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Profile of *Morinda lucida* Leaf Fractions on Blood Glucose and Lipids in Normal and Alloxan-Induced Hyperglycaemic Rats

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ABSTRACT

Background: Ethanolic decoction made from the fresh leaves of *Morinda lucida* Benth. is highly valued in the local management of diabetes mellitus among the Nigerian herbalists. Of the different solvent fractions (diethyl ether, chloroform, butanol and the residue) made from the crude ethanolic leaf extract of *Morinda lucida* (MLE). **Objective:** the present study aims to determine and evaluate the most effective antihyperglycaemic and antihyperlipidaemic fraction in normal and alloxan-induced diabetic rats for 14 days using various solvents successively and determining the secondary metabolites/phytochemicals in the effective solvent fractions of MLE. **Material and Methods:** MLE was successively partitioned in diethyl ether, chloroform and butanol and 50 mg kg^{-1} of each of these fractions was administered to normal and alloxan-induced hyperglycaemic rats for 14 days. The effect of each fraction was on Fasting Blood Glucose (FBG) on the 1st, 8 and 15th day post-treatment was evaluated using glucose monitoring system. The effect of the fractions on serum triglyceride and total cholesterol was also determined using standard procedures. In addition, qualitative phytochemical analysis was conducted in MLE_b and MLE_c using standard procedures. **Results:** In the normal and alloxan-induced diabetic rats, oral treatment with MLE_c and MLE_b resulted in significant ($p<0.05$, $p<0.01$ and $p<0.001$) time-dependent lowering of FBG, serum triglyceride and total cholesterol in the treated rats with MLE_c producing the most significant ($p<0.001$) antihyperglycaemic and antihyperlipidaemic effects. Qualitative phytochemical analysis of MLE_c showed the presence flavonoids, alkaloids and anthraquinones while that of MLE_b showed the presence of flavonoids, alkaloids, tannins and saponin. **Conclusion:** Results of this study shows MLE_c to be the most effective antihyperglycaemic and antihyperlipidaemic fraction of all the solvent fractions of MLE tested.

Key words: *Morinda lucida* ethanolic leaf extract, solvent fractions, alloxan-induced hyperglycaemic rats, antihyperglycaemic and antihyperlipidaemic effects

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INTRODUCTION

Diabetes Mellitus (DM) remains the most common endocrine disorder of carbohydrate metabolism with over 170 million adult sufferers estimated to have been affected worldwide and about two-thirds of this figure residing in the developing countries[1]. This estimate is expected to double by the year 2030[1,2]. In view of the growing prevalence of the disease, there is an increasing interest towards developing integrated approaches in the prevention and management of DM by exploring the potentials offered by the indigenous herbal therapies[3]. Herbal drugs are prescribed widely because of their effectiveness, relatively low cost and based on the general belief that they are free of intolerable side-effects[4]. Also, World Health Organization[5] has directed further evaluation of the traditional practices and methods (including herbal practices) of managing the disease. In compliance with this directive, many indigenous medicinal plants are currently been screened and evaluated for their antihyperglycaemic potentials. In African herbal medicine, there are various native plants that are employed in the local management of DM, one of which cuts across the West African region is *Morinda lucida* Benth.

Morinda lucida Benth., belonging to the family Rubiaceae, is a tropical West Africa rainforest tree with the English name "Brimstone tree". It is known as Sangogo or Bondoukou alongua (in Cote d'Ivoire), Twi, Kòn kròmà or Ewe amake (in Ghana), Ewe amake or Atak ake (in Togo) and Òruwó or ruwó amongst the Yoruba tribe (South-West Nigeria)[6]. Amongst the Igbo (South-East Nigeria), it is locally known as "Huka" and "Eze-ogu"[7]. Decoctions made from the plant leaves, stem bark and roots are highly valued in the local DM management[8,9]. The leaves and stem bark of *Morinda lucida* are used as purgative, emetic and diuretic[7]. In Nigeria, a mixture of fresh leaves of *Morinda lucida*, *Momordica charantia*, *Vernonia amygdalina* and *Dalbergiella welwitschi* are

