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Anti-diabetic and hypolipidaemic activities of *Solenostemon monostachyus*

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ABSTRACT

Background & Aim: *Solenostemon monostachyus* has remain invincible in Ibibio ethnomedicine for the management of numerous ailment including diabetes mellitus. Many of these ethnomedicinal claims are yet to be pharmacologically verified. The purpose of this study therefore was to subject the extract/fractions of *Solenostemon monostachyus* used in folkloric management of diabetes to scientific assay.

Experimental: The crude extract and fractions of *S. monostachyus* (75 -225 mg/kg) were evaluated for antidiabetic activity in alloxan – induced diabetic rats. The antidiabetic activity during acute and prolong studies were investigated. Glibenclamide, 10 mg/kg, was used as positive control. The Blood Glucose Level (BGL) was measured by using a glucometer and the various lipids level were estimated using Randox diagnostic kits.

Results & Discussion: Treatment of alloxan diabetic rats with the extract/fractions caused a significant (p<0.001) reductions in BGL of the diabetic rats both in acute and prolong treatment (two weeks). The activities of extract and fractions were comparable to that of glibenclamide in prolonged study. *S. monostachyus* treatment showed considerable lowering of serum total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol and an increase in HDL cholesterol in the treated diabetic group.

Industrial and practical recommendations: These results suggest that the extract of *S. monostachyus* possesses anti-diabetic and hypolipidaemic effect on alloxan-induced diabetic rats which can be exploited in the management of diabetes.

1. Introduction

Solenostemon monostachyus P. Beauv (family Lamiaceae) is an important herb that is widespread in West and Central Africa. It occurs as an annual weed in anthropogenic habitats and rocky savannahs. It is slightly succulent, aromatic and grows up to 100 cm tall (Mba and Menut, 1994). The aerial parts of the plant are used in various decoctions traditionally by the Ibibios of the Niger Delta of Nigeria to treat stomach ulcer, fever/malaria (Ajibesin *et al*., 2008; Adebayo and Krettli, 2011), hemorrhoid and other inflammatory

diseases. The decoction of the plant is also used to treat hypertension as well as a diuretic (Koffi *et al*., 2009). The infusion of the leaves is used to treat diabetes in part of Nigeria and Côte d'Ivoire (Olabanji *et al*., 2008; Djama *et al*., 2012), Phytochemical studies on *Solenostemon monostachyus* leaves have revealed the presence of water, proteins, lipids, glucids, calcium, phosphate (Buisson *et al*., 1965), essential oil (Mve-Mba *et al*., 1994) and phyto-constituents such as diterpenoids (Toshio *et al*. 1980), flavonoids, coumarin, polyphenol (Datte *et al*., 2010; N'guessan *et al*., 2011). The leaf essential oil of *S. monostachyus* has been reported to contain; β-pinene, oct-1-en-3-ol, β-caryophyllene, octan-3-ol and (*E, E*)-α-farnesene (Mvé-Mba *et al*., 1994). The plant has been reported to possess antimicrobial (Ekundayo and Ezeogu, 2006), antioxidant (Datte *et al*., 2010; N'guessan *et al*., 2011; Okoko and Ere, 2012), antihypertensive (Fidele *et al*., 2012) and antiulcer activities (Okokon *et al*., 2015). We report the antidiabetic and hypolipidaemic activities of *Solenostemon monostachyus* in alloxan induced diabetic rats to provide scientific basis for it use in traditional medicine to treat diabetes and associated diseases.

2. Materials and Methods

2.1. Plants collection

The plant material *Solenostemon monostachyus* (aerial parts) was collected in a farmland in Uruan area, Akwa Ibom State, Nigeria in August, 2014. The plant was identified and authenticated by Dr. Margaret Bassey of Department of Botany and Ecological Studies, University of Uyo, Uyo, Nigeria. Herbarium specimen (FPUU 573) was deposited at Department of Pharmacognosy and Natural Medicine Herbarium.

2.2. Extraction

The plant aerial parts were washed and shade-dried for two weeks. The dried plants' materials were reduced to powder using mortar and pistle. The powdered material was soaked in 50% ethanol. The liquid filtrates were concentrated and evaporated to dryness in vacuo 40°C using rotary evaporator. The extract (2g) was partitioned with a 50:50 mixture of distilled water and chloroform. The aqueous fraction was evaporated to dryness in a water bath at 60^{O}C and the chloroform fraction air-dried. The ethanol extract, the aqueous and chloroform fractions were stored at - 4°C. until used in a refrigerator.

