

**Research Paper**

*Afr. J. Traditional,
Complementary and
Alternative Medicines*
www.africanethnomedicines.net

ISSN 0189-6016©2009**HYPOGLYCAEMIC AND ANTIHYPERGLYCAEMIC ACTIVITY OF *AGERATUM CONYZOIDES* L. IN RATS.****Nyemb Nyunai^{ab*}, Njifutié Njikam^a, El Hassane Abdennebi^c, Joseph Tanyi Mbafor^d, Driss Lamnaouer^c**

^aDepartment of Animal Biology and Physiology, Faculty of Science, University of Yaoundé 1, P.O. Box 812 Yaoundé, Cameroon. ^bCentre for Medical Research, Institute of Medical Research and Medicinal Plants Studies, P.O. Box 3805 Yaoundé, Cameroon. ^cDépartement des Sciences Biologiques et Pharmaceutiques Vétérinaires, Institut Agronomique et Vétérinaire Hassan II, BP 6202, Rabat-Instituts, Rabat, Maroc. ^dDepartment of Organic Chemistry, Faculty of Science, University of Yaoundé 1, P.O. Box 812 Yaoundé, Cameroon.

***E-mail:** nyunain@yahoo.fr**Abstract**

The hypoglycaemic and antihyperglycaemic properties of the aqueous extracts of the leaves of *Ageratum conyzoides* L. were evaluated in normoglycemic and in streptozotocin-induced diabetic rats, in order to validate its use in folk medicine. Tested animals were given the aqueous extracts of the plant at the doses of 100, 200 and 300mg/kg. These doses were tested also on glucose loaded normal male rats (Oral Glucose Tolerance Test). Of all the doses, the aqueous extracts at 200 and 300mg/kg showed statistically significant hypoglycaemic and antihyperglycaemic activities. For the oral glucose tolerance test, 100mg/kg dose only attenuated significantly the rise of blood glucose in normal fasted rats. Consequently, these results confirmed the hypoglycaemic properties of the leaves of *Ageratum conyzoides*.

Key word: *Ageratum conyzoides*, hypoglycaemic activity, antihyperglycaemic activity, Oral glucose tolerance test.

Introduction

Diabetes mellitus is a metabolic disorder of the endocrine system. The disease occurs worldwide and its incidence is increasing rapidly in most parts of the world. People suffering from diabetes are not able to produce or properly use insulin, so they have high blood glucose. As a very common chronic disease, diabetes is becoming the third 'killer' of mankind, after cancer, cardiovascular and cerebrovascular diseases, because of its high prevalence, morbidity and mortality (Li *et al.*, 2004).

In modern medicine, no satisfactory effective therapy is available to cure diabetes mellitus, although it can be managed by exercise, diet and chemotherapy. However, pharmaceutical drugs used in diabetic therapy are either too expensive or have undesirable side-effects or contraindications (Pari and Amarnath Satheesh, 2004). Therefore, the search for more effective and safer hypoglycaemic agents has continued to be an area of active research all over the world (Lemhadri *et al.*, 2004; Stanely *et al.*, 2004). Previously, the hypoglycaemic activity of a number of indigenous African medicinal plants has been reported. Several of these plants reduced blood sugar levels in the alloxan-diabetic rats only, whereas some caused hypoglycaemia both in normal and diabetic rats (Sokeng *et al.*, 2001). *Ageratum conyzoides* L. (Asteracées) is a well-known medicinal plant that has been used in several countries for treating various diseases including diabetes mellitus (Lavergne and Véra, 1989; Tsabang *et al.*, 2001; Duke, 2005).

So far, the claims of *Ageratum conyzoides* L antidiabetic effect have not been confirmed experimentally. Therefore, the present study was designed to evaluate the hypoglycaemic efficiency of *Ageratum conyzoides* leaves in normal and streptozotocin-induced diabetic rats.

Materials and Methods

Collection and preparation of plant material

Mature *Ageratum conyzoides* L. was collected during the month of February 2006 in Yaoundé, Centre province, Cameroon. Botanical identification was performed at the National Herbarium of Yaoundé, in comparison with the voucher specimen N°19050/SFR/Cam. The leaves were shade-dried and ground into powder.

