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Anti-diabetic and some haematological effects of aqueous and ethanol leaf extract of *Eriosema psoraleoides* in alloxan-induced diabetic Wistar rats

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This study investigates the anti-diabetic and some hematological effects of aqueous and ethanol leaf extracts of *Eriosema psoraleoides* in alloxan-induced diabetic Wistar rats. Forty-eight albino mice were used for the lethal dose (LD_{50}) study, while twenty-eight Wistar rats were used for the diabetic and haematological study. The result of the phytochemical analysis shows some important phytochemicals that could confer some health benefits. The extracts had lethal doses (LD_{50}) of 4000 and 5000 mg/kg^{-1} body weight, which indicate that the extract was safe to a greater extent. The baseline blood glucose concentration presents non-diabetic glucose level 86.25±8.26 mg dL^{-1}. Diabetes was induced with alloxan monohydrate. A significant decrease ($p<0.05$) in blood glucose levels in the test animals were observed when compared with positive control. The extracts had a significant effect on blood glucose and haematological levels of the treated rats closer to that of the standard drug (glibenclamide) with significant ($p<0.05$) increase in red blood cell (RBC) and significant ($p<0.05$) decrease in neutrophils and lymphocytes in all test groups relative to positive control. However, white blood cell (WBC) showed significant decrease ($p<0.05$) in groups which received aqueous extracts when compared with positive control. The results of the study showed that the extracts of *E. psoraleoides* leaves exhibited significant anti-diabetic activities against alloxan-induced diabetes Wistar rats. It suggests the extracts possess bioactive compounds that when properly harnessed could help in improving the health state of diabetic patients.

Key words: *Eriosema psoraleoides*, anti-diabetic, alloxan induced diabetic rats, haematological parameters.

INTRODUCTION

Diabetes mellitus has become a major public health concern, especially in the developing countries. It is characterized by absolute or relative deficiencies in insulin secretion, action or both associated with chronic

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hyperglycemia and disturbances in carbohydrate, lipid, and protein metabolism (Rahmati et al., 2013). It is characterized by chronic high blood glucose that could lead to morbidity and mortality (Mohammed et al., 2007). There is an alarming rate of diabetes cases worldwide. It is predicated that about 366 million people are likely to be diabetic by the year 2030 (Wild et al., 2004). This is because none of the antidiabetic drugs could give a long term glycaemic control without causing any adverse side effects (Singh et al., 2007). Meanwhile, medicinal plants that are effective in controlling plasma glucose level with minimal side effects are commonly used in under developed countries as alternative therapy. In Africa, hundreds of plants are used traditionally for the management and/or control of diabetes mellitus. Unfortunately, only a few of such medicinal plants have been scientifically validated (Tanko et al., 2007). One of the plants commonly used in *Eriosema psoraleoides* ((Lam.) G. Don) is a tropical plant belonging to the family Leguminosae. It is an erect herb or sub-woody shrub that can grow 1 to 2.5 m high from a perennial woody root-stock. It is widely distributed throughout Tropical Africa and South Africa (Hyde and Wursten, 2010). In Nigeria, the locals of Nsukka call it *ENYI AGBAOKWU AGBUGBA*, in Senegal it is *MANDING-BAMARA* nomko blé (JB) and in Sierra Leone they are *KORANKO* kouŜe (NWT) and yaŋgune (NWT) *LOKO.* The fruits, leaves and roots are mostly used traditionally for the treatment of various diseases and infections such as cutaneous and subcutaneous parasitic infections, diabetes, diarrhoea and pulmonary troubles. It is also used as diuretics, pain-killers, emetics, sedatives abortifacients, antiabortifacients, ecbolics, vermifuges, genital stimulants/degressants, etc. The aim of this study was to determine lethal dose concentration (LD_{50}), the effects of aqueous and ethanol leaf extracts of *E. psoraleoides* on the blood glucose level and some haematological parameters of alloxan-induced diabetic rats.