2.3. Phytochemical Screening

Phytochemical screening of the crude extract was carried out employing standard procedures and tests (Trease and Evans, 1989, Sofowora, 1993), to reveal the presence of chemical constituents such as alkaloids, flavonoids, tannins, terpenes, saponins, anthraquinones, reducing sugars, cardiac glycosides among others.

2.4. Animals

Albino male rats (110 – 130 g) of either sex were obtained from the University of Uyo animal house. They were maintained on standard animal pellets and water *ad libitum*. Permission and approval for animal studies were obtained from the College of Health Sciences Animal Ethics committee, University of Uyo.

2.5. Determination of median lethal dose (LD_{50})

The median lethal dose (LD_{50}) of the extract was estimated using albino mice by intraperitoneal (*i.p*) route using the method of Lorke (1983). This involved intraperitoneal administration of different doses of the extract (100-1000 mg/kg) to groups of three mice each. The animals were observed for manifestation of physical signs of toxicity such as writhing, decreased motor activity, decreased body/limb tone, decreased respiration and death. The number of deaths in each group within 24 hours was recorded. The LD_{50} was calculated as geometrical means of the maximum dose producing 0% (a) and the minimum dose producing 100% mortality (b).

$$LD_{50} = \sqrt{ab}$$

2.6. Evaluation of anti-diabetic and hypolipidemic activity of the Extract and fractions

2.6.1. Induction of diabetes and animal treatment: Diabetes was induced in 24 h fasted animals (male rats) by a single intraperitoneal injection of a freshly prepared solution of alloxan monohydrate (150 mg/kg) in ice cold 0.9% saline (NaCl) solution. The animals were given 2 ml of 5% dextrose solution using orogastric tube immediately after induction to overcome the drug induced hypoglycemia. 72 hours later, rats with blood glucose level (BGL) above 200 mg/dl were considered diabetic and selected for the experiment.

The animals were randomly divided into seven groups of 6 rats each and treated as follows:
Group I: Diabetic rats administered *Solenostemon monostachyus* extract (75 mg/kg/day) orally for 14 days.
Group II: Diabetic rats given *Solenostemon monostachyus* extract (150 mg/kg/day) orally for 14 days.
Group III: Diabetic rats administered orally with *Solenostemon monostachyus* extract (225 mg/kg/day) for 14 days.
Group IV: Diabetic rats administered orally with chloroform fraction of *C. lutea* (150 mg/kg/day) for 14 days.
Group V: Diabetic rats administered orally with aqueous fraction of *Solenostemon monostachyus* (150 mg/kg/day) for 14 days.
Group VI: Diabetic rats given Glibenclamide (10 mg/kg/day) for 14 days orally.
Group VII: Diabetic control rats receiving normal saline (10 ml/kg) for 14 days.

The change in body weight and fasting BGL of all the rats were recorded at regular intervals during the experimental period. For acute study, the BGL was monitored after 1, 3, 5 and 7h of administration of a single dose of the extract and at the end of 1, 3, 5, 7 and 14 days for prolonged treatments. The BGL was monitored in the blood of the diabetic rats by tail tipping method. The blood was dropped on the dextrostix reagent pad. This was inserted into microprocessor digital blood glucometer and the readings were recorded (WHO, 1980).

2.7. Evaluation of hypolipidemic activity of the extract and fractions

After 14 days of treatments with the extract/fractions (24 h after the last dose), the rats were anaesthetized with ethyl ether vapor and the blood was collected through cardiac puncture into sample bottles devoid of anticoagulant. The samples were centrifuged at 1000 rpm for 15mins to obtain the sera. Serum cholesterol, triglyceride and High Density Lipoprotein (HDL) levels were measured by enzymatic colorimetric methods using Randox diagnostic kits. All samples were analyzed with a wine light Unicam spectrophotometer. The concentrations of low density lipoprotein (LDL) and very low density lipoprotein (VLDL) were calculated from the formula of Friedwald *et al.,* (1972). These analyses were done at Department of Chemical Pathology, University of Uyo Teaching Hospital, (UUTH), Uyo.