Preparation of the extracts

The leaves of the plant were first dried, at room temperature, and grounded to fine powder (138g), and then boiled in distilled water (2.25 L) for 30min. The decoction was taken and allowed to cool for 30min at room temperature ($24 \pm 5^\circ \text{C}$). This decoction was filtered twice and the filtrate was dried in an oven (55°C) for 3 days. The yield was about 29% (w/w) of the dried plant powder.

Drugs and chemicals

Glibenclamide was purchased from Strides Arcolat Ltd. Bangalore, India and Streptozotocin from Sigma-Aldrich Co Ltd, United Kingdom.

Animals

Male albino *Wistar* rats (180–220 g) were maintained on standard laboratory diet and tap water *ad libitum* in the Animal House of the Institute of Medical Research and Medicinal Plants Studies, Cameroon. Prior to the experiment, the rats were divided into 15 experimental groups of 5 animals each. The animals were subjected to fasting for 16h but allowed free access to water. The study was carried out with the approval by the Institutional Animal Ethics Committee.

Study of aqueous leaves extract of *Ageratum conyzoides* in normal rats

Group I, II, III were given the aqueous extract leaves of *Ageratum conyzoides* (suspended in distilled water 10ml/kg) orally at the doses of: 100, 200 and 300mg/kg. Animals of group IV received glibenclamide at a dose of 10mg/kg as a standard while those of group V served as a normal control and received appropriate volumes of vehicle (distilled water) orally. Blood samples for glucose determination were obtained from the tip of tail of the rats before administration of drugs and at 1.5 h, 3h, 5h, and 8 h thereafter.

Induction of experimental diabetes

Groups VI to X were rendered diabetic intravenously, by an intravenous injection of a freshly prepared streptozotocin (STZ) solution at the dose of 52mg/kg body weight in acidified saline solution (0.9%; pH 4.5), as described by Szkudelski, 2001. In this case, the control animals received only the acidified saline solution. After 72h, when the condition of diabetes was stabilized, the animals with blood glucose levels above 200mg/dl were selected for the study.

Study of aqueous leaves extract of *Ageratum conyzoides* in diabetic rats

Groups VI to VIII received by the oral route the aqueous leaves extract of *Ageratum conyzoides* (suspended in distilled water at the dose of 10ml/kg) at the doses of 100, 200, 300mg/kg body weight respectively. The animals in group IX were kept as a diabetic control and received distilled water, while group X received glibenclamide at a dose of 10mg/kg body weight and served as a standard. Blood samples for glucose determination were obtained from the tip of tail of the rats before administration of drugs and at 1.5h, 3h, 5h, and 8 h thereafter.

Oral glucose tolerance test

An Oral Glucose Tolerance Test (OGTT) was performed in normal fasted rats. Animals were deprived of food for 16h before and during the experiment but were allowed free access to water. 100, 200 and 300mg/kg of aqueous extract were administered orally to 3 groups (XI to XIII) of 5 rats each; 30min before glucose load (3g/kg). Two groups (XIV and XV) of 5 rats each, considered as controls, received distilled water (10ml/kg) or glibenclamide (10mg/kg) instead of aqueous extract, and 3g/kg body weight of glucose. Blood samples were

taken before and after the administration of the extract and blood glucose level was subsequently measured at 30min, 1h, 1.5h, 2h, and 2.5h after oral administration.

Collection of blood and determination of blood glucose:

Blood glucose level was determined using a glucometer, Glucotrend[®]2 (An Accu-Chek system of the Roche Group Germany, Roche diagnostics GmbH D-68298 Mannheim, Germany) in all animals. The percentage of glycaemia changes was calculated as a function of time by applying the formula of Jimenez *et al.* (1986) as follows:

% glycaemia changes = $((G_x - G_0) / G_0) * 100$. Where G_x = glycaemia values at x hrs time interval, and G_0 = initial glycaemia values.

Statistical analysis

All values were expressed as mean \pm S.D. The data were statistically analysed by the classical student's paired t -test.

