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NEWBOULDIA LAEVIS LEAF FACILITATES INSULIN SECRETION, GLUCOSE UPTAKE AND PANCREATIC FUNCTION IN ALLOXAN-INDUCED HYPERGLYCAEMIA IN WISTAR RATS

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Keywords:

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ABSTRACT: The antihyperglycaemic activity of aqueous leaf extract of *Newbouldia laevis* (ALENL) was evaluated in rats. Twenty-five rats of both sexes (120 - 160 g) were divided into five groups (A-E) of 5 animals each. Group A (control) rats were administered 0.5 ml of distilled water (DW) orally while those in group B received 100 mg/kg body weight of ALENL. Animals in groups C, D and E which were induced into hyperglycaemia (intraperitoneal administration of 150 mg/kg body weight of alloxan) were also administered DW, 100 and 200 mg/kg body weight of ALENL respectively, once daily for 14 days. Blood glucose levels (BGL) were determined at interval of two days. Alloxan significantly ($p<0.05$) increased BGL in the DW treated hyperglycaemic animals (DWTHA) from 48.00 ± 1.79 to 142.80 ± 2.35 mg/dl after 24 h. After 2 days, administration of the extract at 100 and 200 mg/kg body weight increased blood glucose level but this increase was not statistically significant ($p>0.05$) when compared with the DWTHA. On day 4, the extract at both doses decreased blood glucose level but this decrease was not statistically significant ($p>0.05$) when compared with the DWTHA. On days 6, 8, 10, 12 and 14, the extract at both doses decreased blood glucose level but this decrease was statistically significant ($p<0.05$) when compared with the DWTHA. The study indicates that the extract at both doses possess antihyperglycaemic properties which may have acted by stimulating glucose utilization by peripheral tissues or increasing insulin production by the pancreas from regenerated β-cells.

INTRODUCTION: Hyperglycaemia or high blood sugar is a metabolic condition in which an excessive amount of glucose circulates in the blood plasma [1].

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Acute hyperglycemia involves glucose levels that are extremely high and most often seen in persons who have uncontrolled insulin-dependent diabetes [2]. In untreated hyperglycemia, a condition called ketoacidosis may develop because decreased insulin levels increase the activity of hormone sensitive lipase, thus affecting the heart, and may result in chronic hyperglycemia [3, 4]. Symptoms associated with acute or chronic hyperglycemia include polyphagia, polydipsia, polyuria, weight loss, fatigue, blurred vision, poor wound healing,

feet tingling, erectile dysfunction, external ear infection, cardiac arrhythmia, stupor, coma, seizures *etc*. Causes of hyperglycaemia are diabetes mellitus, drugs [5], critical illness and oxidative stress [6].

Hyperglycaemia-induced oxidative and nitrosative stress has also been singled out as one of the major links between diabetes and diabetic complications [6, 7]. Hyperglycaemia leads to generation of free radicals due to autoxidation of glucose and glycosylation of proteins. The persistent increase in reactive oxygen species (ROS) and reactive nitrogen species (RNS) accompanied by a decrease in antioxidant activity lead to the occurrence of oxidative and nitrosative stress which can cause endothelial dysfunction, insulin resistance as well as alterations in number and functions of pancreatic β-cells which may eventually result in diabetic microvascular and macrovascular complications [8]. Diabetes mellitus is therefore a group of metabolic diseases characterized by hyperglycemia, resulting from defects in insulin secretion, insulin action, or both. Report have it that protection against the alloxan-induced hyperglycaemia can be achieved by a combination of superoxide dismutase and catalase, which completely prevents redox imbalance between alloxan, ROS species generation and antioxidant status [9, 10]. Studies have also been reported in the open scientific literature on induced hyperglycaemia following administration of alloxan and or extracts of medicinal plants [5, 11, 12, 13, 14]. This has therefore necessitated more researches on the effects of medicinal plants on alloxan-induced hyper-glycaemia in animals.