2.8. Statistical analysis

All the group data were statistically analyzed with one – way ANOVA, followed by Tukey – Krammer multiple comparison posttest. Values of $p<0.01$ were considered significant.

3. Results and discussion

Phytochemical screening of the crude extract of *Solenostemon monostachyus* revealed that the crude extract contained tannins, saponins, cardiac glycosides, anthraquinones, flavonoids, steroids and terpenes, alkaloids and phlobatannins.

The median lethal dose (LD_{50}) was calculated to be 748.331 mg/kg. The physical signs of toxicity included excitation, paw licking, increased respiratory rate, decreased motor activity, gasping and coma which was followed by death

There were observable changes in the body weight of treated and untreated alloxan-induced diabetic rats. Treatment of alloxan-induced diabetic rats with ethanol crude extract/fractions of *Solenostemon monostachyus* or glibenclamide considerably improved the weights of treated diabetic rats compared to untreated diabetic rats (Table 1).

The crude extract (75–225 mg/kg) produced dose-dependent reductions in blood glucose level (BGL) alloxan-induced diabetic rats relative to control during acute studies. These effects were statistically significant ($p < 0.05 – 0.001$) and progressed for 7 hours (Table 2). The effect of the highest dose of the extract (225 mg/kg) at the end of 7 hr as well as that of chloroform fraction were more significant than that of the standard drug, glibenclamide (Table 2).

On prolonged treatment (14 days), the extract produced sustained reductions of BGL in diabetic rats. These reductions were significant ($p < 0.05$ - 0.001) when compared to control (Table 3). The effect of the highest dose of the extract and that of the chloroform fraction was comparable to that of standard drug, glibenclamide, 10 mg/kg, on day 14.

Table 1. Effect of ethanolic extract/fractions of *Solenostemon monostachyus* on body weights of alloxan - induced diabetic rats.

Treatment	Dose (mg/kg)	Day 0	Day 15	Change in body weight
Control	0.2ml	126.8 ± 8.65	102.5±6.20	- 24.30
Extract	75	122.4 ±5.14	124.1±4.35	1.70
	150	126.2 ±8.11	130.5± 7.42	4.33
	225	125.8 ±6.55	130.5±9.52	4.70
Chloroform fraction	150	126.8±9.86	133.4±9.67	6.60
Aqueous fraction	150	124.8±6.65	131.5±8.54	6.70
Glibenclamide	10	128.6±7.16	138.3±5.21	9.70

Data are represented as mean ± SEM. (n=6) .

Table 2. Effect of ethanol extract and fractions of *Solenostemon monostachyus* aerial parts on blood glucose level of alloxan-induced diabetic rats during acute study.

Treatment	Dose	Blood glucose level (mg/dl) in hours				
	(mg/kg)	0hr	1hr	3hr	5hr	7hr
Control	0.2ml	240.4± 5.82	245.0± 4.33	250.0± 5.22	258.4 ± 6.65	254.2± 6.26
Crude extract	75	235.2 ± 3.19	231.2 ± 3.64	224.2 ± 3.90[a]	215.0 ± 7.28[a]	218.0 ± 6.89[b]
	150	240.4 ± 5.68	236.4 ± 6.30	220.2 ± 3.12[c]	194.0 ± 14.10[c]	187.4±.4.10[c]
	225	242.8± 6.77	234.7 ± 3.48	211.8 ± 2.84[c]	188.9 ± 2.43[c]	175.4±2.58 [c]
Chloroform fraction	150	237.2 ± 4.90	229.3 ± 4.37	197.0± 5.26 [c]	161.0 ± 3.69[c]	157.6± 2.70[c]
Aqueous fraction	150	243.4±7.60	223.6 ± 5.12	215.0 ± 9.22[c]	196.2± 10.00[c]	184.8±8.99[c]
Glibenclamide	10	242.4± 4.36	235.2 ± 3.24	216.4± 3.18[c]	197.8 ± 9.25[c]	180.0 ± 3.17[c]

Data are expressed as mean ± SEM. Significant at [a]p< 0.05, [b]p< 0.01, [c]p< 0.001. When compared to control.
(n=6).