MATERIALS AND METHODS

Animals

A total of forty-eight albino mice of the male sex weighing 22 to 28 g were used for the acute toxicity study (LD_{50}). Twenty-eight adult Wistar rats weighing 180 to 220 g of the male sex were used for the anti-diabetes study. All animals were obtained from the Faculty of Veterinary Medicine, University of Nigeria, Nsukka, Enugu State, Nigeria. They were acclimatized for seven days in the Department of Biochemistry Animal house before the experiments and maintained *ad libitum* on water and growers mash (vital feeds).

Plant

The plant materials (leaves) were collected from Eha-Ndiagu in Nsukka Local Government Area of Enugu State, Nigeria. Botanical identification and authentication were performed by Mr. Ozioko of the International Center for Ethno-medicine and Drug Development Nsukka, Enugu State, Nigeria, where a herbarium sample with voucher specimen number Intercedd/16170 was prepared and deposited.

Chemical and drugs

All chemicals and reagent used in this study were of analytical grade. They included Alloxan monohydrate (Sigma-Aldrich, St. Louis, USA), Glibenclamide (Aventis Pharma Ltd., Verna, Goa), Tween 80 (S.D. Fine-Chem limited, Mumbai), Accu-chek® Active Glucometer, Roche Diagnostic Corporation, Germany, and blood gluco-strips (Roche Diagnostic Pvt. Ltd., Mumbai, India). Standard commercial test kits were also used for the study.

Extraction procedure

The aqueous extract of *E. psoraleoides* leaves was obtained by macerating 200 g of the powdered leaves in 800 ml water for 24 h with intermittent shaking. Following filtration through Whatman No. 1 filter paper, the filtrate was freeze-dried to obtain solid residue. The yield was recorded. The extract was reconstituted in distilled water in appropriate concentration before administration.

The ethanol extract of *E. psoraleoides* leaves was prepared by soaking 200 g of the powdered leaves in 800 ml of 95% ethanol for two days. The crude extract was evaporated to dryness *in vacuo* on a rotary evaporator. The yield was recorded and used in this study.

Phytochemical analyses

Preliminary phytochemical analyses of the plant extracts were performed for the presence of secondary metabolites, using the methods of Harborne (1984) and Evans (1996).

Acute toxicity (LD_{50}) studies

The LD_{50} determination for each of the extracts was conducted separately using modified method acute toxicity testing (Lorke, 1983). For each of the extracts, the evaluation was done in two phases. In phase one, three groups of three mice each were treated with 10, 100 and 1000 mg extract/kg body weight orally, respectively. The control groups received normal saline and 3% Tween 80. The rats were observed for clinical signs and symptoms of toxicity within 24 h and death within 72 h. Based on the results of phase one for the aqueous extract, 15 fresh mice with three per group were each treated with 1600, 2900 and 5000 mg extract/kg orally, respectively. The control groups received normal saline and 3% Tween 80. Clinical signs and symptoms of toxic effects and mortality were then observed within 24 h and death within 72 h. The LD_{50} were then calculated as the geometric mean of the consecutive doses for which 0 and 100% survival rates were recorded in the second phase.

Induction of experimental diabetes mellitus

The animals were fasted for 16 to 18 h with free access to water prior to the induction of diabetes. Induction of diabetes was carried out by single intraperitoneal injection of alloxan monohydrate (Sigma St Louis, M.O., USA) dissolved in 0.9% v/v normal saline solution at a dose of 130 mg/kg body weight. The diabetes was assessed in alloxan-induced rats by determining the blood glucose concentration 72 h after injection of alloxan monohydrate. The rats with blood glucose level above 200 mg/dl were then selected for the study.