Medicinal plants are sources of direct therapeutic agents or new raw material base for the synthesis of useful antihyperglycaemic drug [15, 16]. The use of plants in traditional medicine referred to as herbalism or simply botanical medicine falls outside the mainstream of the western or orthodox medicine [17, 18]. Plants contain active components (secondary metabolites) which possess medical properties that are harnessed for the treatment of different diseases [19]. Worldwide, more than 171 million people suffer from diabetes, making it one of the most common non-communicable diseases and the number of affected individuals with diabetes is expected to double by 2025 [20].

The countries with the largest number of diabetics are India, China, and United states [21]. In the past decades, research has been focused on scientific evaluation of traditional drugs of plant origin, and screening of more effective and safe anti-hyperglycaemic agents has continued to be a quarrying domain [22, 23]. A very large area of Nigeria ecological zones is populated with many plant species which have found their usefulness either directly or indirectly for humans [24]. The medicinal values of many of these plants cannot be over emphasized in the light of oral traditions and folklores from the distant past that have continued to extol the healing virtues of these plants and their extracts. This has therefore prompted more studies on the possible effects of medicinal plants on alloxan-induced hyperglycaemia in animals. One plant of interest *is Newbouldia leavis*.

Newbouldia leavis (Bignonicaceae) is commonly known as African Border tree or boundary tree in English [25]. It is called "Aduruku" in Hausa; "Ogirisi" in Igbo; "Ikhimi" in Edo and "Akoko" in Yoruba language [26]. It grows to a height of about 7.8 (up to 15 metres), more usually a shrub of 2 - 3 metres, with many stemmed forming clumps of gnarled branches. It is easily recognized by its short branches, coarsely toothed leaflets as well as purple and white flowers [27]. *Newbouldia leavis* is native to tropical Africa and grows from Guinea Savannahs to dense forests, or moist and well-drained soils [28]. One remarkable thing about this plant is that it hardly dies hence it is used to indicate boundary marks among the Igbo people of South Eastern Nigeria [29]. Previous reports have shown that *N. laevis* leaves possess sedative[30], antidiabetic[31] haematological [32], erythrocyte stability / membrane protection [33], fertility [34], and antioxidant [35] activities.

Although, the aqueous leaf extract of *N. laevis* have been reportedly evaluated by Omonkhelin *et al.*, and Owolabi *et al.,* for its antihyperglycaemic activity at 100, 200 and 400 mg/kg body weight [31, 36] as well as Ajah *et al.,* and Osigwe *et al.,* at 200 and 250, 500, 1000 mg/kg body weight [37, 38] respectively in alloxan-induced hyperglycaemic rats, there is dearth of information in the open scientific literature on the possibility of antidiabetic activity of *N. laevis* leaf on alloxan-induced hyperglycaemia especially at the specific pharma-

cologic dose of 100 and 200 mg/kg body weight. Therefore, the present study was undertaken to provide information on the anti-hyperglycaemic effects of aqueous leaf extract of *N. laevis* on alloxan-induced hyperglycaemia in rats.

MATERIALS AND METHODS:

Materials:

Collection of Plant Materials and Authentication: Fresh leaves of *Newbouldia laevis* were gotten from a farm at Okofia in Nnewi and authenticated by a botanist in the Department of Plant Biology, Nnamdi Azikiwe University, Akwa, Anambra State, Nigeria while the botanical authentication of the plant was confirmed at the Forestry Research Institute of Nigeria (FRIN) Ibadan, Nigeria where a voucher specimen (no. FHI 107753) was deposited for future reference.

Experimental Animals: Albino rats (*Rattus norvegicus*) of both sexes weighing 120 - 160 g were obtained from the animal house of the Department of Human Physiology, Nnamdi Azikiwe University, College of Health Sciences, Nnewi Campus, Nigeria. The animals which were housed in aluminium cages placed in well ventilated standard housing conditions (temperature: 28-31 ºC; photoperiod: 12 h; humidity: 50 - 55%) were allowed free access to rat pellets (Bendel Feeds and Flour Mills Ltd., Ewu, Nigeria) and tap water.

