Efficacy and Safety Assessment of *Launaea cornuta* Extracts in the Management of Diabetes Mellitus

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Abstract  This study investigated safety and hypoglycemic efficacy of ethyl acetate and aqueous extracts of *L. cornuta* in male BALB/c mice. Diabetes was induced by intraperitoneal administration of 186.9 mg/kg body weight dose of 10% alloxan monohydrate to overnight fasted mice. Diabetic mice were treated with 50, 100 and 200 mg/kg body weight doses of extracts and 3 mg/kg body weight of reference drug, glibenclamide. Blood glucose levels were compared with those of normal and diabetic untreated mice after every 2 hours for 8 hours post oral administration. Safety was evaluated by oral administration of 1 g/kg body weight of extracts to mice daily for 28 days. Changes in body weight were determined after every 7 days up to the 28th day. On the 28th day the mice were sacrificed; hematological and biochemical parameters determined by standard methods. These parameters included, total cells counts, AST, ALT, and ALP among others. Ethyl acetate extract was found to significantly reduce blood sugar in a dose independent manner, while aqueous extract did not exhibit hypoglycemic effect. Aqueous extracts significantly lowered body weight, RBCs, PCV, platelets and WBCs but increased MCHC and had no effect on growth rate of the diabetic mice compared to normal mice. Ethyl acetate extracts significantly increased WBCs, MCH and MCHC and lowered platelets and had no effect on RBCs, PCV and MCV. Similarly, ethyl acetate extracts had comparable effects to normal control mice on growth rate and body weight. Oral administration of aqueous extract significantly increased AST, CK and lowered ALT, ALP and had no effect on BUN compared to the normal control mice. Oral administration of ethyl acetate extract significantly lowered BUN, AST, ALP, and CK; and had no effect on ALT compared to normal control mice. The study findings suggest that *L. cornuta* ethyl acetate extract is efficacious and safe in the management of diabetes.

Keywords  Ethyl acetate, Diabetes mellitus, *Launaea cornuta*, Safety and efficacy

1. Introduction

Plants have been used medicinally for thousands of years by cultures all over the world. According to the World Health Organization (WHO), 80% of the world's population rely on plant-based remedies for primary healthcare[1]. There is a significant growth in the use of complementary and alternative medicine (CAM) across the developed world due to a discontentment and disillusionment with conventional medicines[2]. Since herbs contain a wide array of secondary metabolites such as; alkaloids, terpenes and phenolics, their effective uses depend on extensive and thorough knowledge of chemical compositions, safety and efficacy.

*Launaea cornuta* belongs to the family Asteraceae, and is an upright perennial shrub with hollow stems up to 1.5 m high and creeping rhizomes[3]. The leaves form a rosette at the base, alternate on the stem, sessile, up to 25 cm long by 3 cm wide, entire or with two to three pairs of lobes acute-pointed near the base. Inflorescence large, diffuse with numerous flowers heads on peduncles about 2.5 cm long[4]. *Launaea cornuta* is native in African countries of Cameroon, Central African Republic, Ethiopia, Kenya, Malawi, Mozambique, Nigeria, Rwanda, Somalia, Sudan, Tanzania, Uganda, Zaire, Zambia, and Zimbabwe[4, 5].

*L. cornuta*, a drought resistant plant is considered among Kenyan communities to have medicinal effects on stomach related ailments, and is used in the treatment of amoebiosis, typhoid and lack of appetite. In Sudan, some parts of Kenya and Tanzania it is used as a salad or vegetable for making stew[6]. Fresh roots are chewed to cure swollen testicles and roots may be pounded and soaked in water or boiled and the
decoction drunk for treatment of typhoid. For measles, the whole plant is boiled and the warm water used for washing the infected body. Pounded leaves are soaked in water and given to chickens to treat chicken fever or coccidiosis and the dried root powder is applied to treat warts[5, 7]. In Southern Africa, the leaves are commonly eaten as a vegetable and are added fresh to maize porridge or a relish prepared from them, mixed with other vegetables[3].

