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ANTIDIABETIC AND HYPOLIPIDEMIC EFFECTS OF *MORINGA OLEIFERA* ETHANOLIC LEAF EXTRACT ON EXPERIMENTALLY-INDUCED DIABETES IN WISTAR RATS

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ABSTRACT

This study investigated the effect of *Moringa oleifera* in diabetic Wistar rats. The effect of methanol extract of *M. oleifera* at doses of 200, 400 and 800mg/kg body weight was compared to non-diabetic rats, diabetic control rats and diabetic rats treated with rosiglitazone (2mg/kg b.w.). Glucose levels were monitored within 24 hours and on day 15 of treatment. Blood samples were collected on day 16 of treatment to determine serum lipid profile, proteins and its fractions, non-protein metabolites and liver enzymes. On day 15 of treatment, glucose levels of diabetic control rats decreased by 13.33%, rats treated with the doses of the extract decreased by 52.37%, 53.62% and 53.93%, and rats treated with rosiglitazone, 58.8%. Weight gain was consistent in all groups of rats except in diabetic control with significant weight loss (-37.12g). The lipid profile showed rats treated with the extract had higher triglyceride levels, but significantly ($p<0.05$) lower total cholesterols with lower levels of LDL-C and VLDL-C, and higher HDL-C. Total proteins were increased with significant ($p<0.05$) increases in the albumin fraction. Liver enzymes, urea and creatinine levels were also reduced in the extract treated rats. In conclusion, the extract of the leaves of *Moringa oleifera* reduced blood glucose levels, corrected dyslipidemias of the diabetic rats, and protected the liver from alloxan-induced injury.

Keywords: Diabetes, *Moringa oleifera*, Wistar rat

INTRODUCTION

Moringa oleifera, the only genus in the plant family Moringaceae, is a plant grown in several tropical and sub-tropical parts of the world for its nutritional and medicinal value in both humans and animals (Fahey, 2005; Anwar *et al.*, 2007). It was originally a native of sub-Himalayan regions of North-West India, but now indigenous to several countries in Africa, Asia, South America, Philippines and the Caribbean Islands (Morton, 1991; Anwar and Bhanger, 2003; Anwar *et al.*, 2005). *M. oleifera* is a rapidly growing and draught resistant slender tree of approximately 10m high, which does not tolerate cold weather conditions (Anwar *et al.*, 2007). The leaves are very palatable and a rich source of vitamins A, B_6 and C, magnesium, calcium, potassium and proteins (Gopalan *et al.*, 1989; Anwar *et al.*, 2007; Peter, 2008; Rol-

off *et al.*, 2009). The flowers and young seed pods are also edible, while cooking oil called ben oil can be pressed from mature seeds and the seeds can also be eaten roasted (Schneider, 2001).

The seeds of *M. oleifera* are traditionally used in several developing countries such as Sudan and Malavi for purification and softening of water. This has been scientifically proven by many workers (Kalogo *et al.*, 2000; Broin *et al.*, 2002; Sharma *et al.*, 2006). In the Philippines, it is used as a galactogogue (Siddhuraju and Becker, 2003; Anwar *et al.*, 2007). All parts of the plant; the leaves, flowers, seeds and oil, bark, sap and roots, have folkloric uses in traditional medicine of several countries in Asia, Africa and South America. The antibacterial, antiviral and anti-hypertensive activity of this plant has been scientifically proven (Faizi *et al.*, 1998; Dangi *et al*., 2003; Nikkon *et al.*, 2003; Ndong *et al.*, 2007; Peixoto *et al.*, 2011). Several researchers have also reported the anti-inflammatory, antioxidant and anti-cancer activity of *M. oleifera* (Murakami *et al.*, 1998; Lalas and Tsaknis, 2002; Bharali *et al.*, 2003; Siddhuraju and Becker, 2003; Mahajan *et al.*, 2007).

However, there is dearth of information on the effect of this plant on diabetes and its management, one of its traditional indications. Also, the biochemical changes that may accompany the consumption of *M. oleifera* extract for protracted period of up to 15 days is yet to be reported. Related information is limited to its hypocholesterolemic effect in high-fat diet fed rats and hypercholesterolemic rabbits (Ghasi *et al*., 2000; Mehta *et al.*, 2003). This experiment was aimed at studying the effect of *Moringa oleifera* in diabetic rats and the serum biochemical changes that accompanied management of diabetes with *Moringa oleifera* extract.

