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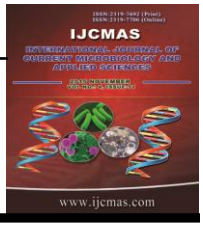

Original Research Article

Antidiabetic, Hypolipidemic and Antiathrogenic Properties of Leaf Extracts of *Ageratum conyzoides* in Streptozotocin-Induced diabetic rats

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Keywords

Ageratum conyzoides, Antilipidemic, Ethylacetate and water, Serum, metformin

A B S T R A C T

Parts of *Ageratum conyzoides* are widely used by traditional medicine practitioners in Eastern Nigeria for management/treatment many diseases such as diabetes, cardiovascular disorders, skin infections, etc. Hence, the present research investigated antidiabetic, antilipidemic and antianthrogenic effects of leaf extracts of *Ageratum conyzoides* in streptozotocin-induced diabetic rats. Extractions were performed with distilled water and ethylacetate. A total of fifty-five (55) adult male albino rats, used in the study, were placed in ten (10) test (A-J) and one control (K) groups of five rats in each group. Diabetes was induced in groups A-J with a single dose of 150mg/kg body weight of streptozotocin (STZ) intraperitoneally. Subsequently, groups A, B, C and D were given oral administration of 200, 400, 600 and 800mg/kg body weight of the aqueous extract, while E- H received the same corresponding doses of ethylacetate extract. Groups I and J were treated with 10 mg/kg of body weight of metformin (an antidiabetic drug) and normal saline respectively. The treatments lasted fourteen (14) consecutive days.Blood glucose, lipid profile and atherogenic index (AI) were measured before and after induction of diabetes, and after treatment. The glucose, total cholesterol, triglycerides and low density lipoprotein (LDL) concentrations and AI of all the groups treated with streptozotocin were significantly higher ($P<0.05$), while high density lipoprotein (HDL) was significantly lower ($P<0.05$) than in the untreated one. After treatment with the extract and the drug (metformin), there was a significant reduction ($P<0.05$) in glucose, total cholesterol, triglycerides and LDL concentrations and AI, whereas HDL increased significantly ($P<0.05$) in the treated groups relative to the untreated. The effect was linearly dose-dependent. The difference between the group given 800mg/kg of aqueous extract and the one treated with metformin was not significant ($P>0.05$). The effect of the aqueous extracts was significantly higher ($P<0.05$) from that of ethylacetate extract. These findings indicate leaf extracts of *Ageratum conyzoides*possess antidiabetic, antilipidemic and antianthrogenic potentials which may be responsible for the use of the leaves in management/treatment of diabetes and cardiovascular disorders.

Introduction

Medicinal plants continue to provide valuable therapeutic agents, both in modern and traditional medicines. As powders, extracts, decoctions, or infusions, plants are used by traditional medicine practitioners in many parts of the world, especially in rural communities, for the control, management, and/or treatment of a variety of human and animal ailments. The current worldwide trends towards utilization of plant-derived natural remedies have, therefore, created a dire need for accurate and up-to-date information on the properties, uses, efficacy, safety, and quality of medicinal plant products [1]. The plant kingdom has become a target for the search by multinational drug and biologically active lead compounds [2].

All plants produce chemical compounds as part of their normal metabolic activities. These can be divided into primary metabolites, such as fat and sugar found in all plants, and secondary metabolites such as alkaloids and tannins, found in the smaller range of plants, some only in a particular genus or species [3]. The secondary metabolites are responsible for most pharmacological activities of plants [4].

Diabetes mellitus is a chronic metabolic disorder, mainly characterized by disruption in carbohydrates, protein, and fat metabolism caused by the complete or relative insufficiency of insulin action [5]. When the amount of blood glucose increases, for example, after a meal, it triggers the release of the hormone insulin from the pancreas. Insulin stimulates muscle and fat cells to remove glucose from the blood and stimulates the liver to metabolize glucose, causing the blood sugar level to decreases to the normal levels, as glucose is not metabolized; high amount of glucose is circulating in the blood (hyperglycemia). To keep the normal level of glucose in blood, the kidney removes the extra sugar from the blood and excretes it in the urine. [6].

