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RESEARCH PAPER

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Hypoglycemic Properties of Ethanolic Extracts of *Gongronema latifolium, Aloe perryi, Viscum album* and *Allium sativum* Administered to Alloxan Induced Diabetic Albino Rats (*Rattus norvegicus*)

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ABSTRACT

The ethanolic extracts of Gongronema latifolium, Aloe perryi, Viscum album (leaves) and Allium sativum (bulb) were investigated for their phytochemical/biochemical constituents and hypoglycemic properties. Hypoglycemia was induced in rats by a single dose (140 mg/kg) of intra-peritoneal injection of alloxan monohydrate in citrate buffer (pH 4.5). Suspensions of the ethanolic extracts were administered by intra-peritoneal injection at doses of 2 mg/kg/16 h for 54 h. Collection of blood samples for estimation of fasting blood glucose (FBG) was carried out at regular time intervals of 0, 16, 32, 48 and 54 h, using the glucose oxidase method. Phytochemical and biochemical screening showed the presence of saponin, tannins, flavonoids, proteins and carbohydrates in the four plant tissues under investigation. A. sativum and G. latifolium tested positive for the presence of alkaloids. The capacities of the four ethanolic extracts to reduce FBG concentrations in treated rats at the 54th h of the experiment were in the order: A. perryi > G. latifolium > A. sativum > V. album. Comparatively, at t = 16 h, FBG concentration of V. album treated rats was not significantly different (p > 0.05) from those of G. latifolium treated group. Likewise, FBG concentration of rats treated with extract V. album did not show significant difference (p > 0.05) compared to the group administered with extract of A. sativum. The four plant extracts used in the present study exhibited approximately the same capacity to act as hypoglycemic agents in the treated rats and correlates with the therapeutic capacity of the standard drug-Glimepiride.
Keywords: Hypoglycemia, phytochemical, A. perryi, G. latifolium, A. sativum and V. album

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia and glucosuria produced by an absolute or relative insulin insufficiency {(Insulin-Dependent Diabetes Mellitus (IDDM)} or insulin resistance by peripheral cells {(Non-Insulin-Dependent Diabetes Mellitus (NIDDM)} or both (Gwarzo *et al.,* 2010). The disease presents other metabolic and anatomic distortions and disturbances. Strikingly amongst which are retinopathy, neuropathy, nephropathy, hyperlipidemia, hypercholesterolemia, ketosis, atherosclerotic coronary artery and peripheral atherosclerotic vascular diseases (Ugochukwu *et al.,* 2003; Dewanjee *et al.,* 2008). The individual also experiences weight loss, pathologic changes in the eye, renal dysfunction and neuropathy (Ene *et. al.,* 2007; Andrew *et al.,* 2010). Oxidant free radicals have been implicated in the pathogenesis of IDDM (Baynes, 1991; El-Missiry and El-Gindy, 2000; Gwarzo *et al.,* 2010). In experimental animals, injection and subsequent metabolism of 2, 4, 5, 6-tetraoxypyrimidine (alloxan) induces specific DNA fragmentation in pancreatic islets and cell damage has been attributed to the production of toxic free radicals (Lankin *et al*., 2004; Gwarzo *et al.,* 2010). Alloxan treated animals are widely used as models for IDDM studies (Dhandapani *et al.* 2002, Visser *et al*. 2002; Dewanjee *et al.,* 2008; Gül *et al.,* 2008; Gwarzo *et al.,* 2010; Rotimi *et al.,* 2011; Sharma and Kumar, 2011). The reason for the high sensitivity of β-cells to alloxan is not clear, although there are speculations on connection between alloxan sensitivity and incidence of IDDM.

Plants offer a wide range of natural compounds of medicinal values to humans and domestic animals. *Gongronema latifolium*, commonly called 'arokeke' and 'utazi' in the South Western and South Eastern parts of Nigeria, is a tropical rainforest plant primarily used as spice and vegetable in traditional folk medicine (Ugochukwu *et al.,* 2003; Eleyinmi, 2007). Akuodor *et al.,* (2010) reported that *G. latifolium* has anti-plasmodial activity; this supports the traditional use of the leaf extract of the plant for local treatment of malaria. Reports by Egunyomi *et al.,* (2009) showed that *G. latifolium* has antisickling activities and effective in the treatment of sore gums, colic, dyspepsia and anti-helminthic. *Aloe perryi* belongs to the family of *Liliaceae* and Ashafa *et al.,* (2011) documented the use of *A. vera* for the alleviation of constipation in Wistar rats. There are no reports on the use of *A. perryi* in ameliorating DM in human. Another member of the *Liliaceae* family, *Allium sativa* (garlic), apart from its medicinal purposes, is also used as seasoning in Africa, Southern Europe and Asia. It is a natural source of selenium to the body for proper immune response, and acts as an antioxidant (*http://www.complete-herbal.com/details/garlic.html*). Extracts from *Viscum album* (Mistletoe) are widely used as alternative cancer and cardiovascular disease therapies in Europe and have been recognised to induce apoptosis (Büssing and Schietzel. 1999; Hajto *et al.,* 2005; Shahaboddin *et al.,* 2011; European Medicines Agency, 2011). The hypoglycemic and antioxidant activity of *V. album* extract was investigated by Shahaboddin *et al.,* (2011).