MATERIALS AND METHODS

Fresh leaves of *Moringa oleifera* were harvested from the Federal University of Agriculture, Abeokuta farm. The plants were authenticated by an expert at the Department of Forestry and Wildlife, Federal University of Agriculture, Abeokuta. The leaves were air dried at room temperature and pulverized after drying. Cold extraction using methanol as solvent was carried out. The extract was filtered by draining the filtrate through cotton wool and filter paper. The filtrate was clarified by filtration through celite on water pump and were then concentrated *in vacuo* using a rotary evaporator (Rotavapor R-210, Switzerland).

Experimental animals

Forty eight adult male Wistar rats weighing between 150g and 250g were obtained from the Experimental Animal Unit of University of Agriculture, Abeokuta and managed under standard environmental conditions of 12 hr light: dark. They were fed with pelletized rat ration and allowed access to water *ad libitum*. The rats used in this study were confirmed to be normoglycaemic before they were included in the study. The rats were randomly and equally divided into six groups of 8 rats each.

Experimental protocol

Rats in group I served as the normal control rats and diabetes was not induced in these rats. Rats in groups II – VI were fasted overnight and diabetes was induced after this period by intraperitoneal injection of alloxan monohydrate at a dose of 100mg/kg body weight. Fasting blood glucose level was estimated at the time of induction of diabetes and 2 hours post prandial with the use a touch glucometer (Lifescan, Johnson and

Johnson California). Glucose levels were monitored 24hrly to ensure the hyperglycemic state of glucose levels of ≥190mg/dl was attained (data not shown). Rats with glucose levels lower than 190mg/dl 6 days post-injection of alloxan monohydrate were excluded from the study at this point.

Administration of physiological saline, *M. oleifera* extract or rosiglitazone was commenced on the 7th day post-injection of alloxan, and this was noted as day 1 of treatment. Rats in group II were administered orally with 0.9% physiological saline (10mg/kg), the vehicle used and these served as diabetic control rats for the study. Rats in groups III, IV and V were administered orally with the leaf extract of *Moringa oleifera* at doses of 200mg, 400mg and 800mg/kg body weight respectively. Group VI rats were administered orally with a standard antidiabetic drug, Rosiglitazone maleate® (Glaxo Welcome, S.A., Aranda de Duero, Spain) at a dose of 2mg/kg b.w. Treatment with physiological saline, extract or standard drug was continued for 15 days consecutively. On day 1 of treatment, blood glucose levels were monitored every 6hours (0 hour, 6hours, 12 hours, 18 hours and 24hours) and also on day 15 of treatment.

Blood collection and analysis

On day 16, the rats were first weighed and then anesthetized with ether. About 3ml of blood was collected from the retro-orbital sinus vein into lithium heparinized bottles. This was centrifuged at 2,000rpm for 10minutes and serum was harvested for biochemical analysis. Serum biochemical parameters assayed included lipid profile [total cholesterol (TC), high density lipoprotein cholesterol (HDL–C), low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and triglycerides (TG) levels], total protein and its constituent fractions; albumin and globulin, non-protein metabolites (urea and creatinine), serum enzymes (alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP).

RESULTS

Glucose levels and weight of rats

Blood glucose levels decreased in rats administered with the methanol leaf extract of *Moringa oleifera* with significant ($p<0.05$) decreases observed from 18 hours post administration of graded doses of the extract (184.05±2.30, 188.25±3.46 and 178.27±4.34 mg/dl) compared with their 0 hr observations. Significant ($p<0.05$) reduction in the glucose levels was also observed in rats administered with rosiglitazone at the 18 hour observation (195.34±2.25 mg/dl). On the other hand, diabetic rats administered with the vehicle only recorded a steady increase in their blood glucose levels through the 24 hour post-treatment observation (209.20±3.79 mg/dl) (Table 1).

The blood glucose levels of the rats treated with the extract and rosiglitazone had returned to normal levels by day 15, but the diabetic untreated rats had maintained high blood glucose levels (169.12±2.25 mg/dl). A significant reduction in the blood glucose levels was observed between the 0 hr and day 15 observations with 52.37%, 53.62% and 53.93% decrease in blood glucose of rats treated with the extract, 58.80% decrease in rats treated with rosiglitazone, but 13.33% decreased in untreated rats.