Diabetes and its complications remain a major public health problem worldwide [7]. It is even more disturbing to note that regions where the disease was previously uncommon have become endemic in diabetes, particularly type 2 diabetes [8]. Over the past few decades, the understanding of the pathogenesis of diabetes has improved significantly andthis has increased treatment options. The drugs currently used to treat diabetes mostly target the lowering of blood glucose concentrations to normal levels [9]. However, the side effects of these various forms of treatments, as well as, the seemingly unabated increase in the incidence of diabetes and its complications, has prompted research into alternative means of treating this disease. There is growing evidence that the different aspects of diabetes pathogenesis must be targeted to offer a holistic approach to its treatment [10]. Long term complications arising from diabetes are major causes of diabetes morbidity and mortality. The alteration of the serum lipid profile by diabetes mellitus is a particularly bothersome effect of the disease. This leads to increased risk of cardiovascular diseases in diabetics [11]. The reversal of diabetes dyslipidemia is thus a major strategy in diabetes treatment. The use of plant based extracts to treat diabetes in traditional societies is well documented. Many researchers believe that medicinal plant preparations, which contain different phytochemicals, may combat diabetes at multiple points producing faster and perhaps better resolution of diabetes symptoms [10].

*Ageratum conyzoides*belongs to the family of Asteraceae. It is an erect, annual, branched, slender, hairy and aromatic plant

which grows to approximately one meter in height. It is a native of central America, Southeast Asia, South China, India, West Africa, etc [12][13]. It has been known since ancient times for its curative properties and has been utilized for the treatment of various ailments, such as burns and wounds, diabetes, headaches, pneumonia, inflammation, asthma, spasmodic and haemostatic diseases, stomach ailments, gynecological diseases, leprosy and other skin diseases [14].

The medicinal applications of various parts of *Ageratum conyzoides* are yet to be fully investigated in this part of the world. Hence, the present research studied investigated the antidiabetic, antilipidemic and antianthrogenic effects of leaf extracts of *Ageratum conyzoides.*

Materials and Methods

Collection and preparation of plant materials: Fresh leaves of *Ageratum conyzoides* were collected from Okposi in Ohaozara L.G.A of Ebonyi state. They were identified and authenticated by Prof. S.C Onyekwelu, a botanist in Applied Biology Department of Ebonyi State University, Abakaliki. They were air-dried and ground into a powder which was stored in an air-tight contain.

Preparation of extract:

The methods of extraction used by Agbafor [15]were adopted, utilizing distilled water and ethylacetate as solvents. The extract was concentrated using rotorevaporator to get gel-like extracts.

Experimental animals and handling:

Adult male albino rats, weighing 180 –215g, were selected for experimental study.

Ethical approval for use of animals in research was given by Ebonyi State University Research and Ethics Committee.

Induction of diabetes

Hyperglycemia was induced by injecting a single dose of 150mg/kg body weight of STZ intraperitoneally. After 48 hours, the animals were tested for glucosuria using Diastex strips [16]. Twelve days after the STZ injection, rats with fasting blood glucose levels greater than 200 mg/dl were considered diabetic.

Animal grouping and treatment

A total 50 diabetic rats were randomly distributed into 10 groups (A – J) of 5 animals in each, while 5 rats which were not given STZ were kept in group K, the control. Groups A, B, C and D were orally treated with 200, 400, 600 and 800mg/kg body weight of aqueous extract, while E, F, G and H were administered 200, 400, 600 and 800mg/kg body weight of ethylacetate extract. Groups J and K received 10mg/kg body weight of metformin and 5ml/kg body weight of normal saline. The treatment lasted for fourteen consecutive days.

Blood glucose and lipid profile were measured before induction of diabetes, after induction of diabetes and after treatment. Serum lipid profile (total cholesterol, triglycerides, high density lipoproteins and low density lipoproteins) was determined according tothe methods contained in their kits (Randox kits, United Kingdom).AI was calculated as:

Atherogenic Index (AI) = LDL-cholesterol/HDL-cholesterol [17].