Although varieties of drugs are available for the treatment and management of DM, herbal preparations are still being prescribed widely as alternatives to synthetic ones, even when their biologically active compounds are unknown, because of their minimum side-effects and relatively low cost. Furthermore, from time immemorial, plants have been used medicinally for the treatment of diverse disorders/ailments and there are numerous documented claims of herbal remedies for DM. Almost five decades ago, Jain *et al.* (1975), posited that ingestion of

Allium cepa (onion) and *A. sativum* (garlic) juice resulted in better utilization of glucose in rabbits. Recently, the applications of natural substances for the prevention, management and treatment of DM have been reported by several researchers and there are increasing search for herbal hypoglycemic agents (Ahmed *et al.,* 2010; Rotimi *et al.,* 2011; Sharma and Kumar, 2011; Mungle *et al.,* 2012). In view of this, it has been considered pertinent to investigate the hypoglycemic properties of various extracts of *G. latifolium, A. perryi, V. album* and *A. sativum* in alloxan induced diabetic *Rattus norvegicus*.

MATERIAL AND METHODS

Collection of plant specimens

Fresh samples of *G. latifolium, A. perryi, V. album* and *A. sativum* were harvested between October and November 2011, from the Botanical Gardens of Imo State University and Federal University of Technology, Owerri, Nigeria. The plant specimens were identified and authenticated by Dr. F. N. Mbagwu at the Herbarium of the Department of Plant Science and Biotechnology, Imo State University, Owerri. A voucher specimen was deposited at the Herbarium for reference purposes.

Preparation of extracts

The samples were washed under continuous current of distilled water for 15 min and air-dried at room temperature for 5 h. The separate leaves were further dried for 5 h in an oven at 60 °C to become crispy, and ground with ceramic mortar and pestle. Twenty-five grams (25 g) of each of the pulverized specimen was suspended in 250 mL of ethanol/water mixture (1:2 *v/v*) in stoppered flasks and allowed to stand for 24 h. The suspensions were filtered with Whatman No 24 filter papers. The filtrates were concentrated in a rotary evaporator at 50 °C and dried in vacuum desiccators. The yield was calculated to be *G. latifolium* (3.4% *w/w*), *A. perryi* (3.1% *w/w*), *V. album* (2.2% *w/w*) and *A. sativum* (3.5% *w/w*). These extracts were finally suspended in phosphate buffered saline (PBS) solution (extract vehicle), osmotically equivalent to 100 g/l NaCl {NaCl (90.00 g), $Na_2HPO_4.2H_2O$ (17.10 g) and $NaH_2PO_4.2H_2O$ (2.43 g)/ L}, and used in all the studies with doses expressed in milligram per kilogram body weight (mg/kg) of the animals.

Phytochemical and biochemical study

Phytochemical and biochemical screening was carried out for the presence of tannins, carbohydrates, flavonoids, saponin, alkaloids, glycosides and proteins as described by Ayoola *et al.* (2008).

Experimental animals

Wistar albino rats (8–10 weeks), weighing 17-21 g of both sexes was obtained from the animal house of University of Port Harcourt, Port Harcourt, Nigeria. Before and during the experiment, rats were fed with standard commercial feed (Ewu Feed Mills, Edo State, Nigeria) and water, *ad libitum*, in well ventilated stainless steel cages. After randomization on weight basis, the rats were acclimatized for a period of 7 days at ambient temperatures of 25 ± 5 °C, 30-55% of relative humidity and 12 h light/12 h darkness cycle. The handling of the animals was in accordance with the standard principles of laboratory animal care of the United States National Institutes of Health (NIH, 1978).