The current report investigated the efficacy and safety of ethyl acetate and aqueous extracts of Launaea cornuta in male BALB/c mice in the management of diabetes mellitus.

2. Methodology

2.1. Collection and Preparation of the Plant Materials

L. cornuta shrubs were collected in February and March, 2011, from Mbeu Village, Tigania, Meru County of Kenya. The plant was authenticated by a taxonomist at the Department of Plant and Microbial Sciences, Kenyatta University, Kenya and a voucher specimen deposited at the Kenyatta University Herbarium for future reference. They were cut into small portions, and dried at room temperature under shade for one month. The dried plant material was ground using an Electric mill (Christy and Norris Ltd, England), and the powder kept at room temperature away from direct sunlight in air-tight, dry plastic bags[8].

One hundred grams (100 g) of the powder was extracted in 1 liter of distilled water at 60°C in a metabolic shaker for 6 hours. After extraction, the extract was decanted into a clean dry conical flask and then filtered through folded cotton gauze into another clean dry conical flask. The filtrate was then freeze dried in 200ml portions using a Modulyo Freeze Dryer (Edward England) for 48 hours. The freeze-dried material was then weighed and stored in an airtight container at -20°C until used for bioassay. Similarly, 100g of plant material was extracted in 1 litre of ethylacetate at room temperature in a metabolic shaker for six hours. The extracts were filtered using a Whatman Filter Paper No 540 and the filtrate concentrated in a Rotary Evaporator. The extracts were weighed and stored in air-tight amber containers at 4°C ready for use[8].

2.2. Experimental Animals

The study used male BALB/c mice, 3-5 weeks old weighing 20-30 g with a mean weight of 25g. The animals were allowed to acclimatize for a period of two weeks in the animal house at the Department of Biochemistry and Biotechnology, Kenyatta University prior to the study. The mice were housed in polypropylene cages, maintained under standard laboratory conditions of 12 hour light and dark sequence, at ambient temperature of 25±2°C and 35-60% humidity. The animals were fed with standard mice pellets obtained from Unga Feeds Limited, Kenya, and water ad libitum. The experimental protocols and procedures used in the study were approved by the Ethics Committee for the Care and Use of Laboratory Animals of Kenyatta University, Kenya.

2.3. Induction of Hyperglycemia

Prior to initiation of this experiment, the animals were fasted for 8-12 hours[7], but allowed free access to water. Hyperglycemia was induced experimentally by a single intraperitoneal administration of 186.9 mg/kg body weight [8], of a freshly prepared 10% alloxan monohydrate (2,4,5,6 tetraoxypyrimidine; 5-6-dioxyuracil) obtained from Sigma (Steinhein, Switzerland). Forty-eight hours after alloxan administration, blood glucose level was measured using a glucometer. Mice with blood glucose levels above 2000 mg/L were considered diabetic and used in the study[7].

2.4. Experimental Design

The experimental animals were male BALB/c mice of comparable age and body weight. They were randomly divided into six groups of five animals each. Group I consisted of normal mice orally administered with 0.1ml physiological saline; Group II consisted of alloxan induced diabetic mice orally administered with 0.1ml physiological saline; Group III consisted of alloxan induced diabetic mice orally administered with 0.075 mg of glibenclamide (3 mg/kg body weight) in 0.1 ml physiological saline; Group IV consisted of alloxan induced diabetic mice orally administered with 1.25 mg extract (50 mg/kg body weight) in 0.1 ml physiological saline; Group V consisted of alloxan induced diabetic mice orally administered with 2.50 mg extract (100 mg/kg body weight) in 0.1 ml physiological saline; and Group VI consisted of alloxan induced diabetic mice orally administered with 5 mg extract (200 mg/kg body weight) in 0.1 ml physiological saline.

2.5. Blood Glucose Determination

Blood for glucose determination was obtained by bleeding tail sterilized with 10% alcohol. This was done at the start of the experiment, and then after 2nd, 4th, 6th and 8th hours. At each time point blood glucose levels were determined with a glucose analyser model (Contour ® TS, Bayer Pty, Ltd; Healthcare Division, Japan).