Experimental design

A total of twenty-eight rats were used and were divided into seven groups:

Group 1: Control (normal rats not treated with extract);
Group 2: Positive control (alloxan-induced diabetic rats not treated with extract);
Group 3: Alloxan-induced diabetic rats given 200 mg/kg body weight aqueous leaf extract of *E. psoraleoides*;
Group 4: Alloxan-induced diabetic rats given 400 mg/kg body weight aqueous leaf extract of *E. psoraleoides*;
Group 5: Alloxan-induced diabetic rats given 200 mg/kg body weight ethanol leaf extract of *E. psoraleoides*;
Group 6: Alloxan-induced diabetic rats given 400mg/kg body weight ethanol leaf extract of *E. psoraleoides*;
Group 7: Alloxan-induced diabetic rats given 0.3 mg/kg body weight glibenclamide (standard control).

On day 7, the rats were anaesthetized at the time of sacrifice by being placed in sealed cotton wool soaked chloroform inhalation jar.

Determination of blood glucose concentration

Fasting blood glucose levels were determined by using the glucose oxidase method with Accu-check glucometer (Activie) and results were reported as mg/dl.

Determination of haematological parameters

After treatment with the two extracts, 2 ml blood was withdrawn from the media canthus of the eyes of the rats by occipital puncture using heparinized capillary tube and the haemoglobin concentration (Hb), red blood cells (RBC), white blood cell count (WBC) and its differential counts were determined using the method of Ochei and Kolhaktali (2008), Cheesbrough (2000) and Ramnik (2003).

Statistical analysis

All the data are expressed as mean ± standard error of mean (SEM). Statistical comparisons were performed by one way analysis of variance (ANOVA) with repeated measures and one-way ANOVA followed by Duncan's multiple range tests (Duncan et al., 1977). The results were considered statistically significant if the values are 0.05 higher or lower.

RESULTS

Acute toxicity studies

In the investigation of acute toxicity, there was no sign of toxicity and mortality in the first phase of the study in both the aqueous and ethanol leaf extracts of *E. psoraleoides* but recorded the death in the second phase in the group that received 5000 mg/kg body weight of ethanol extract. The LD_{50} was then calculated as the geometric mean of the consecutive doses for which 0 and 100% survival rates were recorded in the second phase. The LD_{50} of the AE and EE were thus:

$\sqrt{5000 \times 5000}$ = 5000 mg extract/kg body weight for AE

$\sqrt{2900 \times 500}$ = 3807.87 mg extract/kg body weight for EE

The acute toxicity (LD_{50}) value of ethanol leaf extract of *E. psoraleoides* leaves was calculated to be 3807.87 mg/kg body weight. The result of the oral acute toxicity (LD_{50}), studies showed aqueous and ethanol leaf extract of *E. psoraleoides* to be lethal at does 4000 and 5000 mg/kg body weight, an indication that the LD_{50} of the plant is less than 4000 mg/kg for EE and greater than 5000 mg/kg for AE. This result places *E. psoraleoides* at category 5 (>2000 to 5000 mg/kg) according to the Globally Harmonized System of Classification and Labeling of Chemicals (2013).

Effects of daily doses of aqueous and ethanol leaf extracts of *E. psoraleoides* on blood glucose concentration of alloxan-induced diabetic rats

Table 2 shows that the extracts and glibenclamide produced significant ($P<0.05$) decrease in the blood glucose concentration of alloxan-induced diabetic rats on day 7 when compared with group 2 (diabetic untreated). The mean differences are all greater than the LSD (52.60) for means separation of groups. The mean differences between group 1 and that of groups 3 and 4 do not exceed the LSD (52.60) on day 7. On day 6, only the extracts of *E. psoraleoides* produced significant ($P<0.05$) decrease in the blood glucose concentration of the alloxan-induced diabetic rats when compared with that of group 2 (diabetic untreated) which shows, they have close effect on the blood glucose concentration. The table also shows that in groups 3, 4, 5, 6 and 7, there is significant ($p<0.05$) decrease in the blood glucose concentration of the rats on days 6 and 7 when compared with that of days 4 and 5 as can be inferred from the LSD (21.41) for means separation of days.