Statistical analysis

Data generated were expressed as mean ±

SD. Statistical significance of difference was determined using the program SPSS 12 (SPSS, USA) by performing one-way ANOVA with post-hoc comparisons between the control group and each of the treated groups by Ducan's multiple comparison test. A P-value less than 0.05 was considered statistically significant.

Results and Discussion

The glucose concentrations of the animals before and after induction of diabetes are presented in table 1. Administration of STZ produced a significant increase ($P<0.05$) in glucose concentration of all the treated animals, that of the control did not change significantly ($P>0.05$). Streptozotocin is widely used to induce experimental diabetes in animals. The mechanism of action of this diabetogenic agent in B cells of the pancreas is mediated by reactive oxygen species. Streptozotocin enters the B cell *via* a glucose transporter (GLUT2) and causes alkylation of DNA. DNA damageinduces activation of poly ADP-ribosylation, a process that is more important for the diabetogenicity of streptozotocinthan DNA damage itself. Poly ADP ribosylation leads to depletion of cellular NAD+ and ATP. Enhanced ATP dephosphorylation after streptozotocin treatment supplies a substrate for xanthine oxidase resulting in the formation of superoxide radicals. Consequently, hydrogen peroxide and hydroxyl radicals are also generated. Furthermore, streptozotocin liberates toxic amounts of nitric oxide that inhibits aconitase activity and participates in DNA damage. As a result of the streptozotocin action, B cells undergo the destruction by necrosis[18].

Table.1 Blood glucose levels (mg/dl) of the rats before and after induction of diabetes and after treatment with extracts and standard drug

Group	Before induction	After induction	After treatment
A	104.46 ± 5.07^{a}	259.44 ± 6.02^{b}	130.15 ± 3.45^{a}
B	100.65 ± 4.22^{a}	254.78 ± 6.53^{b}	124.20 ± 2.55^{a}
C	102.40 ± 3.33^{a}	269.46 ± 4.87^{b}	114.12 ± 2.09^{a}
D	108.44 ± 4.12^{a}	270.22 ± 5.56^{b}	100.60 ± 3.04^{a}
E	109.67 ± 3.17^{a}	258.65 ± 6.07^{b}	174.22 ± 3.57^{c}
F	104.55 ± 3.45^{a}	269.70 ± 4.45^{b}	157.63 ± 2.97^{c}
G	114.88 ± 5.22^{a}	270.36 ± 5.50^{b}	144.56 ± 4.20^{c}
H	100.91 ± 3.22^{a}	262. 16 ± 4.11b	118.40 ± 3.32^{a}
I	121.09 ± 2.07^{a}	280.40 ± 6.74^{b}	102.05 ± 1.79^{a}
J	110.46 ± 4.11^{a}	273.88 ± 4.60^{b}	310.50 ± 3.06^{d}
K	115.76 ± 3.56^{a}	119.75 ± 5.67^{a}	116.08 ± 3.30^{a}

Values are mean ± SD; N = 5. Values with different superscripts vary significantly ($P<0.05$).

Key: Group A = 200mg/kg water extract; Group B = 400mg/kg water extract; Group C = 600mg/kg water extract; Group D = 800mg/kg water extract; Group E = 200mg/kg ethylacetate extract; Group F = 400mg/kg ethylacetate extract; Group G = 600mg/kg ethylacetate extract; Group H = 800mg/kg ethylacetate extract; Group I = 10mg/kg metformin; Group J = negative control; Group K = normal control.

