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Antidiabetic Effects of Aqueous Extracts of *Bannufera Mangii* Roots and *Mannufera Jangii* Leaves on Alloxan Induced Diabetic Rats

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ABSTRACT

Diabetes is one of the leading causes of death world over, with no known scientifically proved cure so far. The present study evaluated the serum glucose lowering potentials of aqueous extracts of *Bannufera mangii* roots and *Mannufera jangii* leaves on alloxan induced diabetic rats.

The most potent extract was further studied for its effects on serum insulin.

Administration of 80 mg/kg of alloxan monohydrate have significantly increased blood glucose level and affect the serum insulin and lipid profile as well as oxidative stress makers.

Treatments of diabetic rats with 300mg/kg body weight of the two extracts and conventional antidiabetic drug showed significant reduction in blood glucose levels by 35.2%, 59.2% and 67.0% for *B. mangii, M. jangii* and metformin respectively.

The remarkable antihyperglycaemic, antihyperlipidemic, antioxidants and non-toxic (at 3000 mg/kg) potentials exhibited by *M. jangii*, validates its traditional use as an antidiabetic plant. Therefore, the plant has demonstrated a potential as another source of alternative therapeutic agent for the treatment of diabetes mellitus.

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycaemia, resulting from defects in insulin secretion, insulin action or both [1]. The complications of chronic hyperglycaemia in diabetes is associated with long term damage, dysfunction and failure of various organs especially eyes, kidney nerves, heart and blood vessels. It has also been associated with the resurgence of tuberculosis, and the prevalence of end stage kidney disease, erectile dysfunction, stroke and has also led to higher numbers and majority of cases of lower extremity amputations (LEA) in Nigeria [2]. The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), rising to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. The prevalence is higher in urban (10.8%) than rural (7.2%) areas, and in high-income (10.4%) than low-income countries (4.0%) [3]. In Nigeria prevalence of DM has continued to increase despite a great deal or research and resources [4].

Traditional plant treatment have been used throughout the world to treat diabetes [5]. WHO estimated that 80% of the population of some Asian and African countries presently use herbal medicine for some aspect of primary healthcare. Herbal medicines are seen by some as treatment to be preferred to pure synthetic compounds which have been industrially produced [6]. These medicinal plants are effective in controlling plasma glucose levels with minimal side effects and are commonly used in developing countries as an alternative therapy for the treatment of diabetes mellitus [6]. The use of traditional medicines in this regard among the Hausa Fulani tribes of North Western Nigeria has been reported by Abubakar *et al.*, [7]. Shinkafi *et al.*, [8] reported over 50 fifty different medicinal plants used in the treatment of diabetes by the Hausa Fulani of Sokoto, North Western Nigeria. A defined alternative treatment for the menace of diabetes mellitus therefore, becomes necessary. Ignorance and poverty have been identified as basic contributors to the problems of diabetic care, presentation to and delay at the traditional healers, compound the problems of appropriate diabetes management.

METHODOLOGY

All chemicals and reagents used for the purpose of this research were of analytical grade. Standard equipment/instruments were also used for this research.

Plant Collection and Identification

Roots of Bannu and leaves of Mannu were collected from Bulasa forest reserve Birnin Kebbi, Kebbi State Nigeria. The plants were Botanically authenticated by Abdulazeez Salihu, a Botanist at the Herbarium unit,Department of Biological sciences, Usmanu Danfodiyo University Sokoto, Nigeria and voucher specimens (UDUS/ANS/0247 and UDUS/ANS/0205) were deposited.

Extract Preparation

The plant materials were air dried in the shade and crushed into small pieces using mortar and pestle. The pieces were then stored until required for analysis. The dried roots and leaves were independently powdered and used for extraction. One kilogram (1kg) of the dried powdered plant material was extracted with four liters of boiled distilled water using percolation for forty-eight hours (48 hrs). The extracts were filtered, and the filtrate concentrated under reduced pressure by rotary evaporation at 40ºC until therapeutic residues were obtained. The residues were freeze dried until fine powdered materials were obtained and weighed. 300mg of each extract was dissolved in distilled water before administration to experimental rats [7] with slight modifications.

Animal Procurement and Handling

Adult apparently healthy Albino rats of both sex weighing 120-250g were obtained from the animal house, Usmanu Danfodiyo University Sokoto, Nigeria. The animals were kept in well aerated laboratory cages in well ventilated rooms under supervision in the animal house with free access to feed (Vital Agricultural feed Nigeria LTD) and water *ad libitum*, and were kept in the same environment for two weeks to acclimatize.

Estimation of Blood Glucose

Blood was estimated using glucometer (Accu-chek ® Active system 05144469) for Baseline glucose levels, as well as all glucose estimations in all experimental animals. Blood samples were collected from the tip of the rats tails (Ashok *et al.*, 2007).

Principle

The Roche advantage method for measuring blood glucose is based on enzyme technology and micro electronics. When whole blood is applied to the strip, electrons are produced by the conversion of glucose to gluconolactone by the enzyme glucose dehydrogenase and the coenzyme PQQ. The electrons are transferred through a mediator, potassium ferricyanide. The complete reaction creates a harmless electrical current that the meter interprets as blood glucose concentration. Resulting current of electrons is proportional to the glucose level in the blood (Roche, 2012).