A steady weight gain was observed in the normal control rats (8.51±1.14 g) and rats administered with the extract dose at 200 and 400mg/kg (7.97±0.76 and 8.49±0.25 g). A significant ($p<0.05$) increase in the weight gain was observed for rats administered with

800mg/kg dose of the extract (10.95±0.19 g) and rosiglitazone (13.94±0.97 g) compared with the normal control rats. However, the diabetic control rats lost weight (-37.12±2.19 g) when their weight on day 15 (137.88±5.42 g) was compared to their mean weight on day 0 (175.00±2.13) (Table 2).

Lipid profile

The lipid profile showed that serum triglyceride levels in all the diabetic rats increased except in rats administered with the extract at a dose of 800 mg/kg. Significant increases were observed in diabetic control rats treated with the vehicle only (120.14±4.23 mg/dl) and those administered with rosiglitazone (102.13±4.63 mg/dl). Total cholesterol and low density lipoprotein levels were significantly ($p<0.05$) reduced in rats treated with the graded doses of the extract, and high density lipoprotein levels increased in these rats, particularly in rats administered with 400 mg/kg dose of the extract (54.88±4.70 mg/dl) compared to the control group rats (Table 3).

Serum Proteins, enzymes and non-protein metabolites

Serum protein levels increased in rats administered with the extracts at dose of 200 mg/kg (6.11±0.57 mg/dl) 400 mg/kg (6.00±0.34 mg/dl) and 800 mg/kg (5.67±0.37 mg/dl), but reduced in rats treated with rosiglitazone (5.53±0.36 mg/dl) and diabetic control rats (4.33±0.36 mg/dl) compared with normal control rats (5.60±0.24 mg/dl). Albumen fraction of the protein increased, while globulin fraction reduced in rats administered with the extract. All the liver enzymes increased in diabetic untreated rats, but ALP and AST levels reduced in rats administered with the extracts or rosiglitazone, while ALT levels were slightly elevated. Blood urea and creatinine levels also reduced in rats treated with the extract at doses of 200 mg/kg (8.25±0.98 mg/dl and 0.17±0.02 mg/dl), 400 mg/kg (8.00±0.71 mg/dl and 0.14±0.02 mg/dl), and 800 mg/kg (8.50±0.72 mg/dl and 0.14±0.01 mg/dl), and rosiglitazone treated rats (8.13±0.83 mg/dl and 0.13±0.03), but were elevated in the diabetic control rats (14.00±1.20 mg/dl and 0.31±0.04 mg/dl) compared to the normal control rats (8.88±0.90 mg/dl and 0.24±0.03 mg/dl) (Table 4).

Table 1: Effect of *Moringa oleifera* leaf extract on blood glucose levels (mg/dl) of diabetic rats at 0 hr, 6 hr, 12 hr, 18 hr, 24 hr and day 15 post administration of extract

	Normal Control	Diabetic Control	Extract 200mg/kg	Extract 400mg/kg	Extract 800mg/kg	Rosiglitazone 2mg/kg
0 hr	95.62±2.13	195.05±4.69	197.61±2.49	200.5±4.12	202.7±3.90	210.28±3.17
6 hr	98.78±2.78	195.99±4.19	194.33±3.12	199.4±6.89	195.91±5.12	208.00±4.76
12 hr	96.98±1.90	200.40±4.42	191.46±5.10	194.4±3.98	186.98±4.13*	202.73±3.15
18 hr	93.67±2.16	206.30±2.39	184.05±2.30*	188.25±3.46*	178.27±4.34*	195.34±2.25
24 hr	94.58±2.32	209.20±3.79	177.85±1.33*	179.43±4.35*	172.32±2.43*	188.91±2.23*
Day 15	97.38±3.11	169.12±2.25*	94.13±4.27*	93.00±3.81*	93.50±4.538*	86.63±4.12*
↓ %	-0.02%*	13.33%*	52.37%*	53.62%*	53.93%*	58.80%*

Asterisks (*) indicates significant ($p<0.05$) difference compared to normal control rats. ↓ – Percentage decrease in glucose level on day 15.