Induction of diabetes

Diabetes was induced in the rats as earlier described by Mohini *et al.,* **(**2012). A single dose (140 mg/kg) of intra-peritoneal injection of alloxan monohydrate in citrate buffer (pH 4.5) was administered to the rats. Hyperglycemia was confirmed 48 h after alloxan injection (Mandal *et al.,* 1997). Surviving rats with FBG concentrations higher than 250 mg/dL were included in the study (Ghosh and Suryawanshi, 2001; Murali *et al.,* 2002).

Study design and fasting blood glucose estimation

The animals were deprived of food and water for 16 h, *ad libitum*, before the commencement of the feeding experiment. A total of twenty-eight (28) rats were divided into seven groups of four (n = 4) each as follows:

- Group Control-Normal (Control-N): The animals of this group were non-diabetic and received only PBS (1 ml/kg/16 h, i. p.) for 54 h.
- Group Control-Diabetic (Control-D): The animals of this group were diabetic and received PBS (1 ml/kg/16 h, i. p.) for 54 h.
- Group T1 (D + *V. album*): The animals of this group were diabetic and received *V. album* (2 mg/kg/16 h, i. p.) for 54 h.
- Group T2 (D + *A. sativum*): The animals of this group were diabetic and received *A. sativum* (2 mg/kg/16 h, i. p.) for 54 h.
- Group T3 (D + *G. latifolium*): The animals of this group were diabetic and received *G. latifolium* (2 mg/kg/16 h, i. p.) for 54 h.
- Group T4 (D + *A. perryi*): The animals of this group were diabetic and received *A. perryi* (2 mg/kg/16 h, i. p.) for 54 h.
- Group T5 (D + Glimepiride): The animals of this group were diabetic and received Glimepiride (0.09 mg/kg/16 h, i. p.) for 54 h.

Blood samples were drawn from the tip of the tails of the rats at regular time intervals of 0, 16, 32, 48 and 54 h for FBG estimation. FBG was estimated by glucose oxidase method according to the Randox® kit manufacturer's procedure (Randox® Laboratories Ltd. Ardmore, United Kingdom).

Statistical analysis

The results were expressed as mean ± SEM, and statistically analyzed by ANOVA followed by Dunnett test, with level of significance set at $p < 0.05$.

RESULTS

Phytochemical and chemical screenings showed the presence of tannins, saponin, flavonoids, proteins and carbohydrates in the four plant tissues under investigation (Table 1). *A. sativum* and *G. latifolium* tested positive for the presence of alkaloids.

Table 1: Phytochemical and chemical constituents of *V. album*, *A. sativum, G. latifolium* and *A. perryi.*

Phytochemical/Chemical	*V. album*	*A. sativum*	*G. latifolium*	*A. perryi*
Alkaloids	-	+	+	-
Saponins	+	+	+	+
Tannins	+	+	+	+
Flavonoids	+	+	+	+
Proteins	+	+	+	+

Carbohydrates	+	+	+	+

The FBG concentrations (mg/dl) of the seven (7) groups of rats within the experimental time (54 h) are presented in Figure 1. A cursory look at Figure 1 showed that FBG concentrations of the Control-N and Control-D groups registered relatively low variability. The FBG concentration of Control-N group ranged between 96.5±0.54 and 97.5±0.71 mg/dl ($54 \geq t \geq 0$; $p > 0.05$), whereas Control-D group was between 232.5±1.26 and 233.5±1.43 mg/dl ($54 \geq t \geq 0$; $p > 0.05$). Furthermore, an overview of the results showed that all the treated rats (Groups T1-T5) exhibited relative reduction in FBG concentrations as the experimental time progressed except the Group Control-D. Comparatively, the standard drug (Glimepiride) exhibited the highest capacity to reduce FBG concentrations in treated rats (Group T5: D + Glimepiride).