Glucose Meter and Test Strips: Accu-Chek® active compact plus glucometer and Accu-Chek® active test strips were products of Roche Diagnostics, Mannheim, Germany.

Methods:

Ethical Clearance: All the animal experiments were carried out in accordance with the guidelines of the Nnamdi Azikiwe University, Faculty of Basic Medical Sciences, Nnewi Campus Animal Ethical Committee Approval on the use of laboratory animals.

Preparation of Aqueous Leaf Extract of *Newbouldia laevis*: Dried leaves of *Newbouldia laevis* were pulverized using electric blender (Kenwood, Model BL335, Taiwan, China). A known weight (200 g) of the powder was extracted in 2 litre of distilled water for 48 h at room temperature. The mixture was filtered with Whatman no. 1 filter paper (Maidstone, UK). The resulting filtrate was concentrated on steam bath (Model: NL-420S, Newlife® Medical Instrument, England) until a semi-solid residue (brownish black slurry) which weighed 4.38 g was obtained. The percentage yield was calculated and equivalent amount of the residue was separately reconstituted in distilled water to give the required doses of 100 and 200 mg/kg body weight used in the study.

Determination of Blood Glucose and Induction of Hyperglycaemia: After eight hours of fast (without food, but water), blood glucose levels of the animals were determined before the administration of alloxan monohydrate by placing an aliquot (0.6 µL) of the blood on the test strip that had been inserted into the glucometer and reading the blood sugar level. Hyperglycaemia was then induced into animals following intraperitoneal administration of 1 ml corresponding to 150 mg/kg body weight of alloxan monohydrate solution (prepared in sterile physiological saline).

One hour after the administration of alloxan, the animals were equally given their pellet *ad libitum* and 5% dextrose solution to overcome the early hypoglycaemic phase [39]. The blood glucose was again determined after 24 h of alloxan administration. Rats with blood glucose level higher than 180.00 mg/dl was were declared hyperglycaemic and included in the anti hyperglycaemic study [40].

Animal Grouping: Fifteen hyperglycaemic and ten normal rats of both sexes (120 - 160 g) were completely randomized into five groups (A-E) of five rats each as follows:

Group A: Normal rats not induced with diabetes.
Group B: Normal rats that received aqueous leaf extract of *Newbouldia laevis.*
Group C: Alloxan-induced hyperglycaemic rats not treated, to serve as negative control.
Group D: Alloxan-induced hyperglycaemic rats treated with 100 mg/kg body weight of extract.
Group E: Alloxan-induced hyperglycaemic rats treated with 200 mg/kg body weight of extract.

Extract administration was done once daily for 14 days after which blood glucose levels were determined at interval of two days.

Data Analysis: Results were expressed as the mean of five determinations ± SEM. Significant difference was determined by analysis of variance and Duncan's Multiple Range Test at 5% confidence level using SPSS 23.0 Software (Statistical Package for Social Sciences, Inc., Chicago, IL, USA).

RESULTS: Compared with the distilled water treated control animals after 24 h, administration of alloxan significantly ($p < 0.05$) increased fasting blood glucose level from 48.40 ± 2.71 to 132.80 ± 2.96 mg/dl of animals in group C, from 47.40 ± 2.66 to 139.40 ± 2.58 mg/dl of animals in group D and from 48.00 ± 1.79 to 142.80 ± 2.35 mg/dl of animals in group E **Table 1**.