2.6. In vivo Single Dose Toxicity Test

Male mice of comparable age and body weight were randomly divided into three groups of five mice each. Group I consisted of untreated control mice orally administered daily for 28 days with 0.1 ml physiological saline. Group II and III consisted of normal control mice orally administered with aqueous and ethylacetate extracts of L. cornuta at 25 mg (1 g/kg body weight) in 0.1 ml physiological saline. During this period the mice were allowed free access to mice pellet and water ad libitum. They were carefully observed for any signs of general illness, change in behaviour and mortality during the entire experimental period.

The body weight of each mouse was assessed once weekly during the dosing period up to and including the 28th day. On
the 28th day, all the study animals were euthanized and blood obtained by cardiac puncture and divided into two portions. One was collected in K3-EDTA tubes for determination of hematological parameters, while the other was collected in plastic test tubes allowed to stand for 3 hours to ensure complete clotting. The clotted blood was centrifuged at 3000 rpm for 10 min and clear serum samples aspirated off and stored frozen at -20°C until required for biochemical analysis.

2.7. Determination of Hematological Parameters

Blood was examined using standard protocols[9, 10]. Red blood cells (RBC), white blood cells (WBC), hemoglobin (Hb), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), mean cell volume (MCV) and platelets (PLT) were determined using the Coulter Counter System (Beckman Coulter®, ThermoFisher, UK). Differential white blood cell count for neutrophils (N), lymphocytes (LYM), and monocytes (M) were determined from stained blood films using a hemocytometer. Air-dried thin blood filmstained with giemsa stain were examined microscopically using magnification 400 and 1000 for differential WBC counts and cell morphologies, respectively.

2.8. Determination of Biochemical Parameters for Toxicity

Aspartate amino-transaminase (AST) and alanine amino-transaminase (ALT) were determined by the method of Reitman and Frankel[11]. The alkaline phosphatase concentrations in experimental and normal control BALB/c mice were estimated by method of King and Armstrong[12]. Creatine kinase (CK) activity was determined by Rosalkimethod[13], which is based on the primary reaction that is catalyzed by CK resulting in production of creatine and ATP. The blood urea nitrogen (BUN) was analyzed according to the Adrian method[14].

2.9. Statistical Analysis

Data was entered in the Microsoft® Excel spread sheet and cleaned ready for analysis. Results were expressed as Mean±Standard Deviation (SD) of the blood glucose levels per the number of mice used in every study point. One-way ANOVA and post-ANOVA (Bonferroni-Holm) test was used to compare the means of untreated normal control mice with diabetic mice treated with physiological saline, diabetic mice treated with the conventional drug and diabetic mice treated with plants extracts at doses of 50, 100 and 200 mg/kg body weight. Student’s T-test was used to compare the means of body weight and body weight changes, hematological and biochemical parameters of normal control mice administered with 0.1ml physiological saline with those of normal mice administered with 1g/kg body weight plants extracts. P< 0.05 was considered statistically significant.

3. Results

*L. cornuta* ethyl acetate and aqueous extracts yielded light green and dark brown pastes of 183.12 and 50.0 mg/g dry weight, respectively. Oral administration of ethyl acetate extracts at 50, 100 and 200 mg/kg body weight to mice significantly lowered blood glucose levels from the 4th hour through to the 8th hour in a dose independent manner. In the 4th hour, the ethyl acetate extracts at 50, 100 and 200 mg/kg body weight lowered blood glucose levels in mice to 43.6, 60.4 and 58.4%, respectively, compared to glibenclamide treated diabetic mice whose blood sugar levels was lowered to 58.2% within the same hour. In the 6th hour, the ethyl acetate extracts at 50, 100 and 200 mg/kg body weight lowered blood glucose levels in mice to 24.3, 38.2 and 41.1%, respectively, compared to glibenclamide treated diabetic mice whose blood sugar levels was lowered to 32.3% within the same hour. By the 8th hour, the ethyl acetate extracts at 50, 100 and 200 mg/kg body weight lowered blood glucose levels in mice to 24.8, 38.2 and 41.1%, respectively, compared to glibenclamide treated diabetic mice whose sugar levels was lowered to 22.8% within the same hour (Table 1; Figure 1). Oral administration of ethyl acetate extracts at 50, and 100 mg/kg body weight, respectively, produced hypoglycemia that was comparable to that induced by glibenclamide and significantly lowered blood glucose to levels comparable to those in the normal mice at the 6th and 8th hours, respectively. The dose of 200 mg/kg body weight significantly lowered blood glucose compared to glibenclamide and the control animals in the 6th and 8th hour, respectively.