Table 2: Effect of methanol leaf extract of *Moringa oleifera* on body weight of rats before induction of diabetes and day 15 post administration of extract

Group	Day 0 (gm)	Day 15 (gm)	Weight gain (gm)
Norm Control	201.24±1.23	209.75±2.17	8.51
Diab control	175.00±2.13	137.88±5.42	-37.12*
Ext 200mg/kg	150.53±1.54	158.50±1.25	7.97
Ext 400mg/kg	151.01±2.35	159.50±1.15	8.49
Ext 800mg/kg	150.67±2.15	161.62±2.34	10.95*
Rosigl 2mg/kg	151.92±2.34	165.86±2.14	13.94*

Norm – Normal, Diab – Diabetic, Ext- *Moringa oleifera* extract, Rosigl – Rosiglitazone. Asterisks (*) indicates significant ($p<0.05$) difference compared to normal control rats

Table 3: Effect of methanol extract of *Moringa oleifera* leaf on lipid profile of diabetic rats

Group	TG (mg/dl)	TC (mg/dl)	HDL-C (mg/dl)	LDL-C (mg/dl)	VLDL-C (mg/dl)
Norm Control	87.88±7.10	59.00±5.10	42.50±3.09	35.00±5.46	10.38±1.21
Diab control	120.14±4.23*	63.29±5.17	35.86±2.96*	56.71±2.14*	12.57±1.04
Ext 200mg/kg	96.62±4.40	51.50±3.85*	46.13±4.54	28.25±3.30ab*	10.29±0.77
Ext 400mg/kg	93.13±4.94	52.50±4.36*	54.88±4.70*	26.63±4.89*	10.49±0.88
Ext 800mg/kg	85.75±2.20	46.75±5.15*	46.75±5.15	23.88±6.25*	9.10±0.42
Rosigl 2mg/kg	102.13±4.63*	55.63±3.95	40.63±2.89	32.63±2.98	11.86±0.67

Norm – Normal, Diab – Diabetic, Ext- *Moringa oleifera* extract, Rosigl – Rosiglitazone, Trigly – Triglycerides, TC – Total Cholesterol, HDL-C - High density lipoprotein cholesterol, LDL-C - Low density lipoprotein cholesterol, VLDL-C - Very low Density lipoprotein cholesterol. Asterisks (*) indicates significant ($p<0.05$) difference compared to normal control rats

Table 4: Effect of *Moringa oleifera* leaf extract on serum proteins, liver enzymes

	Normal Control	Diabetes Control	Extract 200mg/kg	Extract 400mg/kg	Extract 800mg/kg	Rosiglitazone 2mg/kg
TP (mg/dl)	5.60±0.24	4.33±0.36	6.11±0.57*	6.00±0.34*	5.67±0.37	5.53±0.36
Alb(mg/dl)	3.36±0.23	2.85±0.31	4.40±0.32*	4.00±0.36*	3.75±0.35	3.38±0.31
Glob(mg/dl)	2.21±0.20	1.42±0.30*	1.70±0.43	1.96±0.28	1.89±0.36	2.09±0.29
ALP (µ/l)	87.63±40.9	98.00±4.94	84.63±5.55	81.88±7.61	85.25±6.06	70.75±9.43*
ALT (µ/l)	21.88±1.48	36.29±2.91*	28.00±1.93	25.88±2.38	27.63±2.51	23.00±2.17
AST (µ/l)	53.50±2.34	61.71±4.60*	48.25±2.98	48.50±0.03	47.13±2.00	49.12±1.30
Urea (mg/dl)	8.88±0.90	14.00±1.20*	8.25±0.98	8.00±0.71	8.50±0.72	8.13±0.83
Creatinine (mg/dl)	0.24±0.03	0.31±0.04	0.17±0.02*	0.14±0.02*	0.14±0.01*	0.13±0.03*

Asterisks (*) indicate significant difference compared to normal control rats. Norm – Normal, Diab – Diabetic, Ext- *Moringa oleifera* extract, Rosigl – Rosiglitazone, TP–Total protein, Alb–Albumin, Glob–Globulin, ALP-Alkaline phosphatase, ALT-Alanine aminotransferase, AST- Aspartate aminotransferase

DISCUSSION

In this study, the leaf extract of *Moringa oleifera* significantly ($p<0.05$) reduced elevated blood glucose levels in the diabetic rats and corrected the weight loss and dyslipidaemia observed in diabetes. Elevations in glucose levels accompanied by chronic weight loss, hypercholesterolemia, hypertriglyceridemia, high levels of low density lipoprotein (LDL-C), and low levels of high density lipoprotein (HDL-C) are typical clinical findings associated with diabetes mellitus (ADA, 2007; Otamere *et al.*, 2011). Combinations of these clinical derangements increases risk for development of cardiovascular diseases and other complications of diabetes (Craig *et al.*, 1998; Barrett-Connor *et al.*, 2004). In this study, alloxan was used to induce diabetes. Alloxan is known to rapidly deplete β-cells of Islets of Langerhans by alkylation of DNA and accumulation of cytotoxic free radicals which initiates the inflammatory response, which is followed by infiltration of activated macrophages and lymphocytes. A reduction in insulin release occurs with a stable hyperglycemic state (Devasagayam *et al.*, 2012).