ground together into a fine paste before mixing it with native black soap for bathing a cure for DM[10]. In South-west Nigeria, fresh leaves of the plant are macerated in fresh palm wine and the filtrate taken orally for blood sugar control in suspected diabetic patients[11]. Earlier, Olajide *et al.*[12] reported the antidiabetic effect of the aqueous leaf extract of *Morinda lucida* in streptozotocin-induced hyperglycaemic rats. We also reported the antihyperglycaemic activity of the crude ethanolic leaf extract of *Morinda lucida* in normal and alloxan-induced hyperglycaemic rats[11]. Bearing in mind the fact that identifying and isolating the effective extract fractions and isolating active fractions of a crude extract may prove better therapeutically and probably less toxic than its crude form, the present study aims to evaluate the antihyperglycaemic profile of the solvent fractions of the ethanolic leaf extract of *Morinda lucida* Benth in normal and alloxan diabetic rats for 14 days.

MATERIALS AND METHODS

Plant collection and authentication: Two kilogram of fresh leaves of *Morinda lucida* were collected from the same site (as previously reported by Adeneye and Agbaje[11]) on the outskirt of Low Cost Housing Estate, Oke-Afa, Isolo, Lagos State, Nigeria in the months of October- November, 2009. Plant identification and authentication has earlier been done.

Extract preparation: Five hundred gram of *Morinda lucida* fresh leaves were exhaustively extracted in 1 L of 50% ethanol (Aldrich Chemical Co., USA) for 2 h using Soxhlet extraction procedure. The Soxhlet extractive was filtered using a piece of white cotton cloth and the filtrate obtained was completely dried into an aromatic green-brown solid residue over a water-bath. This procedure was repeated three more times. The residues obtained were pooled and stored in water- and air-tight container and kept refrigerated at -4°C until required for experiment.

Solvent partitioning: Fifty gram of the extract was completely deuterated in 100 mL of double-distilled water. The deuterated solution was then solvent partitioned in a 5 L burette using between 1 L to 1.5 L of different partitioning solvents (diethyl ether, chloroform, and butan-1-ol) in the order of their increasing solubility gradients. The fraction obtained with each partitioning solvent was concentrated *in vacuo* using rotary evaporator (BÿUÿCHI Rotavapor® Model R-215, Switzerland) with Vacuum Module V-801 EasyVac®, Switzerland) set at a revolution of 70 rpm and a temperature of 35°C. The "extract residue" and the concentrate of each fraction were completely air-dried in an aerated oven preset at 35°C. The residues left after oven drying were then weighed. This procedure was repeated for 5 more times and each residue was pooled together and stored in clean and dry, water and air-proof containers and preserved in the refrigerator until required for experimentation.

Preliminary Phytochemical analysis of MLE_b and MLE_c: The presence of saponins, tannins, alkaloids, flavonoids, anthraquinones, glycosides and reducing sugars were determined by the simple and standard qualitative and quantitative methods described by Trease and Evans[13] and Sofowora[14]. The simple quantitative analysis of the extract was based on the intensity of the colour change. Briefly described, the qualitative phytochemical analysis of MLE_b and MLE_c was determined as follows:

Tannins: Two hundred miligram of each of the solvent fraction was dissolved in 10 mL of distilled water and then filtered. A 2 mL of filtrate was pipetted into a test tube after which 2 mL of 15% $FeCl_3$ was added and resultant colour change was observed. Blue-black presence indicated the presence of tannins.

Alkaloids: Two hundred miligram of the plant material was extracted with 200 mL of methanol for 20 min on a water bath and then filtered. To 2 mL of the cold water extract in different tubes, was added 6 drops of different alkaloids reagents, namely: Dragendorff's or Mayer's or Wagners's reagent. Presence and colours of any precipitate were noted. Creamish precipitate or brownish-red precipitate or orange precipitate indicated the presence of respective alkaloids.

Cyanogenic glycosides: Two hundred miligram of the solvent fraction was placed in each of 3 different test tubes labeled A, B and C, respectively. The solvent fraction in test tubes A and B were moistened with 5 mL of water, while that in test tube C was left dry. Three pieces of freshly prepared sodium picrate paper were inserted into the mouth of each tube and stoppered. Test tube B was placed in a water bath while test tube A and C were kept at room temperature. After 30 minutes the colour of the picrate papers in each of the test tube were observed and recorded.