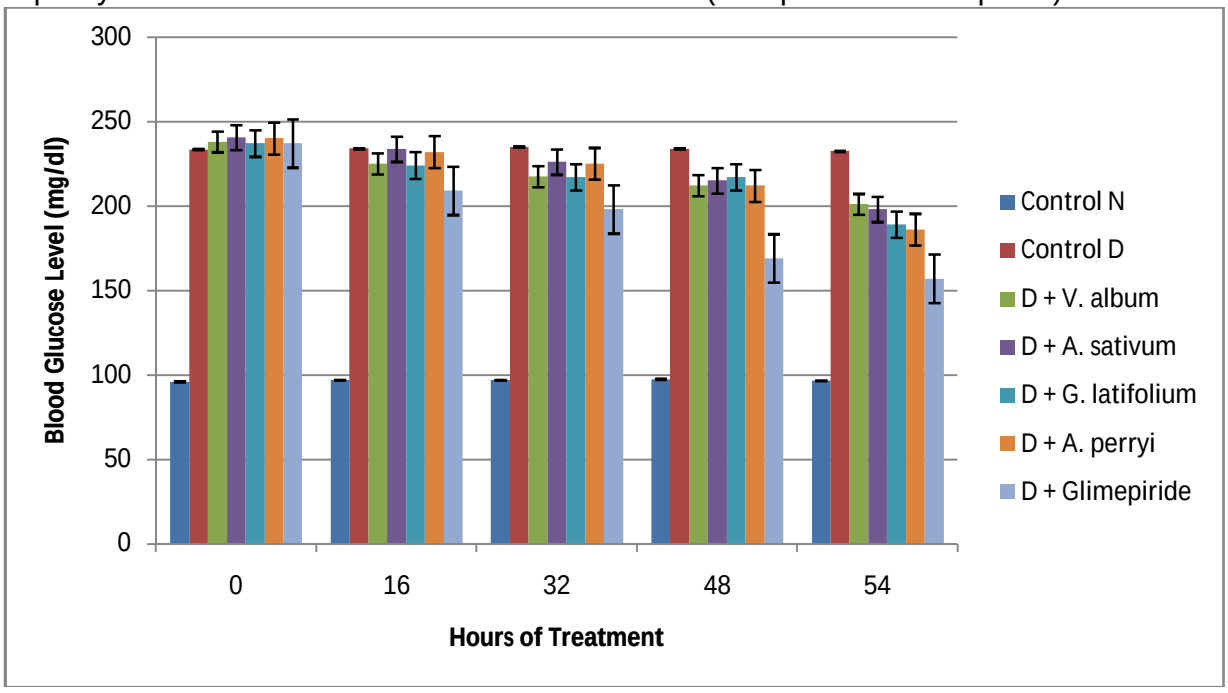

Figure 1: Comparative effect of ethanolic extracts of *V. album*, *A. sativum*, *G. latifolium* *A. perryi* and Glimepiride on FBG in alloxan-induced diabetic rats.

The capacities of the four ethanolic extracts to reduce FBG concentrations in treated rats at the 54th h of the experiment were in the order: *A. perryi* > *G. latifolium* > *A. sativum* > *V. album* (Table 2). Specifically, extract of *A. perryi* administered to rats caused the reduction of FBG concentration from 240±1.11 mg/dl (t = 0 h) to 189±1.02 mg/dl at t = 54 h, representing 22.50% reduction in FBG concentration. The administration of extract of *V. album* to the rats caused a reduction of FBG by 15.55±0.92 % at t = 54 h (Table 2). The FBG concentrations of *V. album, A. sativum* and *A. perryi* treated rats as well as the standard control group (D + Glimepiride) showed significant difference ($p < 0.005$) between each preceding time intervals of treatment when $t > 16$ h, whereas extracts of *G. latifolium* caused no significant ($p > 0.005$) reduction in FBG concentration between the 32 and 48 h. Generally, within the experimental time range ($54 \geq t \geq 0$) h, the four extracts caused a progressive reduction in FBG concentrations but did not

exhibit the capacity to return FBG concentration to normality (96.8±0.57 mg/dl) in the rats during the experimental period.

Table 2: Reduction in levels FBG concentrations in the presence of ethanolic extracts of *V. album*, *A. sativum, G. latifolium A. perryi* and Glimepiride in alloxan-induced diabetic rats.

	Percentage (%) Reduction in FBG Concentration				
Time (h)	D + *V. album*	D + *A. sativum*	D + *G. latifolium*	D + *A. perryi*	Glimepiride
16	5.46±1.08	2.87±1.23	5.49±1.20	3.33±1.09	11.81±0.88
32	8.61±0.99	6.03±0.96	8.44±0.89	6.25±0.95	16.46±1.11
48	10.93±0.89	10.60±1.00	8.44±0.99	11.67±1.07	28.69±0.89
54	15.55±0.92	17.67±0.78	20.25±0.92	22.50±1.02	33.76±0.99

Comparatively, at t = 16 h, FBG concentration of D + *V. album* rats was not significantly different ($p > 0.05$) from those of D + *G. latifolium* group. Likewise, FBG concentration of rats treated with extract *V. album* did not show significant difference ($p > 0.05$) compared to the group administered with extract of *A. sativum* (Table 2).