Table.2 Serum total cholesterol concentrations (mg/dl) of the rats before and after induction of diabetes and after treatment with extracts and standard drug

Group	Before induction	After induction	After treatment
A	194.88 ± 4.06[a]	321.55 ± 3.02[b]	230.22 ± 3.40[a]
B	206.22 ± 3.25[a]	328.34 ± 3.15[b]	226.56 ± 5.33[a]
C	188.50 ± 4.19[a]	318.76 ± 4.44[b]	198.25 ± 4.77[a]
D	180.45 ± 3.60[a]	310.75 ± 2.18[b]	169.80 ± 2.90[a]
E	200.55 ± 2.60[a]	328.36 ± 3.04[b]	256.45 ± 3.67[c]
F	205.11 ± 5.10[a]	331.32 ± 4.11[b]	243.08 ± 3.63[c]
G	190.44 ± 3.26[a]	314.47 ± 2.88[b]	212.75 ± 2.84[a]
H	195.76 ± 2.53[a]	315.17 ± 2.68[b]	207.44 ± 3.3 5[a]
I	210.21 ± 3.62[a]	338.33 ± 4.78[b]	181.22 ± 4.04[a]
J	187.82 ± 4.50[a]	316.55 ± 3.25[b]	324.15 ± 3.60[d]
K	202.15 ± 2.75[a]	211.55 ± 3.12[a]	204.50 ± 4.12[a]

Values are mean ± SD; N = 5. Values with different superscripts vary significantly (P<0.05).

Key: Group A = 200mg/kg water extract; Group B = 400mg/kg water extract; Group C = 600mg/kg water extract; Group D = 800mg/kg water extract; Group E = 200mg/kg ethylacetate extract; Group F = 400mg/kg ethylacetate extract; Group G = 600mg/kg ethylacetate extract; Group H = 800mg/kg ethylacetate extract; Group I = 10mg/kg metformin; Group J = negative control; Group K = normal control.

Table.3 Serum triglycerides concentrations (mg/dl) of the rats before and after induction of diabetes and after treatment with extracts and standard drug

Group	Before induction	After induction	After treatment
A	129.09 ± 1.45[a]	261.56 ± 3 .12[b]	194.34 ± 2.50[c]
B	131.70 ± 3.43[a]	287.04 ± 3.02[b]	209.70 ± 4.01[c]
C	126.78 ± 2.24[a]	260.12 ± 3.65[b]	146.35 ± 2.33[a]
D	133.55 ± 2.22[a]	288.50 ± 4.55[b]	124.28 ± 3.30[a]
E	124.05 ± 3.30[a]	255.22 ± 2.65[b]	206.88 ± 3.80[c]
F	125.44 ± 3.05[a]	259.20 ± 3.07[b]	192.62 ± 2.75[c]
G	122.75 ±1.88[a]	254.40 ± 4.17[b]	176.08 ± 3.03[c]
H	130.90 ± 2.65[a]	278.67 ± 2.78[b]	183.19 ± 2.62[c]
I	137.59 ± 2.45[a]	302.11 ± 2.48[b]	133.56 ± 2.60[a]
J	128.41 ± 3.06[a]	263.61 ± 1.86[b]	283.34 ± 3.71[b]
K	122.35 ± 2.65[a]	126.55 ± 2.75[a]	123.73 ± 4.05[a]

Values are mean ± SD; N = 5. Values with different superscripts vary significantly (P<0.05).

Key: Group A = 200mg/kg water extract; Group B = 400mg/kg water extract; Group C = 600mg/kg water extract; Group D = 800mg/kg water extract; Group E = 200mg/kg ethylacetate extract; Group F = 400mg/kg ethylacetate extract; Group G = 600mg/kg ethylacetate extract; Group H = 800mg/kg ethylacetate extract; Group I = 10mg/kg metformin; Group J = negative control; Group K = normal control.

Table.4 Serum HDL concentrations (mg/dl) of the rats before and after induction of diabetes and after treatment with extracts and standard drug

Group	Before induction	After induction	After treatment
A	45.64 ± 2.05[a]	21.22 ± 1.56[b]	29.65 ± 2.12[b]
B	52.33 ± 1.65[a]	23.62 ± 1.90[b]	33.71 ± 2.08[b]
C	44.72 ± 1.68[a]	17.83 ± 2.04[b]	38.69±1.55[a]
D	48.40 ± 3.04[a]	20.50 ± 1.59[b]	52.44 ± 2.33[a]
E	49.60 ± 2.15[a]	18.88 ± 2.08[b]	24.33 ± 2.16[b]
F	41.98 ± 2.01[a]	17.95 ± 1.61[b]	28.29 ± 1.70[b]
G	49.54 ± 1.79[a]	22.78 ± 3.13[b]	36.46 ± 1.58[c]
H	52.10 ± 2.10[a]	27.05 ± 2.12[b]	45.74 ± 3.33[a]
I	53.02 ± 1.49[a]	25.60 ± 1.85[b]	59.60 ± 2.03[a]
J	56.20 ± 3.12[a]	29.34 ± 2.48[b]	23.72 ± 1.67[b]
K	49.51 ± 2.55[a]	41.45 ± 1.76[a]	47.44 ± 2.16[a]