This study showed that the methanol extract of *Moringa oleifera* significantly ($p<0.05$) reduced the blood glucose levels of the diabetic rats within 18 hours of its administration, with gradual return to normal levels by day 15 observation. The weight gain of these rats was consistent with that of the non-diabetic rats through the course of the experiment, while the diabetic control rats showed all the clinical signs typical of diabetes. The extract also significantly ($p<0.05$) lowered the levels of total cholesterol, triglycerides, LDL-C and VLDL-C and increased the levels of HDL-C in a dose dependent pattern. The extract was more effective in reversing the dyslipidemia associated with diabetes than rosiglitazone, a known thiazolidinedione anti-diabetic agent.

One of the major focuses of management of diabetes is lowering of cardiovascular risk factors alongside maintaining normal range levels of blood glucose. Lipoproteins play an essential role in determination of these risk factors (Saba and Oridupa, 2012). Very low density lipoprotein (VLDL-C) contains the largest amount of cholesterol, followed by LDL-C (Carmena *et al.*, 2004). The leaf extract of *M. oleifera* effectively lowered these atherogenic lipoproteins and total cholesterol levels, but increased high density lipoprotein (HDL-C). HDL-C contains the least amount of cholesterol and the ratio of HDL-C to LDL-C represent the atherogenic index which can be used to determine risk of development of cardiovascular diseases, a major complication of diabetes (Khera *et al.*, 2011; Saba and Oridupa, 2012). In this study, diabetic rats treated with *M. oleifera* leaf extract showed a remarkable lowering of their risk factors and better management of the diabetes compared to rosiglitazone –treated rats.

Other damages done by alloxan importantly include liver injury (El-Demerdash *et al.*, 2005; Ragavan and Krishnakumari, 2006; Daryoush *et al.*, 2011). Most drugs including alloxan are detoxified in the liver, which makes it prone to hepatotoxicity and this may be detected by increases in serum levels of liver enzymes; alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) (Jansen and Muller, 1999). Liver enzymes of extract-treated rats in this study were significantly lower than that observed in the diabetic control rats which clearly showed that alloxan produced liver damage, but the extract reversed the damage(s) done. Other essential func-

tions of the liver such as glucose store, glycolysis and gluconeogenesis in the body were normal in the extract treated rats but hyperglycemia was observed in the diabetic control rats. This shows the storage ability of the liver in these diabetic rats had been compromised with the evidence of disruption in normal glucose storage mechanisms.

The liver is also responsible for synthesis of proteins which are vital carriers and maintain colloidal pressure in the blood (Saba *et al.*, 2010). In the study, it was observed that the extract of *M. oleifera* increased protein synthesis, particularly the albumin fraction of proteins in a manner comparable to the effect of rosiglitazone. Other non-protein metabolites such as urea, bilirubin and creatinine also are conjugated and excreted via bile from the liver. The extract lowered serum levels of metabolites which further rules out the presence of hepatic injury (Moseley, 1999; Wiwanitkit, 2001; Waikar and Bonventre, 2006), expected from alloxan toxicity. All these taken together, this plant can be said to prevent and attenuate the development of nephropathies associated with diabetic complications.

CONCLUSION

In conclusion, this study has elaborately studied the effect of the methanol extract of the leaves of *Moringa oleifera* on diabetes. It was observed that the extract of the leaves did not only lower blood glucose levels and correct the dyslipidemia associated with diabetes, but also protected the liver from injuries caused by alloxan. Thus, normal liver functions such as glucose store, protein synthesis, conjugation and excretion of metabolites were enhanced. *M. oleifera* is known to possess anti-oxidant activity (Kumar and Pari, 2003; Santos *et al.*, 2012) which we believe must have reversed the hepatotoxicity in this study. Further studies are hereby recommended to determine the mechanism of hepato-protection by *Moringa oleifera*.

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