Table 3. Effect of ethanol extract and fractions of *Solenostemon monostachyus* aerial parts on blood glucose level of alloxan-induced diabetic rats during prolonged treatment

Treatment	Dose in	Blood glucose level (mg/dl) in days			
	(mg/kg)	Day 0	Day 1	Day 7	Day 14
Control	0.2ml	240.4± 5.82	254.0± 7.31	260.0 ± 9.34	267.2 ± 10.67
Crude extract	75	235.2 ± 3.19	222.2± 9.38	186.2 ± 10.78 [a]	139.4 ± 8.33[c]
	150	240.4 ± 5.68	186.5±6.64 [c]	140.4 ± 8.12 [a]	95.6± 4.15 [c]
	225	242.8± 6.77	185.6± 8.26 [c]	135.5± 8.10[a]	82.2 ± 2.26 [c]
Chloroform fraction	150	237.2 ± 4.90	202.3 ± 10.38 [b]	120.0± 10.14[a]	85.8± 5.98 [c]
Aqueous fraction	150	243.4±7.60	212.5 ± 9.63 [a]	146.8 ± 8.84 [a]	118.6 ± 5.96 [c]
Glibenclamide	10	242.4± 4.36	175.2 ± 8.20 [c]	106.0 ± 11.76 [a]	80.2 ± 6.44 [c]

Data are expressed as mean ± SEM. Significant at [a]p<0.05; bp< 0.01,cp<0.001 when compared to control (n = 6).

Table 4. Effect of ethanolic leaf extract and fractions of *Solenostemon monostachyus* on serum total cholesterol, triglycerides, HDL – cholesterol, LDL – cholesterol and VLDL – chol of alloxan- induced diabetic rats.

Drug	Dose mg/kg	Average Serum lipids profile (mMOL/L)				
		Total Cholesterol	Triglycerides	HDL Cholesterol	LDL Cholesterol	VLDL Chol
Control(Normal saline)	0.2ml	4.22±0.14	2.40±0.17	0.74±0.11	2.21±0.14	1.20±0.17
Crude Extract	75	3.92±0.37 ^{c}	2.10±0.12	1.02±0.14	1.52±0.20	0.92±0.04^{c}
	150	3.71±0.12 ^{c}	1.49±0.28^{a}	1.16±0.18^{c}	1.12±0.16	0.74±0.06^{c}
	225	3.24±0.15 ^{a}	1.25±0.31^{c}	1.38±0.15^{c}	1.05±0.06^{c}	0.68±0.12^{c}
Chloroform fraction	150	3.31±0.26 ^{c}	1.28±0.26^{c}	1.58±0.12^{c}	0.68±0.11	0.59±0.09^{c}
Aqueous fraction	150	3.40±0.14 ^{c}	1.35±0.23^{c}	1.50±0.15^{b}	0.86±0.12^{c}	0.45±0.05^{c}
Glibenclamide	10	3.02±0.18^{c}	1.05±0.48 ^{c}	1.60±0.14^{c}	0.55±0.12^{c}	0.42±0.08^{c}

Data are expressed as mean ± SEM. Significant at $^{a}p < 0.05$, $^{b}p< 0.01$, $^{c}p<0.001$. When compared to control (n=6).

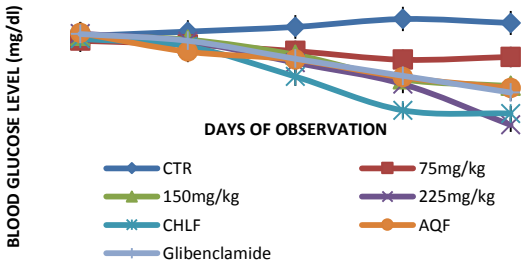

Fig. 1. Blood glucose level in days of observation.

Solenostemon monostachyus leaves are used in different decoctions to treat diabetes in parts of Nigeria and Côte d'Ivoire (Olabanji *et al*., 2008; Djama *et al*., 2012). In this study, evaluation of antidiabetic and hypolipidemic activities of *Solenostemon monostachyus* aerial parts extract/fractions (75-225 mg/kg) were carried out in alloxan-induced diabetic rats. The extract which showed moderate toxicity was observed to demonstrate significant antidiabetic and hypolipidemic activities in alloxan-induced diabetic rats following treatment with the extract for two weeks.