TABLE 1: BLOOD GLUCOSE LEVEL BEFORE AND AFTER ALLOXAN INDUCTION FOR THE DIFFERENT GROUPS (AFTER 24 h)

Group n = 5	Before Induction Mean ± SEM (mg/dl)	After Induction Mean ± SEM (mg/dl)
A	S47.80 ± 2.26	
B	47.40 ± 2.25	
C	48.40 ± 2.71[a]	132.80 ± 2.96[b]
D	47.40 ± 2.66 [a]	139.40 ± 2.58[b]
E	48.00 ± 1.79 [a]	142.80 ± 2.35[b]

Data are mean of five determinations ± SEM. Test values with superscript different from their respective group across the row are significantly different ($p<0.05$)

Day 2: When group D was compared with the hyperglycaemic control group C, there was an increase in blood glucose but this was not statistically significant ($p>0.05$). Also, when group E was compared with the hyperglycaemic control group C, there was an increase in blood glucose level but this was not also statistically significant ($p>0.05$). Group E when compared with group D was higher but this was not statistically significant ($p>0.05$) **Table 2**.

Day 4: When group D was compared with the hyperglycaemic control group C, there was a decrease in blood glucose but this was not statistically significant ($p>0.05$). Also, when group E was compared with the hyperglycaemic control group C, there was a decrease in blood glucose level but this was not also statistically significant ($p>0.05$). Group D when compared with group E was higher but this was not statistically significant ($p>0.05$) **Table 2**.

TABLE 2: COMPARISON BETWEEN THE VARIOUS DIABETIC GROUPS FOR DAY 2 AND DAY 4 AFTER INDUCTION

Group n=5	Day 2 Mean ± SEM (mg/dl)	Day 4 Mean ± SEM (mg/dl)
C	135.40 ± 2.50[a]	138.40 ± 2.50[a]
D	141.20 ± 2.31[a]	135.40 ± 2.05[a]
E	142.20 ± 2.13[a]	134.00 ± 1.76[a]

Data are mean of five determinations ± SEM. Test values with superscript different from their respective group down the column per day are significantly different ($p<0.05$)

Day 6: When group D was compared with the diabetic control group C, there was a decrease in blood glucose which was statistically significant ($p<0.05$). Also, when group E was compared with the diabetic control group C, there was a decrease in blood glucose level which was also statistically significant ($p<0.05$). Group D when compared with group E was higher but this was statistically significant ($p<0.05$) **Table 3**.

Day 8: When group D was compared with the diabetic control group C, there was a decrease in blood glucose which was statistically significant ($p < 0.05$). Also, when group E was compared with the diabetic control group C, there was a decrease in blood glucose level which was also statistically significant ($p < 0.05$). Group D when compared with group E was higher but this was statistically significant ($p < 0.05$) **Table 3**.

TABLE 3: COMPARISON BETWEEN THE VARIOUS DIABETIC GROUPS FOR DAY 6 AND DAY 8 AFTER INDUCTION

Group n=5	Day 6 Mean ± SEM (mg/dl)	Day 8 Mean ± SEM (mg/dl)
C	138.20 ± 2.44[a]	139.00 ± 2.21[a]
D	130.00 ± 1.76[b]	121.80 ± 1.07[b]
E	120.80 ± 1.11[c]	111.20 ± 1.07[c]

Data are mean of five determinations ± SEM. Test values with superscript different from their respective group down the column per day are significantly different ($p<0.05$)

Day 10: When group D was compared with the diabetic control group C, there was a decrease in blood glucose which was statistically significant ($p<0.05$). Also, when group E was compared with the diabetic control group C, there was a decrease in blood glucose level which was also statistically significant ($p<0.05$). Group D when compared with group E was higher but this was statistically significant ($p<0.05$) **Table 4**.

Day 12: When group D was compared with the diabetic control group C, there was a decrease in blood glucose which was statistically significant ($p<0.05$). Also, when group E was compared with the diabetic control group C, there was a decrease in blood glucose level which was also statistically significant ($p<0.05$). Group D when compared with group E was higher but this was statistically significant ($p<0.05$) **Table 4**.

Day 14: When group D was compared with the diabetic control group C, there was a decrease in blood glucose which was statistically significant ($p<0.05$). Also, when group E was compared with the diabetic control group C, there was a decrease in blood glucose level which was also statistically significant ($p<0.05$) **Table 4**.