Cardiac glycosides

Kedde's test for lactone ring in cardiac glycosides: Five hundred miligram of the solvent fraction was dissolved in 10 mL of methanol. To 2 mL of this, 1 mL of a solution of 2% of 3, 5-dinitrobenzoic acid in methanol and 1 mL of 5.7% sodium hydroxide were added. The result was recorded after 5 min.

Liebermann-Burchard reaction for steroidal/ triterpenoidal nucleus: 500 mg of the dried solvent fraction was dissolved in 2 mL of acetic anhydride and allowed to cool. With the test tube inside ice pack and slanted at an angle of about 45°C, 2 mL of concentrated tetraoxosulphate (VI) acid was carefully poured by the side of the test tube. Colour obtained was noted. Blue-green ring indicated the presence of terpenoids.

Keller-Kiliani test for de-oxy sugars in cardiac glycosides: 50 mg of the solvent fraction was dissolved in 2 mL chloroform. Tetraoxosulphate (VI) acid was added to form a layer and the colour at interphase recorded.

Legal test: The solvent fraction was dissolved in pyridine and 5 drops of 2% sodium nitroprusside together with 4-5 drops of 20% sodium hydroxide were added. Deep colour indicated the presence of cardenolides.

Salkowski's test: 200 mg of the solvent fraction was dissolved in 2 mL of chloroform. Concentrated tetraoxosulphate (VI) acid was carefully added to form a lower layer. A reddish-brown at the interface indicated the presence of a steroidal ring (i.e. aglycone portion of the cardiac glycoside).

Experimental animals: Healthy young adult male albino Wistar rats (120-150 g) used in this study were obtained from Zoology Department of the University of Ilorin, Kwara State, Nigeria. The rats were housed in polypropylene cages and handled in accordance with international principles guiding the Use and Handling of experimental animals[15]. Rat feed (Ladokun Feeds, Ibadan, Nigeria) and tap water were provided *ad libitum*. The rats were maintained at an ambient temperature between 25-28°C, humidity of 56±5% and 12 h day/night photoperiod.

Oral treatment of normal rats with MLE fractions: To identify the biologically active fraction(s) of MLE, 50 mg kg^{-1} of the diethyl ether fraction, chloroform fraction and butanol fraction each was constituted in 10 mL of 5% Tween-20 in distilled water was orally administered to each rat in each treatment group for 14 days. Thirty-six, young in-bred adult male white albino Wistar rats (120-140 g) were randomly allotted to 6 groups. The rats were then fasted overnight for 12-14 h but had free access to drinking water. The basal fasting blood glucose of each rat was first determined using One Touch Basic Blood Glucose Monitoring System® (LifeScan Inc., Milpitas, California, U.S.A.). This was then followed by the following treatments:

Group I: Rats were orally administered 10 $mLkg^{-1}$ of 5% Tween-20 in distilled water, **Group II:** Rats were orally treated with 20 $mgkg^{-1}$ of metformin while, **Group III-VI:** Rats were orally treated with a single daily dose of 50 $mgkg^{-1}$ of diethyl ether (MLE_d), chloroform fraction (MLE_c), and butanol fraction (MLE_b) and the "extract residue" (MLE_r), respectively, for 14 days. The effect of each extract fraction on the blood glucose concentration was then determined on the 15th day after an overnight fasting of the treated rats.

Induction of alloxan-hyperglycaemia in rats and their oral treatment with MLE fractions: Following a 24-h fast, rats were made hyperglycaemic by injecting each rat with a single intraperitoneal dose of 120 mg kg^{-1} of alloxan monohydrate (Sigma Chemical Company, St. Louis, U.S.A.) dissolved in 3 mM of freshly prepared cold citrate buffer (pH 4.5). The baseline fasting blood glucose was first determined before alloxan treatment. Six hours after alloxan injection, rats were orally infused with 20% Dextrose (Unique Pharmaceuticals, Sango-Otta, Ogun State, Nigeria) at an oral dose of 10 mL kg^{-1} so as to prevent the onset of fatal hypoglycaemia which often accompanies administration of alloxan as a result of acute massive pancreatic release of insulin[16]. Gradual onset of hyperglycaemia was confirmed on the 3rd day post-induction but a steady hyperglycaemic state was achieved by the 5th day post-alloxan treatment. By the 5th day, rats with fasting blood glucose of equal or greater than 200 mg dL^{-1} were considered hyperglycaemic. Thirty-seven of the alloxan-treated rats had the fasting blood glucose concentration over 200 mg dL^{-1} while the remaining three rats had spontaneous resolution of their hyperglycaemia.