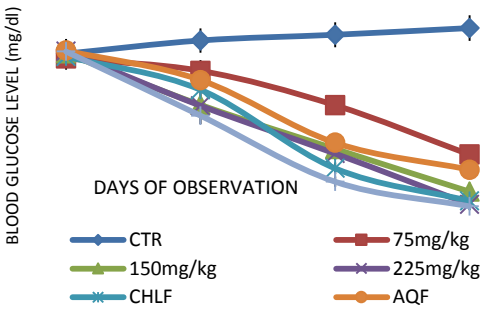

Fig. 2. Blood glucose level in days of observation.

Repeated administration of the extract and fractions of *Solenostemon monostachyus* aerial parts for a period of 2 weeks to diabetic rats caused significant decrease in BGL of treated diabetic rats compared to untreated diabetic rats. These results corroborate those of Amaechi *et al.*, (2015) who worked on streptozotocin-induced diabetic rats using a single dose and reported significant antidiabetic activity of the leaf extract of *S. monostachyus*. Thus confirming strongly the antidiabetic potentials of this plant as claimed in ethnomedicine. Secondary metabolites of plants such as polysaccharides (Tomoda *et al.*, 1985), terpenes and tannins (Reher *et al.*, 1991), steroids (Ivorra *et al.*, 1989), and alkaloids (Karawya and Wahab, 1984) have been reported to possess antidiabetic activity. Phytochemical studies of the *Solenostemon monostachyus* revealed the presence of terpenes, saponins, tannins and alkaloids as well as coumarins, polyphenols, monoterpenes, diterpenoids and sesquiterpenes (Toshio *et al.*, 1980; Mvé-Mba *et al*., 1994; Datte *et al*., 2010; N'guessan *et al.*, 2011). These constituents may in part be responsible for the observed significant activity of this extract either singly or in synergy with one another. Sulphonylureas cause hypoglycemia by stimulating insulin secretion from the pancreas and these compounds are potent in mild alloxan induced diabetes and inactive in intense alloxan induced diabetes whereby nearly all β –cells have been destroyed (Yallow *et al.*, 1960). The reduction in BGL of the diabetic rats by glibenclamide in this study portrays an insevere state of diabetes. The body weights of the treated diabetic rats were found to increase significantly contrary to those of untreated diabetic rats. Diabetes is associated with a severe loss in body weight

due to loss or degradation of structural proteins (Rajkumar *et al.,* 1991). Treatment of the diabetic rats with extract/fractions of *Solenostemon monostachyus* remedied this condition. Several mechanisms of antidiabetic action of plants have been reported. Some plants' extracts are reported to exert hypoglycemic action by potentiating the insulin effect, either by increasing the pancreatic secretion of insulin from the cells of islets of langerhans or its release from bound insulin (Pari and Amarnath, 2004). While others act through extra pancreatic mechanisms by inhibition of hepatic glucose production (Edduoks *et al*., 2003) or corrections of insulin resistance (Hu *et al*., 2003). These extract and fractions may have acted through one of the above mechanisms.

Elevations of serum lipids levels are usually observed during severe diabetes and have been implicated in the development of artherosclerosis (Minorava *et al.,* 2000). In this study also, the serum lipids (total cholesterol, triglycerides, LDL and VLDL) levels of the extract treated diabetic rats were found to be significantly reduced, except that of HDL which was increased, following 2 weeks of treatment with the extract as against that in the untreated diabetic rats in this study. This result is in agreement with the report of Amaechi *et al*., (2015), who reported similar activity with the leaf extract of the plant though employing a single dose. Diabetes–induced hyperlipidemia is attributable to excess mobilization of fat from the adipose due to the under utilization of glucose (Krishnakumar *et al.,* 2000). The alleviation of the diabetic state due to the administration of the extract may have increased the utilization of glucose, thereby depressing the mobilization of fat. Also, the plant extract may have stimulated lipoprotein lipase activities resulting in decrease of plasma triglyceride and probably, increase the uptake of triglyceride from plasma by skeletal muscle and adipose tissues (El-Hazmi and Warsy, 2001).

Phytochemical compounds like phenols, tannins, alkaloids, steroids, cardiac glycosides, flavonoids and terpenes present in this extract have been reported to exert antilipidemic activity (Tandon, 2005). They may in part be responsible for the hypolipidemic activity of this extract.

4. Conclusions

The results of this study show that ethanol extract/fractions of *Solenostemon monostachyus* aerial part possessed antidiabetic and hypolipidemic properties. This confirmation justifies its use in ethnomedical medicine for the treatment of diabetes.

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