TABLE 4: COMPARISON BETWEEN THE VARIOUS DIABETIC GROUPS FOR DAY 10, 12 AND DAY 14 AFTER INDUCTION

Group n= 5	Day 10 Mean ± SEM (mg/dl)	Day 12 Mean ± SEM (mg/dl)	Day 14 Mean ± SEM (mg/dl)
C	139.00 ± 2.07[a]	140.00 ± 1.95[a]	139.60 ± 2.06[a]
D	109.60 ± 0.81[b]	94.20 ± 1.24[b]	84.60 ± 1.29[b]
E	95.00 ± 1.84[c]	84.40 ± 0.81[c]	70.60 ± 1.36[c]

Data are mean of five determinations ± SEM. Test values with superscript different from their respective group down the column per day are significantly different ($p<0.05$)

DISCUSSION: The present study revealed a dose specific pharmacologic activity of the aqueous leaf extract of *N. laevis* at 100 and 200 mg/kg body weight. Alloxan monohydrate is a hydrophilic and unstable compound of glucose analogues that specifically accumulate in pancreatic *β*-cells *via* the Glucose Transporter 2 [41] to induce hyperglycaemia (type I diabetes) [9, 42]. The cytotoxic activity of alloxan monohydrate involves oxidation of essential sulphydryl (-SH) group, inhibition of glucokinase enzymes, generation of free radicals and disturbance of intracellular calcium homeostasis [42].

The presence of intracellular thiols, especially glutathione, generates reactive oxygen species (ROS) in a cyclic redox reaction with its reduction product, dialuric acid [43]. Autoxidation of dialuric acid produces superoxide radicals, hydrogen peroxide and, in a final iron-catalysed reaction step, hydroxyl radicals [44]. These free radicals are ultimately responsible for the death of the beta cells, which have a particularly low antioxidant defence capacity, and the ensuing state of insulin-dependent 'alloxan-induced hyperglycaemia' [45]. This is the fundamental mechanism underlying alloxan-induced hyperglycemia in the distilled water treated hyperglycaemic rats after 24 h of alloxan induction. The increase in blood glucose level by alloxan in the distilled water treated hyperglycaemic animals may also be attributed to over-production (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues [6].

The non-significant increase in blood glucose level after day 2 by the extract at 100 and 200 mg/kg body weight (group D and E) when compared with the animals in group C imply that the extract may not affect glucose metabolism. This might not be unconnected with the 5% dextrose solution administered upon hyperglycaemia to overcome the early hypoglycaemic phase [39]. The non-significant decrease in blood glucose level by the extract at 100 and 200 mg/kg body weight (group D and E) when compared with group C, on day 4, may signal an onset of restoration of the damaged insulin producing pancreatic *β*-cells of the animals [46, 47]. The reduction in elevated blood glucose level by the extract of animals in group D and E when compared with those in group C on days 6, 8, 10, 12 and 14 may be due to the antihyperglycaemic effect of the extract which could have acted by stimulating glucose utilization by peripheral tissues or increasing insulin production by the pancreas from regenerated *β*-cells [48, 49, 50]. Overall, available evidence from the present study suggests that the aqueous leaf extract of *N. laevis* attenuated alloxan-induced hyperglycaemia in Wistar rats.

CONCLUSION: Experimental evidence obtained from this study indicate that the aqueous leaf extract of *N. laevis* at 100 and 200 mg/kg body weight facilitated pancreatic insulin secretion and glucose uptake in alloxan-induced hyperglycaemic rats.

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was completed in a good record time. Indeed, we are sincerely grateful.

COMPETING INTERESTS: Authors have declared that no competing interests exist.

RECOMMENDATION: This investigation suggests the presence of biologically active components (principles) in the 100 and 200 mg/kg body weight of *N. laevis* leaf which may be worthy of further research and elucidation.

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