Values are mean ± SD; N = 5. Values with different superscripts vary significantly (P<0.05).

Key: Group A = 200mg/kg water extract; Group B = 400mg/kg water extract; Group C = 600mg/kg water extract; Group D = 800mg/kg water extract; Group E = 200mg/kg ethylacetate extract; Group F = 400mg/kg ethylacetate extract; Group G = 600mg/kg ethylacetate extract; Group H = 800mg/kg ethylacetate extract; Group I = 10mg/kg metformin; Group J = negative control; Group K = normal control.

Table.5 Serum LDL concentrations (mg/dl) of the rats before and after induction of diabetes and after treatment with extracts and standard drug

Group	Before induction	After induction	After treatment
A	61.55 ± 3.61[a]	133.04 ± 2.19[b]	87.40 ± 3.50[a]
B	59.60 ± 2.11[a]	128.25 ± 2.40[b]	79.62 ± 4.22[a]
C	57.41 ± 3.67[a]	130.65 ± 3.44[b]	78.72 ± 4.03[a]
D	63.09 ± 1.79[a]	151.59 ± 2.55[b]	59.27 ± 2.75[a]
E	60.10 ± 3.55[a]	143.16 ± 3.27[b]	112.49 ± 3.38[b]
F	61.46 ± 3.06[a]	139.54 ± 3.58[b]	108.12 ± 3.08[b]
G	59.23 ± 2.33[a]	131.67 ± 1.85[b]	80.60 ± 2.52[a]
H	64.62 ± 2.56[a]	149.01± 2.41[b]	88.54 ± 2.65[a]
I	60.71± 2.07[a]	142.33 ± 2.45[b]	53.68 ± 2.12[a]
J	58.96 ± 1.75[a]	135.16 ± 3.70[b]	163.06 ± 4.51[b]
K	57.82 ± 3.44[a]	63.20 ± 2.05[a]	59.18 ± 2.54[a]

Values are mean ± SD; N = 5. Values with different superscripts vary significantly (P<0.05).

Key: Group A = 200mg/kg water extract; Group B = 400mg/kg water extract; Group C = 600mg/kg water extract; Group D = 800mg/kg water extract; Group E = 200mg/kg ethylacetate extract; Group F = 400mg/kg ethylacetate extract; Group G = 600mg/kg ethylacetate extract; Group H = 800mg/kg ethylacetate extract; Group I = 10mg/kg metformin; Group J = negative control; Group K = normal control.

Table.6 Athrogenic index of the rats before and after induction of diabetes and after treatment with extracts and standard drug

Group	Before induction	After induction	After treatment
A	1.25 ± 0.10[a]	6.67 ± 0.40[b]	2.45 ± 0.50[c]
B	1.10 ± 0.04[a]	5.11 ± 0.32[b]	2.36 ± 0.15[c]
C	1.26 ± 0.02[a]	7.03 ± 0.30[b]	2.23 ± 0.20[c]
D	1.21 ± 0.09[a]	7.04 ± 0.35[b]	1.18 ± 0.05[a]
E	1.26 ± 0.05[a]	7.70 ± 0.22[b]	4.11 ± 0.51[b]
F	1.35 ± 0.11[a]	7.12 ± 0.65[b]	3.20 ± 0.62[c]
G	1.23 ± 0.04[a]	5.44 ± 0.34[b]	2.11 ± 0.10[c]
H	1.36 ± 0.12[a]	5.11 ± 0.40[b]	1.83 ± 0.11[c]
I	1.24 ± 0.09[a]	5.22 ± 0.34[b]	0.85 ± 0.05[a]
J	1.18 ± 0.13[a]	4.83 ± 0.22[b]	6.67 ± 0.20[b]
K	1.07 ± 0.10[a]	1.41 ± 0.11[a]	1.12 ± 0.13[a]