As depicted in Table 2 and Figure 2, oral administration of aqueous extracts at 50, 100 and 200 mg/kg body weight to mice did not lower blood glucose levels from the second hour through to the 8th hour when compared to untreated diabetic mice. In the 2nd hour, the aqueous extracts at 50 and 200mg/kg body weight increased blood glucose levels in mice to 119.1 and 131.7%, respectively, compared to glibenclamide treated diabetic mice whose blood sugar levels decreased significantly to 49.5% within the same hour. By the 6th hour, the aqueous extracts at 50, 100 and 200mg/kg body weight significantly increased blood glucose levels in mice to 138.8, 113.1 and 166.7%, respectively, compared to glibenclamide treated diabetic mice whose blood sugar levels significantly declined to 49.5% within the same hour. By the 6th hour, the aqueous extracts at 50, 100 and 200 mg/kg body weight significantly increased blood glucose levels in mice to 157.9, 138.1 and 206.3%, respectively, compared to glibenclamide treated diabetic mice whose sugar levels was lowered to 41.9% within the same hour. By the 8th hour, the aqueous extracts at 50, 100 and 200 mg/kg body weight increased blood glucose levels in mice to 167.1, 146.9 and 202.4%, respectively, compared to glibenclamide treated diabetic mice whose glucose levels was lowered to 25.8% within the same hour.

As depicted in Table 3, oral administration of aqueous
extracts significantly lowered body weights although the growth rate was comparable to that of the normal control mice. Ethyl acetate extracts did not affect gain in body weights and growth rates of the mice. As shown in Table 4, oral administration of aqueous extracts at 1 g/kg body weight daily to mice for 28 days significantly lowered the red blood cells (RBCs), haemoglobin; packed cell volume (PCV), mean cell volume (MCV) and platelets. In contrast, the aqueous extract significantly increased the mean cell haemoglobin concentration (MCHC), and did not have any effect on the mean cell hemoglobin compared to the normal control mice. Ethyl acetate extract significantly increased hemoglobin levels, mean cell hemoglobin and mean cell hemoglobin concentration; and significantly lowered platelets and had no effects on the red blood cells count, packed cell volume and mean cell volume compared to the normal control mice.

Results were expressed as Mean±Standard Deviation (SD) of five mice per group. Means in the same column are not significantly different at P ≤ 0.05 by ANOVA and post ANOVA (Bonferroni-Holm) test

Table 1. Hypoglycemic effects of oral administration of ethyl acetate extracts of L. cornuta at 50, 100 and 200 mg/kg body weight in alloxan-induced diabetic male BALB/c mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Blood glucose levels at varying times (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 hr</td>
</tr>
<tr>
<td>Normal control</td>
<td>Saline</td>
<td>5.1±0.1</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>Saline</td>
<td>23.3±2.8</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>Glibenclamide (3 mg/kg body weight)</td>
<td>23.2±3.7</td>
</tr>
<tr>
<td>Diabetic Extracts</td>
<td>50 mg/kg body weight</td>
<td>16.5±0.9</td>
</tr>
<tr>
<td></td>
<td>100 mg/kg body weight</td>
<td>14.4±0.6</td>
</tr>
<tr>
<td></td>
<td>200 mg/kg body weight</td>
<td>21.4±1.1</td>
</tr>
</tbody>
</table>