Estimation of Insulin level

Insulin was estimated by SPI bio rat insulin enzyme immunoassay kit according to Grassi and Pradelles (1991).

Principle

The test is based on the competition between unlabelled rat insulin and acetylcholinesterase linked to rat insulin (tracer) for limited specific guinea-pig anti-rat insulin antiserum sites. The complex guinea-pig antiserum-rat insulin binds to the goat anti-guinea-pig antibody that is attached to the well. The plate is then washed and Ellman's reagent (enzymatic substrate for AChE and chromogen) is added to the wells and the AChE tracer acts on the Ellman's reagent to form a yellow compound which is determined spectrophotometrically at 405nm. The intensity of the colour is proportional to the amount of tracer bound to the well and is inversely proportional to the amount of free rat insulin present in the well during the immunological incubation.

Procedure

Reaction wells were labelled Blank, sample and standard, into the wells,50µlof buffer, serum and standardwere added respectively. This was followed by addition of 50µlof tracer and finally 50µl of antiserum.The plate was covered, incubated at 4ºC for 20 hours, then washed 5 times. To each well, 200µl of Ellman's reagent was dispensed and incubated again in the dark, at room temperature with the aid of orbital shaker. The plate was read at 405nm using Rayto (RT 6000C) plate reader.

Estimation of Insulin Resistance Index

Insulin resistance index would be calculated by Homeostasis Model Assessment- Insulin Resistance (HOMA-IR) as described by Matthews *et al*. (1985). The equation

$$HOMA - IR = \frac{Fastingglucose\ (mmol/l) \times Fastinginsulin(\mu U/ml)}{22.5}$$

RESULTS

Baseline Serum Glucose, Insulin and Insulin Resistance Index of Rats before Induction and Treatment

Baseline serum Glucose, Insulin and insulin Resistance index of experimental Rats before induction and treatment is given in Table 1.

Table 1. Baseline Serum Glucose, Insulin and Insulin Resistance Index

Parameters	Groups							
	I	II	III	IV	V	VI	VII	IIX
Glucose(mg/dl)	108.9±3.93	88.2±4.24	128.7±1.014	95.94±1.014	103.3±4.01	92.34±4.01	97.38±7.42	86.04±3.0
Insulin(µU/L)	6.257±1.231	5.767±0.429	4.710±1.180	6.498±0.820	4.992±1.227	4.495±1.227	9.657±2.284	4.624±0.25
Insulin Index	1.792±0.368	1.267±0.165	1.460±0.230	1.468±0.169	1.272±0.195	0.980±0.284	2.302±0.755	0.983±0.09

LEGEND: Group I-normal control, Group IIInduced but not treated , Group III- induced but treated with Metformin 100mg/kg),Group IV- not Induced but treated with *B. mangii* (300mg/kg)Group V- not induced but treated with 300mg/kg *M.jangii*, Group VI- Induced and treated with *M. jangii* (300mg/kg), Group VII- Induced and treated with *B. mangii* (300mg/kg),Group IIX- Induced and treated with300mg/kg 1:1 mixture of *M. jangii*and B. mangii

Serum Glucose Levels after Induction and Treatment with 300mg/kg Aqueous Leaf Extracts of *B. mangii* and *M. jangii*

Results of the effect of three weeks treatment of diabetic induced rats with 300mg/kg aqueous extracts of *B. mangii* and *M. jangii* are presented in Table 2. Results of fasting glucose levels presented in Table 13.0.Showed significant rise in fasting (P< 0.05) glucose in the Alloxan induced rats when compared to the uninduced groups before commencement of treatment with the extracts. Results of the effects of *B. mangii* and *M. jangii* aqueous extracts on blood glucose levels showed that both extracts independently decreased blood glucose levels. Rats treated with *M. jangii* (Group VI) showed extremely significant decrease in blood glucose levels (P< 0.0001) within the first week similar to decrease in blood glucose in groups treated with Metformin (100mg/kg). *B. mangii* (Group VII) showed very significant decrease in blood glucose (P< 0.001) after three weeks of treatment. Rats treated with 1:1 mixture of the two extracts also showed significant decrease (P< 0.001) after three weeks of treatment. A gradual reduction in blood glucose level that was not significant was observed in the uninduced but treated groups.