Six normal and thirty-five alloxan-induced hyperglycaemic rats were randomly allocated into 7 treatment groups as follows:

- **Group I:** Consists of normoglycaemic rats which were orally treated with 10 mL kg^{-1} of 5% Tween 20 dissolved in distilled water
- **Group II:** Consists of alloxan-induced hyperglycaemic rats orally treated with 10 mL kg^{-1} of 5% Tween 20 in distilled water
- **Group III:** Consists of alloxan-induced hyperglycaemic rats orally pre-treated with 20 mg kg^{-1} of metformin (Glucophage®, Hoechst Marion Roussel Limited, Mumbai, India) dissolved in 5% Tween 20 in distilled water
- **Groups IV-VII:** Consist of alloxan-induced hyperglycaemic rats that were orally pre-treated with 50 mg kg^{-1} of diethyl ether, chloroform, butanol fractions and the "extract residue", respectively. All treatments lasted 14 days after which the fasting blood glucose was determined

Bioassays: FBG was determined on one Touch Basic Blood Glucose Monitoring System using the glucose oxidase method of Trinder[17]. Serum triglyceride and total cholesterol were determined using standard test kits.

Data analysis: Results were expressed as mean±S.E.M. of six observations. Statistical analysis was done using two-way analysis of variance followed by post-hoc test, Student-Newman-Keuls test on SYSTAT 10.6. Statistical significance were considered at $p<0.05$, $p<0.01$ and $p<0.001$.

RESULTS

Extraction: The crude ethanolic extraction of *Morinda lucida* fresh leaves gave a yield of 15.5% while that of solvent fractionation of MLE with diethyl ether, chloroform and butanol gave yield of 2.1, 15.6 and 20.0%, respectively, and 62.3% for the "extract residue".

Effect of MLE fractions on FBG, serum triglyceride and total cholesterol in normal rats: Daily oral treatment of normal Wistar rats with 50 mg kg^{-1} of MLE_c and MLE_b resulted in significant ($p<0.05$, $p<0.01$ and $p<0.001$) time-dependent lowering of FBG in the treated rats with MLE_c inducing the most significant ($p<0.001$) hypoglycemic effect over MLE_b and metformin, particularly, on the 15th day post-treatment (Table 1). However, oral treatment with MLE_d and MLE_r did not produce any appreciable changes in the FBG levels (Table 1). In a similar pattern, MLE_c and MLE_b produced significant time-dependent ($p<0.05$, $p<0.01$ and $p<0.001$) lowering of the serum total cholesterol and triglyceride in the treated rats, with MLE_c producing the most significant ($p<0.001$) hypolipidaemic effect when compared to that of MLE_b and metformin (Table 1). Again, MLE_d and MLE_r produced no significant ($p>0.05$) changes in the serum total cholesterol and triglyceride of the treated rats (Table 1).

Table 1: Effect of *Morinda lucida* leaf fractions on FBG, TG and TC in normal rats

Treatment Group	FBG (mg dL^{-1}) on Day 1	Day 8	Day 15	TG (mg dL^{-1})	TC (mg dL^{-1})
I	58.8±2.8	58.7±4.3	56.0±3.3	91.0±5.7	83.2±4.8
II	60.2±2.2	50.8±1.2[d]	47.5±2.2[e]	72.3±5.7[α]	59.8±2.9
III	60.8±1.8	59.5±2.0	58.8±1.5	96.8±4.6	85.5±7.7
IV	59.7±3.0	50.2±1.9[d]	41.0±1.7[f]	56.2±3.8[∂]	49.8±2.3[γ]
V	59.3±2.3	51.5±2.3[d]	47.5±5.0[e]	63.8±12.4[β]	55.0±9.7[λ]
VI	59.0±3.3	57.8±1.8	58.6±1.8	99.5±5.5	88.0±6.7