Effects of daily doses of aqueous and ethanol leaf extracts of *E. psoraleoides* on haematological effect in alloxan-induced diabetic rats

Table 3 shows that the extracts of *E. psoraleoides* produced significant ($P<0.05$) change in red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, lymphocytes and monocytes; however, they do not have significant ($P>0.05$) effect on haemoglobin. Only 400 mg/kg body weight ethanol extract of *E. psoraleoides* significantly ($P>0.05$) increased RBC in the rats when compared with the rats in group 2. The WBC of the rats treated with aqueous extracts decreased significantly ($P < 0.05$) when compared with that of group 2 (untreated group). All the treated rats showed significant ($P<0.05$) decrease in neutrophils and lymphocytes when compared with diabetic untreated rats. Also, rats treated with the four different doses of the extracts showed significant decrease in the neutrophils when compared with diabetic

Table 1. Phytochemical composition of aqueous and ethanol leaves extracts of *Eriosema psoraleoides*.

Sample	Concentration of phytochemicals in ethanol (mg/100 g)	Aqueous phytochemical concentrate (mg/100 g)
Soluble carbohydrate	2.13 ± 0.03	1.86 ± 0.03
Tannin	3. 45 ± 0.02	2.37 ± 0.02
Flavonoid	6.67 ± 0.20	5.86 ± 0.11
Cyanogenic glycoside	0.02 ± 0.01	0.01 ± 0.03
steroid	2.56 ± 0.15	2.47 ± 0.02
Alkaloids	8.66 ± 0.25	5.64 ± 0.25
saponin	0.57 ± 0.003	0.51 ± 0.03
Reducing sugar	262.47 ± 0.020	130.46 ± 0.06

rats treated with glibenclamide. Monocytes were not found in groups 2, 5 and 7. The groups where monocytes were found are groups 3, 4 and 6 and its levels were significantly low when compared with that of group 1 (Normal rats).

DISCUSSION

The effect of the aqueous and ethanol leaf extracts on rats' blood glucose has implications on its use for nutritional and therapeutic purposes. The observation that the extracts did not significantly cause a change in the glucose concentration of the normoglycemic rats after twenty four hours implies that the extract is safe in a normal subject taking it either as food or for other medical proposes. Apart from its safety in normoglycemic individuals, the extract has a high therapeutic index as the acute toxicity test in mice gave an LD_{50} of about 5000 mg extract/kg body weight for AE and 3807.87 mg extract/kg body weight for EE. It has been reported that flavonoids and tannins and allied phytochemicals present in plant's extracts possesses anti diabetic properties. Their compositions are shown in Table 1. Phytochemical analyses carried out revealed the presence of some bioactive compounds such as flavonoids, alkaloids, glycosides, steroids, reducing sugars, resins, tannins and saponins. The acute toxicity (LD_{50}) was 5000 and 2900 mg/kg body weight for aqueous and ethanol extracts of *E. psoraleoides*, respectively. The dosage of 130 mg/kg body weight of alloxan used in this study caused moderate diabetes (Grover et al., 2000).

As summarized in Table 2, the rats given alloxan showed hyperglycaemia effect across groups on day 3. The result agrees with already existing literature that alloxan induces diabetes mellitus by selectively destroying the beta cells of the pancreas which are involved in the synthesis of storage and release of insulin, the peptide hormone regulating carbohydrate, protein and lipid metabolism (Adeneye and Agbaje, 2008), leading to marked increase in blood glucose concentration observed in the rats after administration and confirms the development of diabetes mellitus (Akindele et al., 2012). The administration of aqueous and ethanol leaf extracts of *E. psoraleoides* for three days after induction of diabetes with alloxan significantly reduced ($p < 0.05$) this, probably meaning that the antidiabetic factors present in both extracts needed to be activated with time. It could also be that, the extracts may be facilitating the uptake of glucose by the peripheral cells. Alloxan induces type 1 diabetes (destruction of the β-cells that produce insulin) in which case the extracts may have some chemical components that exert regenerative effects on β-cells, stimulate these cells to start producing insulin (pancreatotrophic action) or may have some insulin-like substances and induction of regenerative stimulus in diabetic state triggers pancreatic regenerative processes, thereby restoring functional activities of the pancreas (Adewole and Ojewole, 2007). This observation gives credence to the use of the herbal product as a hypoglycemic agent.

