated according to their reported traditional uses for diabetes treatment (data from our survey). Decoction was applied for all plant materials (50 g of powder for 100 mL of water; boiling for 15 min), except for *G. klattianus* bulbs that were macerated (50 g of powder for 150 mL of water at room temperature for 24 h). The different extracts were first filtered on a coffee filter sieve (to remove coarse particles) and then on Whatman® paper no. 1, 25 µm, dried at 45°C under vacuum (Rotavapor®, Buchi, Switzerland) and stored at −20°C for a maximum of 30 days. For administration to animals, the extracts (50 mg/mL) were suspended in distilled water; glucose (200 mg/mL) and glibenclamide (1 mg/mL) were dissolved in distilled water.

Animals. A local strain of guinea pigs (*Cavia porcellus*), 350–400 g, only male sex, was obtained from the Faculty of Agronomic Sciences of the University of Lubumbashi. These animals were fed with a standard diet (MIDEMA/DR Congo) and acclimatized for 10 days under the experimental environmental conditions.

Experimental design. For both hypoglycemic and antihyperglycemic studies, the animals were randomly divided into 11 groups of six animals each. Test solutions were administered by gastric intubation. For hypoglycemic tests, the first two groups received distilled water (4 mL) and glibenclamide (6 mg/kg), respectively; the nine other groups received suspensions of herbal extracts (500 mg/kg). For antihyperglycemic tests [oral glucose tolerance test (OGTT) conditions], the first two groups received glucose (2 g/kg) and glucose (2 g/kg) followed by glibenclamide (6 mg/kg), respectively; the nine other groups received glucose (2 g/kg) followed by suspensions of herbal extracts (500 mg/kg).

Considering that human patients (about 60 kg) are typically treated with 750 mL of decoction/macerate corresponding to 250 g of dried herbal material per day and taking into account the extraction yield (2.2–3.2% m/m; Table 1), tested doses would translate to about 5.5–8.0 g of extract per day for a 60-kg man (92–133 mg/kg/day). The applied dosage of 500 mg/kg

on a guinea pig is thus compatible with traditional use when considering dose translation based on body surface area from human to guinea pig, as proposed by Reagan-Show *et al*. (2007).

The experimental procedure was conducted in accordance with the US National Research Council guide for the care and the use of laboratory animals.

Hypoglycemic and antihyperglycemic assays. Before the experiments were started, the animals were fasted for 16 h with water *ad libitum*.

For tests in glucose baseline conditions, the fasting blood glucose level was determined and animals were administered distilled water, glibenclamide, or an extract solution.

For tests in OGTT conditions, the fasting blood glucose level was determined and hyperglycemia was induced by oral administration of the glucose solution (t = 0 min), immediately followed by the oral administration of glibenclamide (positive control) or an extract solution (experimental groups).

For both hypoglycemic and antihyperglycemic assays, blood samples were obtained by the ear venipuncture method (Yu *et al*., 2014) at times 30, 60, 90, 120, 180, and 210 min after administration. The blood glucose concentrations were determined using a One Touch Vita glucometer and One Touch Vita strips (LifeScan, Johnson & Johnson Company).

Statistical and data analysis. The data were analyzed from 0 to 210 min, using incremental areas under curves (AUC) of blood glucose levels measured by the trapezoidal rule, with the GraphPad Prism software (version 5.0). For tests in glucose baseline conditions, the glucose AUC allowed comparing the different groups with the negative (water) and positive (glibenclamide) control conditions.

For tests in OGTT conditions, the glucose AUC, maximum concentration (Cmax), and time to reach the Cmax (Tmax) were used to compare the different groups with the negative (glucose) and positive (glucose + glibenclamide) control conditions, using one-way analysis of variance (ANOVA) tests. The inhibition rate or hypoglycemic effects were computed at points where there are significant differences in ANOVA-protected t-tests (Bonferroni correction) (Gallagher *et al*., 2003), according to

$$\text{Hyperglycemia inhibition ration} = \frac{\text{AUC glucose group} - \text{AUC extract group}}{\text{AUC glucose group}} \times 100$$

Groups of data were considered to be significantly different at $p < 0.05$.

RESULTS

Some of the tested extracts (*A. adianthifolia*, *C. occidentalis*, and *V. madiensis*) exhibited hypoglycemic properties (Table 2), lowering the blood glucose baseline by 32%, 33%, and 43%, respectively; in the same conditions, the hypoglycemic effect of the positive control, glibenclamide, was 55%. There was a significant ($p < 0.01$) hyperglycemic effect for *G. klattianus* (8.7%) and *R. caffra* (7.9%).