[d, e] and [f] represent significant decreases at $p<0.05$, $p<0.01$ and $p<0.001$, respectively, when compared to basal value on day 1 and when compared to Group I values on days 1, 8 and 15. [α], [β] and [∂] represent significant decreases at $p<0.05$, $p<0.01$ and $p<0.001$when compared to Group I values, Group I: 10 mL kg^{-1} of 5% Tween-20 in distilled water, Group II: 20 mg kg^{-1} of metformin in 5% Tween-20 in distilled water, Group III: Single daily oral dose of 50 mg kg^{-1} of diethyl ether fraction (MLE_d), Group IV: Single daily oral dose of 50 mg kg^{-1} of chloroform fraction (MLE_c), Group V: Single daily oral dose of 50 mg kg^{-1} of butanol fraction (MLE_b), Group VI : Single daily oral dose of 50 mg kg^{-1} of the "extract residue" (MLE_r)

Effect of MLE fractions on FBG, serum triglyceride and total cholesterol in alloxan-induced hyperglycaemic rats: Single intraperitoneal injection with 120 mgkg^{-1} of alloxan monohydrate resulted in significant ($p<0.001$) hyperglycaemia by the 5th day post-induction (Table 2). However, oral daily treatment with 20 mg kg^{-1} of metformin, 50 mg kg^{-1} of MLE_c and MLE_b resulted in significant ($p<0.05$, $p<0.01$ and $p<0.001$) time-dependent hypoglycaemic effect in the alloxan-induced hyperglycaemic rats, with MLE_c producing the most significant hypoglycaemic effect on the 8 and 15th day of treatment (Table 2). In a similar pattern, hyperglycaemia induction with alloxan was associated with significant ($p<0.001$) elevation in the serum triglyceride and total cholesterol concentrations (Table 2). Also, oral treatment with 50 mgkg^{-1} of MLE_c caused the most significant ($p<0.001$) reductions in the serum triglyceride and total cholesterol levels compared to those induced by 20 mgkg^{-1} metformin and 50 mgkg^{-1} MLE_b.

Table 2: Effect of *Morinda lucida* leaf fractions on FBG, TG and TC in normal and alloxan-induced hyperglycemic rats

Treatment groups	Pre-inductionFBG (mg dL^{-1})	Post-induction FBG (mg dL^{-1}) on Day 1	Day 8	Day 15	TG (mg dL^{-1})	TC (mgdL^{-1})
I	58.7±2.7	59.3±1.7	58.7±2.1	58.3±3.0	93.7±5.4	80.8±5.1
II	59.3±2.9	250.0±7.3[c]	259.3±8.2[c]	276.8±12.2[c]	204.8±12.2[c]	179.0±19.3[c]
III	59.7±3.1	265.7±14.0[c]	151.2±14.9[e]	115.2±9.2[a,f]	116.8±13.5[e]	105.8±13.5[e]
IV	59.5±3.5	254.3±5.8[c]	260.3±11.0[c]	252.2±11.9[c]	182.5±6.8[d]	148.7±8.0[b,d]
V	59.7±2.7	252.2±2.6[c]	140.5±8.0[e]	107.5±9.5[a,f]	106.8±18.7[f]	86.2±16.2[f]
VI	58.8±2.6	250.8±6.3[c]	207.0±10.7[d]	153.2±14.6[b,e]	141.8±13.2[e]	128.8±8.4[a,e]
VII	60.17±2.50	253.5±10.5[c]	237.7±9.1[c]	233.2±6.8[c]	173.5±11.8[d]	148.2±8.2[b,d]

[a, b] and [c] represent significant increases at $p<0.05$, $p<0.01$ and $p<0.001$, respectively, when compared to pre-induction FBG values and Group I values while [d, e] and [f] represent significant decreases at $p<0.05$, $p<0.01$ and $p<0.001$, respectively, when compared to Group II: Values on days, 1 8 and 15, Group I: 10 mL kg^{-1} of 5% Tween-20 in distilled water+ normal rats, Group II: 10 mL kg^{-1} of 5% Tween-20 in distilled water+alloxan hyperglycemic rats, Group III: 20 mg kg^{-1} of metformin in 5% Tween-20 in distilled water+alloxan hyperglycemic rats, Group IV : Single daily oral dose of 50 mg kg^{-1} of diethyl ether fraction (MLE_d) + alloxan hyperglycemic rats, Group V: Single daily oral dose of 50 mg kg^{-1} of chloroform fraction (MLE_c) +alloxan hyperglycemic rats, Group VI: Single daily oral dose of 50 mg kg^{-1} of butanol fraction (MLE_b) +alloxan hyperglycemic rats, Group VII : Single daily oral dose of 50 mg kg^{-1} of the "extract residue" (MLE_r) +alloxan hyperglycemic rats

Preliminary phytochemical analysis of MLE_b and MLE_c: Preliminary phytochemical analysis of the two biologically active solvent fractions of MLE (MLE_b and MLE_c) showed the presence of flavonoids, alkaloids and anthraquinones only in MLE_c and flavonoids, alkaloids, tannins and saponin in MLE_b.