Results

The oral administration of the aqueous extracts of *Ageratum conyzoides* leaves at 200mg/kg produced a significant hypoglycaemic effect in normal fasted rats after 3h. The most pronounced effect was observed after 8h ($p < 0.001$) (Table 1). This dose reduced the blood glucose level of the normal fasted rats from an initial mean value of 87.90 ± 5.41 at the initial time (0h) to a mean value of 58.90 ± 5.20 (33%) at the end of the 8 hrs. Whereas, in the group that received 300mg/kg body weight of the extract, there was a significant reduction in blood glucose level in fasted normal rats (36.35%) after 8h ($p < 0.01$). At 100mg/kg, there was a less significant ($p < 0.01$) hypoglycaemic effect 5h after administration of aqueous extract. Oral treatment with glibenclamide (10mg/kg) caused a highly significant reduction in blood glucose levels up to 8h ($p < 0.0001$). However, the reduction in the blood glucose level caused by extract at all doses is less than that of standard drug, glibenclamide (Table 1).

The aqueous extracts of *Ageratum conyzoides* leaves given at 200mg/kg and 300mg/kg produced significant antihyperglycaemic effects ($p < 0.01$ and $p < 0.1$) in diabetic rats after 1.5h for up to 8h (Table 2). Treatment of diabetic rats with glibenclamide (10mg/kg) produced a slight but significant fall ($p < 0.01$) in blood glucose after 8h (15.48%). The maximum decrease was observed with the dose of 300mg/kg, 8h after administration of the extract when compared to that of 100 and 200mg/kg. The aqueous extract at 100mg/kg dose gradually decreased blood glucose level (4.28%-6.29%-17.72%-20.13%), but this fall was only significant at 1.5h and 8h ($p < 0.1$) after administration of the extract (Table 2).

Blood glucose increased rapidly in all groups 30min after administration of glucose and thereafter decreased gradually. When the three different doses of the extract (100, 200 and 300mg/kg) were given orally before glucose administration, only 100mg/kg caused a non significant increase of glycemia when compared to initial value (Table 3). With the dose of 200mg/kg, the pick of increasing of glycemia appears significantly 60min after glucose loading and began decreasing thereafter. The level of glycemia in rats that received 300mg/kg of the extract remained high ($p \leq 0.005$) through out the experimental period, after giving the dose of glucose (3g/kg) 30 mins into the experiment. Contrary to the extract, glibenclamide (10mg/kg) used as the positive control decreased the level of glycemia significantly during the course of the experiment ($p \leq 0.005$), except 30 mins after administration of glucose (4.75%).

Discussion

The aim of the present study was to confirm the hypoglycemic effect of *Ageratum conyzoides* leaves in normal, glucose loaded and streptozotocin-induced diabetic rats. Our results showed that the aqueous extract of *Ageratum conyzoides* leaves decreased blood glucose levels in normal and streptozotocin-induced diabetic rats, as compared to the initial values of glucose levels. The hypoglycaemic potential of the extract was compared with that of glibenclamide in normal and in diabetic rats. For normal rats, all the three doses showed significant reduction in blood glucose level. The 200mg/kg dose showed maximum effect of all the three tested doses.

In glucose loaded rats, only the 100mg/kg dose of *A. conyzoides* extract inhibited significantly the rise of glycemia. This observation suggests that the extract may act by potentiating the pancreatic secretion or increasing the glucose uptake. Among all the doses of aqueous extract of *Ageratum conyzoides* leaves used in this study, 200mg/kg and 300mg/kg doses significantly lowered ($p < 0.01$) blood glucose levels of streptozotocin-

diabetic rats as compared with the initial values before administration of extracts. The maximum reduction (27.15%; $p < 0.01$) was observed 8h, after administration of the extract at 300mg/kg, this reduction was persistent for the dose of 200mg/kg except at 5h after administration of the extract, but that reduction was less pronounced ($p < 0.1$). The efficiency of these doses was higher than that of 100mg/kg and that of glibenclamide (10mg/kg).

As a standard drug, glibenclamide (10mg/kg) caused a slight but significant antihyperglycaemic activity in diabetic rats at 1.5h ($P < 0.1$) and 8h ($P < 0.01$) after administration of extract (15.48%). Glibenclamide at 10mg/kg appears to be less efficient than the extract of *Ageratum conyzoides* at 200mg/kg and 300mg/kg. This result appeared to be in agreement with the early suggestion that glibenclamide was effective in moderately streptozotocin-induced diabetic animal and ineffective in severe diabetic rats (Ivorra et al., 1988; Sharma et al., 1997).