Table 2: Serum Glucose Levels After Induction and Treatment with 300mg/kg Aqueous Extracts of *B. mangii* and *M. jangii*

Duration of Treatment (Weeks)	Concentration (mg/dl) Groups							
	I	II	III	IV	V	VI	VII	IIX
0	113.46±5.21	242.43±21.77	204.36±5.066	118.67±14.10	118.46±14.99	211.27±25.84	210.67±16.1	206.07±17.04
1	103.33±9.87	240.00±33.45	179.33±22.37	108.67±15.14	108.66±15.14	112.67±6.11	152.33±17.95	178.33±19.86
2	101.33±8.20	190.33±19.14	123.33±16.26	102.33±6.51	102.33±6.51	95.67±6.51	145.67±8.24	185.66±6.56
3	105.00±9.53	194.00±35.76	67.67±10.39	99.33±4.62	99.33±4.62	86.00±6.93	136.00±11.36	153.50±7.78

LEGEND: Group I-normal control, Group IIInduced but not treated , Group III- induced but treated with Metformin 100mg/kg),Group IV- not Induced but treated with *B. mangii* (300mg/kg) Group V- not induced but treated with 300mg/kg *M.jangii*, Group VI- Induced and treated with *M. jangii* (300mg/kg), Group VII- Induced and treated with *B. mangii* (300mg/kg),Group IIX- Induced and treated with300mg/kg 1:1 mixture of *M. jangii*and *B. mangii*

Effect of Three Weeks Treatment of Diabetic Induced Rats with M. Jangii on Blood Glucose, Insulin and Insulin Resistance Index

Results of the effects of *M. jangii* aqueous extract on blood glucose, serum insulin and insulin resistance index is presented in table 3. The results indicated a significant decrease in blood glucose levels (P<0.001) between the treated and untreated groups.Decrease in blood glucose observed between control and treated groups was not significant (P>0.05). The results also indicated an increase in

insulin levels (P.<0.01) and insulin resistance index(P<0.01) between the *M. jangii* treated groups and the diabetic untreated group. No significant difference (P>0.05) was observed in insulin levels between the control and treated groups. However, no significant change was observed in the architecture of the islet cells when pancreatic tissue was viewed under light microscopy as shown in the Photomicrographs in plate 5.

Table 3. Effect of *M. jangii* Aqueous Extract on blood Glucose, Insulin and Insulin Resistance index.

Parameter	Groups			
	I	II	III	IV
Glucose(mg/dl)	104.25±7.32[a]	205.20±6.52[c]	68.10±5.85[b]	82.50±9.0
Insulin(µU/ml)	2.13±0.30[a]	0.58±0.23[b]	1.71±0.48[a]	1.82±0.24
Insulin Index	0.55±0.09[a]	0.27±0.08[b]	0.29±0.11[b]	0.37±0.02

LEGEND: Group I- Normal Control, Group II- Diabetic induced untreated, Group III-Diabetic Induced and treated with 100mg/kg Metformin, GroupIV-Diabetic induced treated with 300mg/kg *M. jangii* Groups with the same superscript are not significantly different (P>0.05), Groups with different superscript are significantly different (P<0.05) using ANOVA and Turkey comparism, Instat version 3S.

DISCUSSION

Persistent hypoglycemia is a major contributor to metabolic alterations that lead to the pathogenesis of diabetic complications. This makes reducing blood sugar level a classical target in all forms of diabetes [10]. *In vivo* sugar lowering effect of putative hypoglycemic plant is reported to be a premise to infer their potential efficacy [11]. A number of experimental and clinical studies have shown the efficacy of various herbs in lowering blood glucose in diabetes through various mechanisms that may or may not affect insulin release, increased insulin sensitivity or the insulin like activity of the plant extracts. In the present study, *B. mangii* root extract was observed to have reduced blood glucose significantly (P< 0.01). Reduction in blood glucose in the group administered with *M. jangii* was extremely significant (P<0.001) similar to what was observed by Metformin. 59.5% decreased in blood glucose in this study is similar to the findings of Zhu *et al*. [12] who reported 50.50 reduction in blood glucose in diabetic rats treated with *M. jangii* leaves extract in Bangladash. Several studies have inferred that the antidiabetic activity of medicinal plants is linked to their phytoconstituents. *M. jangii* is rich in flavonoids, saponins and steroids. Flavonoids are known to exhibit their antidiabetic activity by suppressing glucose levels, increasing hepatic glucokinase activity, probably by enhancing insulin release from islet cells [13]. Mishra *et al.,* [11] and Goyal s*et al*., [10] reported that quacetein, a flavonoid in *M. jangii* regenerates pancreatic islet cells, possibly increasing insulin release and also enhances Ca^{2+} uptake from isolated islet cells which suggests a place for flavonoids in non-insulin dependent diabetes. Saponins have been reported to stimulate release of insulin and block formation of glucose in the blood stream. Tannins are also reported to have antioxidant activity with antidiabetic property [14].

Insulin secretion increased significantly in the *M. jangii* treated group when compared to the diabetic untreated group. Stimulation of insulin release, insulin-like action of the phytochemicals in the used extracts and the possible regeneration of β-cells by the medicinal plants could be responsible for the increased insulin levels observed after treatment with *M. jangii* aqueous extracts [15]. Repaire of β-cells structure and function which inturn increases insulin production and release is facilitated by intinsic GPx production that decreases oxidative stress [14].

CONCLUSION

M. jangii aqueous leaves extracts in this study has shown to be safe at a dose of 3000mg/Kg body weight in rats, effective in reducing blood glucose level by increasing insulin levels, anti-dyslipidemic and having good antioxidant properties. These therefore confirms its traditional use as an antidiabetic plant.

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