The assessment of haematological parameters could be used to reveal the deleterious effect of foreign compound including plant extracts on the blood constituents of animal. They are also used to determine possible alterations in the levels of biomolecules such as enzymes, metabolic products haematology and normal function (Magalhaes et al., 2008). The occurrence of anaemia in diabetes mellitus has been reported to be due to the increased non-enzymatic glycosylation of RBC membrane proteins (Oyedemi et al., 2011). Oxidation of these proteins and hyperglycaemia in diabetes mellitus causes an increase in the production of lipid peroxides that leads to haemolysis of RBC (Arun and Ramesh, 2002). Diabetes mellitus causes the development of hypochronic anaemia due to a fall in the iron content of the body resulting from oxidative stress associated with the condition (Colak et al., 2012).

In this study, the RBC membrane lipid peroxide levels in diabetic rats were not measured. However, the red blood cells parameters such as Hb were studied to investigate the beneficial effect of *E. psoraleoides* leaf extracts on the anaemic status of the diabetic rats shown in Table 3. The extracts of *E. psoraleoides* produced

Table 2. Effect of AE and EE of *E. psoraleoides* on blood glucose concentration in alloxan-induced diabetic rats.

Day	Group 1 (Normal control)	Group 2 (Diabetic untreated)	Group 3 (Diabetes treated with AE (200 mg/kg))	Group 4 (Diabetes treated with AE (400 mg/kg))	Group 5 (Diabetes treated with EE (200 mg/kg))	Group 6 (Diabetes treated with EE (400 mg/kg))	Group 7 (Diabetes treated with glibendanide (0.3 mg/kg))
Day 1	86.25±8.26	86.25±6.02	83.75±9.81	89.00±6.38	94.75±16.40	100.75±10.63	90.75±14.41
Day 2	89.50±6.03	102.00±9.70	115.50±5.07	123.75±9.65	114.50±15.15	117.00±12.08	131.00±7.10
Day 3	92.50±12.58	265.00±8.44	360.75±5.63	320.25±6.26	378.75±8.83	252.75±8.07	313.25±9.29
Day 4	90.25±5.38	358.00±7.29	417.75±9.73	429.50±7.81	401.75±6.51	352.25±9.44	403.00±13.95
Day 5	93.50±6.45	369.00±5.52	347.00±9.02	334.00±10.00	315.50±9.54	326.50±9.91	351.75±11.70
Day 6	92.75±6.85	359.68±7.31	246.25±8.43*	271.75±15.76*	265.25±9.71*	268.50±9.43*	348.77±12.72*
Day 7	92.75±11.62	358.49±5.12	121.75±13.57*	128.75±13.98*	181.50±9.33*	192.25±5.74*	193.00±6.98*

AE: Aqueous extract; EE: ethanol extract; *E. Psoraleoides*: *Eriosema psoraleoides*. In all the groups n=4. Mean difference between any pair of days in a group greater than LSD value of 21.41 is significant at 5% level. Mean difference between any pair of groups on any day greater than LSD of 52.60 is significant at 5% level. p-value < 0.05 shows significant difference from Group 2.

Table 3. Effect of aqueous and ethanol leaf extracts of *E. psoraleoides* on some haematological parameters in alloxan-induced diabetic rats.