Values are mean ± SD; N = 5. Values with different superscripts vary significantly (P<0.05).
Key: Group A = 200mg/kg water extract; Group B = 400mg/kg water extract; Group C = 600mg/kg water extract; Group D = 800mg/kg water extract;Group E = 200mg/kg ethylacetate extract; Group F = 400mg/kg ethylacetate extract; Group G = 600mg/kg ethylacetate extract; Group H = 800mg/kg ethylacetate extract; Group I = 10mg/kg metformin; Group J = negative control; Group K = normal control.

Treatment of the animals with the leaf extracts resulted to a dose-dependent significant reduction (P<0.05) in the elevated blood glucose concentration. This suggests that the extracts possess antidiabetic potential which may be attributed to the chemical constituents of the extracts. Although the actual chemical compound responsible for this antidiabetic property is not known at this stage of our research, some phytochemicals have been reported to exhibit the ability lower blood sugar. Antihyperglycemic activity of the plants is mainly due to their ability to restore the function of pancreatic tissues by causing an increase in insulin output or inhibit the intestinal absorption of glucose or to the facilitation of metabolites in insulin dependent processes. More than 400 plant species having hypoglycemic activity have been available in literature, however, searching for new antidiabetic drugs from natural plants is still attractive because they contain substances which demonstrate alternative and safe effects on diabetes mellitus. Most of plants contain glycosides, alkaloids, terpenoids, flavonoids, carotenoids, *etc.*, that are frequently implicated as having antidiabetic effect [19]. According to Patel et al [20], the antidiabetic activity of medicinal plants is attributed to the presence of polyphenols, flavonoids, terpenoids, coumarins and other constituents which show reduction in blood glucose levels.Alkaloids, tannins, saponins, cardiac glycosides, anthraquinones, terpenoids and flavonoids have been reported in leaves of *Ageratum conyzoides*[21]. Flavonoids are also known to regenerate the damaged *β*-cells in diabetic mice [22][23].

The lipid profile of the rats before and after induction of diabetes and after treatment with the extracts is shown in tables 2, 3, 4 and 5. Serum total cholesterol, triglycerides and low density lipoproteins concentrations were elevated significantly (P<0.05) in all the groups treated with STZ, while their values did not alter significantly (P>0.05) in the control. On the other hand, high density lipoproteins decreased significantly (P<0.05) in the test groups, and did not vary

significantly (P>0.05) in the control. After treatment, the elevated cholesterol, triglycerides and low density lipoproteins concentrations were significantly lowered (P<0.05), while the reduced high density lipoproteins increased significantly (P<0.05). These effects show that the extracts have antihyperlipidemic activity which was also found to be dose-dependent. The atherogenic index obtained in the rats showed a significant increase (P<0.05) upon treatment with STZ, and a dose-dependent significant decrease (P<0.05) when they were treated with the extracts. Several components of plant extracts, such as fibre [24], saponins [25] and flavonoids [26], have been reported to possess antihyperlipidaemic effects. These factors significantly reduced the atherogenic index of the treated diabetic rats, thus potentially protecting them from cardiovascular diseases.

The antihyperglycemic, antihyperlipidemic and antiatherogenic properties of leaf extracts of *Ageratum conyzoides*recorded with distilled water extract were significantly higher (P<0.05) than those of ethylacetate extract. Further, the difference between 800mg/kg body weight of distilled water extract and 10mg/kg body weight of metformin, a standard antidiabetic drug, was not significant (P>0.05).

In conclusion, Distilled water and ethylacetate leaf extracts of *Ageratum conyzoides* possess antidiabetic, antilipidemic and antiatherogenic activities. These properties may be due to some of the chemical constituents of the extracts. We are currently on researches to identify the chemical compounds and their possible mechanism of action.

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