For the normal fasted rats, maximal hypoglycemic activity was observed with the dose of 300mg/kg, with a significant decrease ($p < 0.01$) of blood glucose level (36.35%), 8h after the administration of the extract, but the dose of 200mg/kg significantly reduced ($p \leq 0.01$) blood glucose level (17.79%) faster than 100mg/kg and 300mg/kg; 3h after administration of the extract. This effect lasted for up to 8h after administration of the extract. Like the plant extracts, glibenclamide also produced a significant reduction in the blood glucose level in fasted normal rats. On the other hand, glibenclamide caused a more significant ($p < 0.0001$) hypoglycemic effect as compared to different doses of the plant extract. Treatment with *Ageratum conyzoides* aqueous extract of fasted normal rats at the same dose, for the same duration, showed more hypoglycemic activity than in diabetic rats. It is generally accepted that streptozotocin treatment causes permanent destruction of β -cells (Szkudelski, 2001). Furthermore, from these results, it can be suggested that the extract of *Ageratum conyzoides* leaves appear to act in the same way as glibenclamide, by stimulating surviving beta cells to release more insulin in normal rats. At the moment, it is very difficult to draw any logical conclusion on the mechanism of action of such a diverse mixture of chemical compounds contained in the aqueous extract used in this study. Some medicinal plants with hypoglycemic properties are known to increase circulating insulin level in normoglycaemic rats (Lemela et al., 1985; Diatewa et al., 2004). A plausible mechanism of action is that the extract of *Ageratum conyzoides* might have stimulated residual pancreatic beta-cell function or produced the hypoglycemic effect through an extra pancreatic mechanism, probably by increasing peripheral utilization of glucose as postulated by Farjou et al. (1987) to explain the hypoglycemic effects of the extracts of *Artimisia* and Adeneye et al. (2006) who demonstrated the hypoglycaemic mechanism of the aqueous leaf and seed extract of *Phyllanthus amarus* in mice. It is, therefore, conceivable that the hypoglycemic principles of the aqueous extract of *Ageratum conyzoides* exerts their effects by an extra pancreatic mechanism in diabetic rats.

From phytochemical analysis, it was found that the major constituents of the extract were mono- and sesquiterpenes, flavonoids, triterpenoids, sterols, alkaloids, coumarins, essential oils and tannins (Okunade, 2002). Over 150 plants extracts and some of their active principles including flavonoids are known to be used for the treatment of diabetes (Meiselman et al., 1976; Choi et al., 1991; Hassig et al., 1999; Chude et al., 2001). Moreover, tannin-containing drug demonstrated antidiabetic activity (Iwu, 1983, 1980; Klein et al., 2007). However, if the hypothesis of Marles and Farnsworth (1995) which indicates that plants which contain terpenoids and/or coumarins possess hypoglycemic activities in diabetic and normal mammals is worthwhile, it could be suggested that, the hypoglycemic effect of *Ageratum conyzoides* may be partly due to flavonoids, tannins, terpenoids and/or coumarins present in the plant. One or some of the other miscellaneous compounds of the plant may have also contributed to the hypoglycemic effect of the aqueous leaves extract of *Ageratum conyzoides*.

In conclusion, the results of this study have shown that the leaves of *Ageratum conyzoides* possess blood glucose lowering effect in normoglycemic and in streptozotocin-induced hyperglycemic rats, a phenomenon that may validate the use of this plant in folk medicine against diabetes. Thus the folkloric use of this plant may be validated by this study. The leaves of *A. conyzoides* have a promising value for the development of potent phytomedicine for diabetes. More investigations are needed, some of them are initiated in our laboratory, in order to isolate the active(s) principle (s) of this plant and to clarify its mechanism of action.

Acknowledgments

We are very grateful to the "Agence Universitaire de la Francophonie" who financially supported this work (Grant N°P6-411/3089/0368/BAC 2006) in collaboration between the Institute of Agronomy and Veterinary Medicine of Morocco and the University of Yaoundé 1, Cameroon.