Table 2. Hypoglycemic effects of oral administration of aqueous extracts of L. cornuta at 50, 100 and 200 mg/kg body weight in alloxan-induced diabetic male BALB/c mice

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Blood glucose levels at varying times (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 hr</td>
</tr>
<tr>
<td>Normal control</td>
<td>Saline</td>
<td>5.2±0.2</td>
</tr>
<tr>
<td>Diabetic control</td>
<td>Saline</td>
<td>16.0±1.9</td>
</tr>
<tr>
<td>Diabetic Extracts</td>
<td>Glibenclamide (3 mg/kg body weight)</td>
<td>19.8±1.9</td>
</tr>
<tr>
<td>Diabetic Extracts</td>
<td>50 mg/kg body weight</td>
<td>15.2±1.6</td>
</tr>
<tr>
<td></td>
<td>100 mg/kg body weight</td>
<td>16.0±1.6</td>
</tr>
<tr>
<td></td>
<td>200 mg/kg body weight</td>
<td>12.6±1.4</td>
</tr>
</tbody>
</table>

Results were expressed as Mean±Standard Deviation (SD) of five mice per group. Means followed by similar upper case letters in the same column are not significantly different at P ≤ 0.05 by ANOVA and post ANOVA (Bonferroni-Holm) test

Figure 1. Percentage reduction in blood glucose levels at varying times after oral administration of ethyl acetate extracts of L. cornuta at 50, 100 and 200 mg/kg body weight in alloxan-induced diabetic male BALB/c mice
Figure 2. Percentage reduction in blood glucose levels at varying times after oral administration of aqueous extracts of *L. cortuna* at 50, 100 and 200 mg/kg body weight in alloxan-induced diabetic male BALB/c mice

Table 3. Effects of oral administration of ethyl acetate and aqueous *L. cortuna* extracts at 1 g/kg body weight daily in mice for 28 days on body weight and mean weekly body weight change

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Weekly Weight of Mice (g)</th>
<th>Δ Weight/Week</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Control</td>
<td>23.06±1.82</td>
<td>23.31±1.80</td>
</tr>
<tr>
<td>Aqueous</td>
<td>18.00±2.17*</td>
<td>18.58±2.15*</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>23.14±2.87</td>
<td>23.90±2.35</td>
</tr>
</tbody>
</table>

Results are expressed as Mean±Standard Deviation (SD) for five animals in each treatment. *P* < 0.05 is considered significant when the Mean of the control animals is significantly different from that of the extract treated animals by student T-Test

Table 4. Effects of oral administration of *L. cortuna* aqueous and ethyl acetate extracts at 1 g/kg body weight daily in mice for 28 days on some end point hematological parameters in mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>RBC (×10^6/µL)</th>
<th>Hb (g/dL)</th>
<th>PCV (%)</th>
<th>MCH (pg)</th>
<th>MCHC (g/dL)</th>
<th>MCV (fL)</th>
<th>PLT (×10^9/µL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>9.92±1.13</td>
<td>13.66±1.32</td>
<td>56.24±0.47</td>
<td>13.80±0.63</td>
<td>23.32±1.15</td>
<td>59.28±2.82</td>
<td>732.00±202.27</td>
</tr>
<tr>
<td>Aqueous</td>
<td>5.53±0.37*</td>
<td>7.30±1.07*</td>
<td>24.94±1.93*</td>
<td>13.16±1.25</td>
<td>29.16±2.42*</td>
<td>44.74±3.17*</td>
<td>318.06±135.47*</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>8.48±0.84</td>
<td>35.22±3.62*</td>
<td>11.66±1.77</td>
<td>34.58±1.73*</td>
<td>42.70±2.08*</td>
<td>13.06±0.65</td>
<td>482.60±109.21*</td>
</tr>
</tbody>
</table>

Results are expressed as Mean±Standard Deviation (SD). *P* < 0.05 significantly different from control and values without asterisk mean they are comparable with the normal control group. The comparison was performed using T-test for two sample means.