Table 2. Effect of plant aqueous extracts (500 mg/kg) on *Cavia porcellus* in glucose baseline conditions

Tested compound or extract	AUC (mg/dL over 210 min)	Hypoglycemia induction effect (%)
Distilled water	19,835 ± 286	—
Glibenclamide	8,975 ± 218***	54.8***
Albizia adianthifolia	13,320 ± 337***	32.8***
Azanza garckeana	19,143 ± 362^{NS}	3.5^{NS}
Cassia occidentalis	13,490 ± 615***	32.0***
Cassia sieberiana	19,088 ± 495^{NS}	3.8***
Erythrina abyssinica	19,915 ± 745^{NS}	−0.4^{NS}
Gladiolus klattianus	21,565 ± 284***	−8.7**
Rauvolfia caffra	21,400 ± 664***	−7.9**
Strychnos spinosa	19,898 ± 423^{NS}	−0.3^{NS}
Vitex madiensis	11,255 ± 400***	43.3***

***$p < 0.001$.
**$p < 0.01$.
*$p < 0.05$.
$^{NS}p > 0.05$, compared with negative control.

The antihyperglycemic effects, observed in OGTT conditions, are summarized in Table 3.

As expected, glycemia was increased in the control group at t = 30 min after oral administration of glucose; in combination with plant extract or glibenclamide, the hyperglycemia peak was reached either at the same time (*C. sieberiana* and *V. madiensis*) or later at t = 60 min (glibenclamide, *A. adianthifolia*, *A. garckeana*, *C. occidentalis*, *G. klattianus*, and *S. spinosa*) or t = 90 min (*E. abyssinica* and *R. caffra*) (Fig. 1).

All tested extracts induced a sensible reduction in glucose AUC and Cmax, an effect practically comparable with the one observed for glibenclamide. Based on the mean of the highest glycemic values (Cmax) of each experimental group, the hyperglycemic inhibition rate was determined by comparison with the mean peak value of the glucose group (Table 3). The most active herbal extracts were those obtained from *V. madiensis* (62.3%), *A. adianthifolia* (56.9% inhibition), *C. occidentalis* (49.6%), and *C. sieberiana* (49.0%). The hyperglycemic inhibition rate of glibenclamide was 49.6%.

DISCUSSION

Although a series of ethnopharmacological enquiries report many herbs as "antidiabetic," only few thorough biological studies have been performed to validate such claims. To the best of our knowledge, this is the first report of the hypoglycemic and antihyperglycemic activities of the studied plants, except for *C. occidentalis* and *E. abyssinica* for which previous studies have been carried out (Cui *et al*., 2007; Emmanuel *et al*., 2010). The studies on these two species have however mostly assessed the antihyperglycemic properties of methanol extracts and not the aqueous decoctions prepared according to traditional use.

Table 3. Effect of plant aqueous extracts (500 mg/kg) on the hyperglycemia induced in i>Cavia porcellusi>

Tested products	AUC (mg/dL over 210 min)	Cmax (mg/dL)	Tmax (min)	Hyperglycemia inhibition factor (%)
Glucose	48,895 ± 433	384.2 ± 5.5	30	—
Glucose + glibenclamide	24,623 ± 924***	182.3 ± 3***	60	49.6***
Glucose + *Albizia adianthifolia*	21,050 ± 711***	176 ± 3.4***	60	56.9***
Glucose + *Azanza garckeana*	30,872 ± 289***	225.7 ± 8***	60	36.9***
Glucose + *Cassia occidentalis*	24,635 ± 429***	173 ± 3.9***	60	49.6***
Glucose + *Cassia sieberiana*	24,898 ± 1230***	193.3 ± 8.6***	30	49.1***
Glucose + *Erythrina abyssinica*	30,060 ± 704***	222.5 ± 5.3***	90	38.5***
Glucose + *Gladiolus klattianus*	31,780 ± 450***	206 ± 2.2***	60	35.0***
Glucose + *Rauvolfia caffra*	36,260 ± 106**	235.5 ± 3.9**	90	25.8**
Glucose + *Strychnos spinosa*	27,038 ± 333***	184.8 ± 4***	60	44.7***
Glucose + *Vitex madiensis*	18,420 ± 404***	142.7 ± 3.6***	30	62.3***