DISCUSSION

In the present study, diethyl ether, chloroform, butanol and "extract residue" fractions of the crude ethanolic extract of *Morinda lucida* fresh leaves were evaluated for their antihyperglycaemic and antihyperlipidaemic profile in normal and alloxan-induced hyperglycemia models. Alloxan, like its counterpart, streptozotocin has been frequently used to induce either type 1 or type 2 diabetes[18]. Alloxan selectively accumulates in the pancreaticβ-cells via the GLUT2 glucose transporter, where it targets mitochondrial DNA leading to impairment of mitochondrial signaling function and consequent induction of β-cell apoptosis through several mechanisms including caspases activation and Reactive Oxygen Species (ROS) production[19,20]. The ROS mediates the cytotoxic action with the increase in cytosolic Ca^{2+} concentrations, leading to rapid β-cells destruction which results in hypoinsulinaemia and eventual hyperglycaemia[21]. In this study, alloxan-induced DM was most effectively controlled with repeated oral treatment with 50 mg kg^{-1} of MLE_c, as measured by significant lowering of the FBG, serum triglyceride and total cholesterol levels. These observations suggest that the phytochemicals responsible for the antihyperglycaemic activity of ethanolic crude extract of *Morinda* leaf are mostly partitioned into chloroform. Although, the possible antihyperglycaemic mechanism(s) of this fraction was not investigated in the present study, hyperinsulinaemic mechanism is most unlikely since literature has it that for overt DM to become established up to 70% pancreatic β-cells must have been destroyed[21,22]. Thus, it is most likely that effective glycaemic control was achieved via increased action on cellular glucose uptake or intestinal glucose uptake inhibition. Similarly, alloxan is known to induce hyperlipidaemia in diabetic animals via increased mobilization of free fatty acids from the peripheral fat deposits[23]. Since MLE_c significantly lowered the serum triglyceride and total cholesterol levels in the treated rats, it may either be inhibiting mobilization of free fatty acids from the peripheral deposits or increasing their deposition into the peripheral tissues. Another significant finding of this study is the results of the phytochemical analysis of MLE_b and MLE_c. Phytochemical analysis of MLE_b showed the presence of flavonoids, alkaloids, tannin and saponin while MLE_c showed the presence of flavonoids, alkaloids and anthraquinones. Previous independent studies have shown the crude *Morinda lucida* leaf extract to be rich in flavonoids, alkaloids, tannins and saponin[12,24]. Also, oruwacin and anthraquinones[25], anthraquinones and anthraquinols identified as oruwal and oruwalol[26], morindin (glycoside) and tannins have also been isolated from *Morinda lucida* leaves. Literature has equally reported the biological activities of alkaloids and flavonoids to include hypoglycaemia, hypolipidaemia, hypoazotaemia, hypotension among other biological effects[27]. Thus, the observed antihyperglycaemic and antihyperlipidaemic effect observed in this study could be attributed to the presence of flavonoids, alkaloids which were common denominating phytochemicals in both tested solvent fraction (MLE_b and MLE_c). Although the quantitative analysis of the phytocomponents in MLE_b and MLE_c was not undertaken in the present study, it is however, plausible that the concentrations of flavonoid and alkaloids could be higher in MLE_c than in MLE_b in view of the fact that MLE_c exhibited more significant antihyperglycaemic and antihyperlipidaemic effects than MLE_b.

CONCLUSION

Overall, results of the present study showed the chloroform fraction of MLE (MLE_c) to be the most effective fraction in glucose and lipids homeostasis in both normal and alloxan-induced diabetic rats. Further studies geared towards isolating and characterizing the antihyperglycaemic and antihyperlipidaemic compounds in MLE_c will be required in the nearest future.

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