DISCUSSION

The results of the present study corroborate the previous reports of hypoglycemic properties of *Viscum album* leaves extracts (Gray and Flatt, 1999 and Shahaboddin *et al.*, 2011), *Eugenia floccosa* Bedd. Leaves extracts (Kala *et al*., 2012), *Rubus ellipticus* fruit extracts (Sharma and Kumar, 2011), matured fruits extracts of *Diospyros peregrina* (Dewanjee *et al*., 2008), *Vinca rosea* whole plant extracts (Ahmed *et al*., 2010), *Terminalia catappa* Linn. Fruits extract (Nagappa *et al*., 2003) and onion and garlic extracts (El-Demerdash *et al*., 2005). A target based therapeutic approach towards diabetes mellitus using medicinal plants has been extensively discussed by Prabhakar and Doble (2003). Basically, from reports of these previous studies, the active principles of these plant extracts exerted therapeutic benefits by either mimicking the physiologic actions of insulin and/or facilitating insulin secretion.

Early reports by Gray and Flatt (1999) stated that *V. album* contains water soluble and heat resistant natural product(s) that enhanced the release of insulin in hyperglycemic streptozotocin induced diabetic rats. Although their report could not establish whether the β-amyrin, tyramin, quercitin, syringin and flavoyedorinin A and B components of the leaf extract was responsible for its hypoglycemic property, they noted that the hypoglycemic action of *V. album* extract was not mediated by lectins. In the present study, phytochemical screening of *V. album* extract showed the presence of flavonoids (Table 1). Flavonoids are potent hypoglycemic agents as reported by several authors (Zhu *et al*., 2010; Cho *et al*., 2011; Najafian *et al*., 2010). Therefore the presence of flavonoids in the *V. album* extract was responsible for its hypoglycemic activity possibly by the stimulation of insulin secretion (Gray and Flatt, 1999). In another study, Cho *et al*. (2011) stated that flavonoids possessed antioxidant activity as shown by promoting increased activity of superoxide dismutase (SOD) and decreased plasma malondialdehyde (MDA) concentration in diabetic rats. This serves to postulate that the presence of flavonoids could also act to antagonize the generation of free radicals by alloxan and associated pathophysiology of diabetic state.

The hypoglycemic property of *A. sativum* extract reported here conformed with previous reports by Ayodhya *et al*. (2010) and Patel *et al*. (2012). Ayodhya *et al*. (2010) stated that the hypoglycemic activity of the ether extract of *A. sativum* was due to increased insulin-like activity, whereas Chauha *et al*. (2010) posited that oral administration of ethanolic extract of *A. sativum,* facilitated by its Allicin content, acted by stimulating insulin secretion from pancreatic β cells. The phytochemical contents of the ethanolic extract of *A. sativum* (Table 1) showed the presence of varieties of plant natural agents reported to possess hypoglycemic properties. Worthy of note are tannins (Teotia and Singh, 1997; Nagappa *et al*., 2003; Ali *et al*., 2012), flavonoids (Zhu *et al*., 2010; Cho *et al*., 2011; Najafian *et al*., 2010; Ali *et al*., 2012) and alkaloids (Badole *et al*., 2006). β-carotene, which we did not assay for, has also been reported to have hypoglycemic effects (Nagappa *et al*., 2003).

Ugochukwu and Babady (2003) showed that ethanolic extract from *G. latifolium* leaves had hypoglycemic potency, which was thought to be mediated through the activation of hexokinase, phosphofructokinase, glucose-6-phosphate dehydrogenase and inhibition of glucokinase activity in the liver of diabetic rats. In another report, Ngozi *et al*. (2003) posited that ethanolic extract of *G. latifolium* appeared to be more effective in reducing oxidative stress, lipid peroxidation and increased reduced glutathione/oxidized glutathione (GSH/GSSG) ratio, thus confirming the ethnopharmacological use of *G. latifolium* in ameliorating the oxidative stress associated with diabetics. Rajasekaran *et al.* (2005) reported the presence of several hypoglycemic-activity-possessing elements in the gel of *A. perryi*. They further showed that streptozotocin-induced diabetic rats treated with the ash of *A. perryi* also resulted in hypoglycemic action. Thus, the presence of various inorganic trace elements in the gel accounted for the hypoglycemic nature of the plant.

The four plant extracts used in the present study exhibited approximately the same capacity as hypoglycemic agents in the treated rats and correlated with the therapeutic capacity of the standard drug-Glimepiride.

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