***$p < 0.001$.
**$p < 0.01$.
*$p < 0.05$.
$^{NS}p > 0.05$, compared with glucose (negative control).

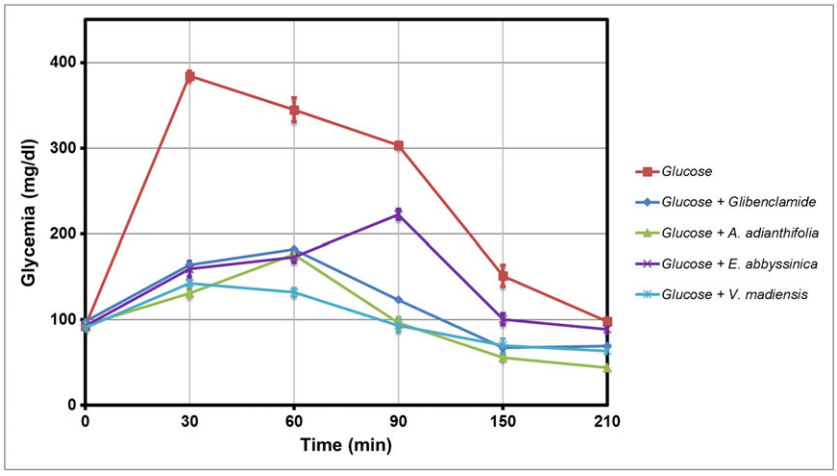

Figure 1. Evolution of blood glucose concentration. [Colour figure can be viewed at wileyonlinelibrary.com]

For tests in OGTT conditions, the delay in glucose blood level apex induced by some herbs may reflect a modification in the absorption process, probably by inhibition of the expression of SGLT-1 or GLUT-2 as previously suggested for some antidiabetic herbs (Schulze *et al*., 2014); indeed, absorption is an important step modulating pharmacokinetics (Zhai *et al*., 2015). The action on glucose transporters is suggested here as a mechanism of action of plant extracts, considering that glucose is a rapid absorption sugar that does not need the intervention of α-glucosidase for its absorption. A delay in glucose absorption indeed indicates another mechanism than the α-glucosidase inhibition previously reported for some herbs (Sivasothy *et al*., 2016). If such SGLT-1 inhibitions were confirmed by further studies, these natural products, as diet supplements, could also be interesting anti-obesity factors (Yang *et al*., 2015; Kazemipoor *et al*., 2016).

All tested plants exhibited antihyperglycemic properties, with inhibition factors ranging from 25.8% to 62.3%. Published antidiabetic studies of herbal drugs on *in vivo* OGTT models have monitored various measurements of hyperglycemia reduction (Dias *et al*., 2010; Chen *et al*., 2015), making difficult the comparison of efficiencies. Indeed published studies differ in animal models, duration of observation, dose of glucose, reference drug, type of plant extract; also investigated herbs probably differ in their mechanisms of action (Patel *et al*., 2012). We may however relate the high antihyperglycemic potency we observed for *A. adianthifolia* and *V. madiensis* to the data reported by Kasali *et al*. (2013) on *Physalis peruviana* L. (Solanaceae).

Albizia adianthifolia, *C. occidentalis*, and *V. madiensis* also showed hypoglycemic activities in glucose baseline conditions. This could be attributed to a possible insulin secretion induction similar to the effect of glibenclamide (Domola *et al*., 2010), maybe consecutive to potassium and calcium channels closing in pancreatic beta cells. Natural products of plant origin able to induce insulin secretion by closing cation channels have already been described in the scientific literature (Noor and Ashcroft, 1998; Akaberi and Hosseinzadeh, 2016). Such a mechanism of action may explain both the delay in glucose blood level apex and the hypoglycemic effect observed.

Globally, it would be important to further study the action of tested plants on cation channels, which could be responsible for (i) antihyperglycemic activity by inhibiting the SGLT or GLUT transporters (Chen *et al*., 2016) and (ii) hypoglycemic properties by stimulating insulin secretion (Sharma *et al*., 2015). Indeed, the literature reports for certain plants species

mechanisms involving both insulin secretion and insulin sensibilization (Thomas *et al*., 2016).

The absence of hypoglycemic activity in the other plants used in traditional medicine against diabetes may only be clearly explained when exploring their clinical use that could point to different mechanisms of action that would not be detected in our experimental settings, for example, action on gastrointestinal glucosidases or on gut microbiote (Bu *et al*., 2010; Schulze *et al*., 2014).

CONCLUSION

This study indicates that the appreciation of baseline-glucose-lowering effects may be inefficient to detect the most interesting extracts; a dynamic exploration, for example, in OGTT conditions, appears essential. On the other hand, these data support the use of some of plants reported for diabetes treatment in traditional Congolese medicine. Further studies are needed to determine which chemical compounds are responsible for the observed biological effects and how they really act.

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Conflict of Interests

The authors state that there is no conflict of interest for this study.

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