Parameter	Group 1 (Normal control)	Group 2 (Diabetic untreated)	Group 3 (Diabetes treated with AE (200 mg/kg))	Group 4 (Diabetes treated with AE (400 mg/kg))	Group 5 (Diabetes treated with EE (200 mg/kg))	Group 6 (Diabetes treated with EE (400 mg/kg))	Group 7 (Diabetes treated with glibendanide (0.3 mg/kg))
RBC × 10^9 L^{-1}	2.83±0.49^{a}	3.15±0.21^{ab}	3.23±0.24^{abc}	3.37±0.06^{bc}	3.65±0.07^{bc}	3.75±0.07^{c}	3.25±0.21^{abc}
Haemoglobin (g/dl)	12.87±1.27	14.18±1.17	12.60±0.93	13.23±0.35	13.40±0.70	14.35±0.49	13.10±0.14
WBC × 10^9 L^{-1}	6533.33±1001.67^{ab}	10425.00±3059.82^{c}	3737.50±717.79^{a}	8056.67±1336.65^{bc}	8460.00±1895.05^{bc}	8835.00±657.61^{bc}	7720.00±961.67^{bc}
Neutrophils (%)	24.67±5.03^{ab}	72.00±4.00^{d}	30.75±6.50^{b}	25.00±5.00^{ab}	15.00±0.00^{a}	32.00±16.97^{b}	45.00±0.00^{c}
Lymphocytes (%)	72.67±4.16^{cd}	27.50±3.79^{a}	68.75±7.46^{c}	74.33±4.04^{cd}	85.00±0.00^{d}	67.00±18.39^{bc}	55.00±0.00^{b}
Monocytes (%)	2.67±1.16^{b}	0.00±0.00^{a}	0.50±1.00^{a}	0.67±1.16^{a}	0.00±0.00^{a}	1.00±1.00^{ab}	0.00±0.00^{a}

AE: Aqueous extract; EE: ethanol extract; RBC: red blood cell count; WBC: white blood cell count. In the groups n = 4. Groups with different superscript(s) are significantly different from each other at 5% level.

significant (P < 0.05) change in red blood cell (RBC) count, white blood cell (WBC), neutrophlils, lymphocytes and monocytes. This observation is consistent with earlier reports (Mahmoud, 2013; Akomas et al., 2014; Chinyelu et al., 2017), but differ from the reports of some others (Mohammed et al., 2009; Verma et al., 2012).

However, the extract did not have significant (P>0.05) effect on haemoglobin. Only 400 mg/kg body weight ethanol extract significantly (P<0.05) increase RBC when compared with the diabetic untreated rats. The alterations of these parameters are well known to cause anaemic condition in man (Balasubraimanian et al., 2009). The white blood cell count of the rats treated with200 mg/kg body aqueous extract had significantly (P<0.05) decreased. These may be attributed to infection on the normal body systems of the rats. Also, a significant (P<0.05) decrease was observed in neutrophils and lymphocyte counts when compared with diabetic untreated.

The presence of some phytochemicals with the ability to stimulate the production of white blood cells in the extract could be responsible for the

observed result in the treated rats. The extract at both dosages significantly improved the levels of WBC and lymphocytes as well glibenclamide when compared with diabetic untreated group. The neutrophils increased significantly in the glibenclamide group as compared to the normal and extracts groups which had same effect. However, the extract did not have any significant effect on monocytes in this study. This gives an indication that the plant extracts may contain some phytochemicals that can stimulate the formation or secretion of erythropoietin in the stem cells of the animals. Erythropoietin is a glycoprotein hormone which stimulates stem cells in the bone marrow to produce red blood cells (Ohlsson and Aher, 2006). The RBC and Hb parameters are used mathematically to define the concentration of haemoglobin and to suggest the restoration of oxygen-carrying capacity of the blood.

Following the data obtained, it is suggested that aqueous and ethanol leaf extracts of *E. psoraleoides* possesses antihyperglycemic properties. In addition, the extract could prevent various complications of diabetes as well as improving some hematological parameters. A further experimental investigation is also needed to exploit its relevant therapeutic effect to substantiate its ethnomedicinal usage on macromolecules.

Conclusion

This investigation was anchored on the antidiabetic properties of *E. psoraleoides* to be compared with the standard drug glibenclamide. Though glibenclamide was more efficacious, going by the safety of herbal therapy, *E. psoraleoides* application still falls within the ambit of antidiabetic medicament. Its phytochemicals are testimonies of its activities and potency and it is strongly recommended for supplementation as food and treatment of type 2 diabetes mellitus.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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