In addition, oral administration of the aqueous extract at 1 g/kg body weight daily to mice for 28 days significantly decreased levels of the white blood cells (WBCs), monocytes, increased neutrophils and lymphocytes relative to that of the control mice. Ethyl acetate extract significantly increased the white blood cells count, granulocytes, lymphocytes and monocytes compared to the normal control mice (Table 5).

Table 5. Effects of oral administration of *L. cortuna* aqueous and ethyl acetate extracts at 1 g/kg body weight daily in mice for 28 days on white blood cells and differential white blood cell count

<table>
<thead>
<tr>
<th>Treatment</th>
<th>WBC (×10^9/L)</th>
<th>DLC (×10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Granulocytes</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>Control</td>
<td>3.70±0.44</td>
<td>0.95±0.12</td>
</tr>
<tr>
<td>Aqueous</td>
<td>8.93±1.59*</td>
<td>1.12±0.27</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>16.27±1.53*</td>
<td>1.75±0.20*</td>
</tr>
</tbody>
</table>

Results are expressed as Mean±standard deviation (SD). *P* < 0.05 significantly different from control and values without asterisk mean they are comparable with the normal control group. The comparison was carried out by T-test for two sample means.
As shown in Table 6, oral administration of aqueous extract significantly increased AST and CK and significantly lowered ALT and ALP and had no effect to BUN compared to the normal control mice. Oral administration of ethyl acetate extract significantly lowered BUN, AST, ALP, and CK; and had no effect on ALT compared to normal control mice.

4. Discussion

The observation that ethylacetate extract of *L. cortuna* (except the aqueous extracts) in various dosage modes lowered blood glucose indicates that the extract contains hypoglycemic constituents. These could be the polyphenols, alkaloids, flavonoids, saponins, tannins, and steroids present in these plants (*unpublished data in our laboratory*), among others, which have been associated with hypoglycemic activity[15-18].

The observed hypoglycemic activity could also be associated with minerals such as iron, chromium, manganese, vanadium, molybdenum, zinc and magnesium which are present in these medicinal plants at various amounts[19-22].

A daily oral administration of ethylacetate and aqueous extracts of *L. cortuna* at a dose of 1g/kg body weight in mice for 28 days induced microcytic hyperchromic anemia. This anemic state may be caused by reduced production of red blood cells and white blood cells due to poisoning and suppression of bone marrow performance by constituents in these plants such as alkaloids, flavonoids, tannins, and saponins which have previously been reported to reduce erythron parameters[23].

Injury of organs resulting from tissue hypoxia may also partly account for the altered serum levels of alkaline phosphatase from liver, kidney and spleen; alanine from liver and aspartate aminotransferase from liver, kidneys, heart and pancreas, and creatine kinase from the heart and skeletal muscle in mice orally administered daily with extracts of *L. cortuna* at 1g/kg body weight daily for 28 days[24]. The significant increase in white blood cells observed on oral administration of plant extracts of *L. cortuna* at 1g/kg body weight daily in mice for 28 days indicates a more accelerated production of these cells and a boosted immunity to mice by these extracts[25].

Both the leaf and stem bark ethylacetate of *L. cortuna* in doses of 50, 100 and 200mg/kg body weight demonstrated in vivoadiabetic activity. The aqueous extracts of *L. cortuna* at 50 and 200mg/kg body weight doses raised blood glucose levels beyond that of the diabetic mice. Oral administration of aqueous leaves extracts of *L. cortuna* at 1g/kg body weight altered the red blood cell count, hemoglobin levels, packed cell volume, mean cell hemoglobin concentration, mean cell volume, platelets; white blood cell count and their differential counts; altered the levels of blood urea nitrogen and the activities of alanine and aspartate aminotransferases, alkaline phosphatase and creatine kinase. The efficacy and safety of these plants extracts could be attributed to phytochemicals present in the plants extracts. The study findings suggest that organic extracts of *L. cortuna* could be used at appropriate doses in management of diabetes.

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