Table 1. Effect of aqueous leaves extract of *Ageratum conyzoides* (A.C) on blood glucose levels after oral administration in normal fasted rats

Group (n=5)	Dose	Blood glucose levels at different hours after the treatment(mg/dl)				
		0h	1.5 h	3h	5h	8h
Control (distilled water)	10ml/kg	89.80±6.69	89±7.31 (-0.89%)	80±6.78 (-10.91%)	82±6.80 (-8.7%)	79±5.87 (-12.03%)
A. C	100mg/kg	90.8±16.95	75±11.66 (-17.4%)	66.38±8.38 (-26.9%)	43.74±7.82* (-51.83%)	53.66±5.36 (-40.90%)
A. C	200mg/kg	87.9±5.41	80.65±5.54 (-8.25%)	72.26±3.96* (-17.79%)	66.15±9.13* (-24.74%)	58.90±5.20** (-33%)
A. C	300mg/kg	85±9.86	57.45±15.98 (-32.41%)	73.50±9.73 (-13.53%)	66.77±7.09 (-21.45%)	54.10±2.30* (-36.35%)
Glibenclamide	10mg/kg	91.60±11.61	68±7.17* (-25.76%)	46.2±9.78* (-49.56%)	38.6±8.50** (-57.86%)	33.60±5.86*** (-63.32%)

The values in brackets represent the percentage reduction in blood glucose vs. initial value.

Values are means blood glucose levels ± S.E.M. of five animals.

*p<0.01, **p<0.001, ***p<0.0001 compared with the initial level of blood glucose of the rats (0h) in the respective group.

Table 2. Effect of aqueous leaves extract of *Ageratum conyzoides* (A.C) on blood glucose levels after oral administration in diabetics rats.

Group (n=5)	Dose	Blood glucose levels at different hours after the treatment(mg/dl)				
		0h	1.5 h	3h	5h	8h
Control (distilled water)	10ml/kg	372±14.53	342.02±24.11 (-8.06%)	361±8.57 (-2.96%)	362.40±9.86 (-2.58%)	363.44±20.46 (-2.30%)
A. C	100mg/kg	365.7±8.30	350.05±6.24* (-4.28%)	342.70±10.47 (-6.29%)	300.9±67.93 (-17.72%)	292.08±15.43* (-20.13%)
A. C	200mg/kg	370±13.55	348.73±11.19** (-5.75%)	314.28±22.80** (-15.06%)	312.43±34.93* (-15.56%)	296±34.64** (-20%)
A. C	300mg/kg	380±40.60	314.11±54.15* (-17.34%)	310.23±24* (-18.36%)	314.30±17.39* (-17.29%)	276.83±22.19** (-27.15%)
Glibenclamide	10mg/kg	369.2±30	342.84±34.38* (-7.14%)	369.2±20.06 (0%)	357.13±35.32 (-3.27%)	312.05±29.44** (-15.48%)

The values in brackets represent the percentage reduction in blood glucose vs. initial value.

Values are means blood glucose levels ± S.E.M. of five animals.

*p<0.1, **p<0.01 compared with the initial level of blood glucose of the rats (0h) in the respective group.

Table 3: Effect of aqueous leaves extract of *Ageratum conyzoides* (A.C) on blood glucose levels after oral loading glucose (3g/kg) in normal fasted rats on oral glucose tolerance test.

Group (n=5)	Dose	Blood glucose levels at different time after the treatment (mg/dl)					
		0	30min	60min	90min	120min	150min
Control (distilled water)	10ml/kg	90±9.44	88.39±8.37 (-1.79%)	170.1±19.77* (89%)	157.8±19.97* (75.33%)	133.66±12.76* (48.51%)	110.7±8.62 (23%)
A. C	100mg/kg	90±15.76	86.21±6.80 (-4.21%)	176.84±21.40 (96.49%)	136.11±9.83 (51.23%)	124.10±13.79 (37.89%)	116.52±5.12 (29.47%)
A. C	200mg/kg	88.4±5.60	88.2±2.28 (-0.23%)	139.38±21.18 (57.67%)	123±9.53* (39.14%)	112.06±8.44 (26.76%)	96.9±14.77 (9.62%)
A. C	300mg/kg	91.8±9.58	109.75±6.46 (19.55%)	189.36±9.1* (106.27%)	167±7.13* (81.92%)	178.85±6.39* (94.83%)	146.33±6.54* (59.40%)
Glibenclamide	10mg/kg	90.1±7.1	67.58±17.7* (-25%)	94.38±12* (4.75%)	85.32±21* (-5.31%)	72.98±23* (-19%)	71.81±20.1* (-20.3%)

The values in brackets represent the percentage reduction in blood glucose vs. initial value.

Values are means blood glucose levels ± S.E.M. of five animals. p<0.005 compared with the initial value (0h).

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