

Treatment with Methanol Root Extract of *Mirabilis jalapa* Suppresses Postprandial Hyperglycemia and Dyslipidemia in Diabetic Rats

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ABSTRACT

The present study demonstrates the postprandial hypoglycemic effects of methanol root extract of *Mirabilis jalapa*. Alloxan induced diabetic rats were treated with 200 mg/kg body weight of the extract for 9 days at 12 hourly intervals. The experiment was designed to assess both fasting and 2 hour postprandial blood glucose levels. Lipid profile and liver function biochemical analyses were conducted using serum obtained from the experimental animals sacrificed after 10 days. The results showed a marked difference in blood glucose levels postprandial in the diabetic group treated with the extract (DTM) (11.02 ± 1.42 mmol/L) when compared with the diabetic untreated group (DU) (19.80 ± 5.37 mmol/L). Similar trends were observed for the fasting blood glucose which remained elevated in the DU group throughout the experiment but was maintained at comparable levels ($4.70 - 6.82$ mmol/L) between healthy control group (HU) and all other groups treated both with extract and standard drug metformin. Triglyceride levels of diabetic groups treated with the extract were also observed to fall within comparable limits with the HU group ($30.79 \pm 4.76 - 65.95 \pm 2.42$ mg/L). In conclusion, treatment with methanol root extract of *Mirabilis jalapa* suppresses hyperglycemia postprandial and probably promotes slow progression to dyslipidemia in experimentally induced diabetes in rats.

Keywords: *Mirabilis jalapa*, Diabetes mellitus, Hypoglycemia, metformin

INTRODUCTION

The global prevalence of diabetes has been on a steady rise since 1980s. By 2014, an estimated 422 million adults were living with the disease (WHO, 2016). This figure is projected to rise to 592 million by 2035 (Guariguata *et al.*, 2014). Recent findings indicates an alarming trend of diabetes (about 8.6% prevalence) in low-middle income countries (LMIC) most of whom live in rural areas (Hwang *et al.*, 2012; Zebatian *et al.*, 2014). According to Ogurtsova *et al.* (2017), 75% of people living with diabetes live in low and middle income countries and this region (Africa and Middle East) is projected to experience high growth in people living with diabetes (140.7% increase by 2040).

Rural populations especially in African communities depend on medicinal plants for treatment of various ailments. Preparations of medicinal plants either as extractives or as part of dietary recipe in the treatment of diabetes

mellitus are common practice in different ethnic groups in Nigeria (Ezurike and Prieto, 2014). Among other reasons such as cultural beliefs, poor accessibility, scarcity and cost of prescription drugs, overstretched health care facilities in these communities are common factors that influence the resort to alternative means for treatment. Most often than not, medicinal plants are considered the solution to this problem.

Mirabilis jalapa commonly known as “four o’clock” plant (Holdsworth, 1992) and locally as *tonaposo* in Yoruba language (Elufioye *et al.*, 2012) belongs to the family *Nyctaginaceae*. It is commonly used in Chinese folk medicine to treat diabetes (Zhou *et al.*, 2012a), constipation (Lee *et al.*, 2008), genitourinary system disorder and injuries (Weckerle *et al.*, 2009). It is also widely used to treat dysentery, diarrhea (Sadiq *et al.*, 2016) muscular pain, and abdominal colics (Walker *et al.*, 2008). Its extract has antibacterial

(Eneji *et al.*, 2011) antiviral, and antifungal functions (Vivanco *et al.*, 1999). This study examines the hypoglycemic and antidyslipidemic effects of oral administration of root extracts of the plant in alloxan induced hyperglycemic rats as compared to treatment with metformin.

MATERIALS AND METHODS

Materials

All chemicals and reagents used were as follows: absolute methanol (Sigma Aldrich, USA), test kits for lipid profile and liver function tests (Randox, Northern Ireland). The chemical alloxan monohydrate was kindly donated by the Department of Biochemistry, Usmanu Danfodiyo University, Sokoto. A glucometer (Finetest, model number IGM-0017B, Infopia Co Ltd, Korea) was used for blood glucose tests. Equipment used included rotary evaporator (Cole-parmer 115VAC), spectrophotometer (AMEX SQ2800), centrifuge (110V desktop electric) and drying chamber.

Plant Material

The whole plant *M. jalapa* was obtained from Igabi local government area, Kaduna State and identified by a botanist at the Herbarium of the Department of Biological Sciences, Ahmadu Bello University, Zaria with a specimen voucher number 2441. The roots were cut into small pieces, dried (under shade) to a constant dry weight, subsequently grinded using pestle and mortar and stored until required.

Experimental Animals

Twenty-five (25) wistar albino rats weighing between 0.14-0.22kg were used for this study. The animals were obtained from Abraham farms, Kaduna and transported to the animal house of Department of Biochemistry, Faculty of Science, Usmanu Danfodiyo University (UDU), Sokoto. In accordance with the Approval and guidelines of the ethical committee, Department of Biochemistry, UDU, Sokoto, the animals were housed in well ventilated plastic cages at 25°C and were fed with pelleted growers feed (Vital feeds, UAC foods) and water ad libitum prior to

experimentation. The rats were allowed to acclimatize for two weeks.

METHODOLOGY

Plant Material Extraction

Exactly 1 kg of ground *M. jalapa* root was macerated in 4 litres of absolute methanol and left in an air tight aspirator bottle for 72hours. The preparation was filtered first using muslin cloth then Whatmann filter paper number 1. The filtrate was concentrated with the aid of a rotary evaporator and drying cabinet set at 45°C. The concentrated extract was kept in a CaCl₂ containing desiccator.

Experimental Design

After acclimatization, the animals were grouped according to their body weights into five groups of five animals per group and were labeled as follows: Group 1: diabetic untreated rats (DU); Group 2: healthy untreated rats (HU); Group 3: diabetic rats treated with *M. jalapa* methanol extract (DTM); Group 4: diabetic rats treated with standard drug metformin (DTS); Group 5: healthy rats treated with *M. jalapa* methanol extract (HTM). Hyperglycemia was induced in the groups DU, DTM and DTS by subcutaneous administration of alloxan monohydrate at a dose of 100 mg/kg body weight per day for three days. The animals were given glucose solution to prevent hypoglycemia. The procedure was repeated until hyperglycemia was confirmed using a glucometer strip test. Animals with fasting blood glucose levels (FBS) >11.0 mmol/L were considered hyperglycemic and were included in the study.

Treatment of Experimental Animals

The experimental animals were treated with a dose of 200 mg/kg body weight administered orally at 12 hourly intervals (12am and 12pm) for 9 days. The rats were fasted for 6 hours (12 am-6 am); after which blood samples were collected from the tail for measurement of fasting blood sugar levels using a glucometer. The animals were then allowed access to feed for 2 hours and blood glucose measurement was again taken.

The animals were humanely sacrificed on day 10, blood samples collected in heparinized tubes, centrifuged at 4000rpm and serum obtained was used for assessment of lipid profile and liver function biochemical parameters according to manufacturer's procedure described in purchased test kits.

Statistical Analysis

All data were expressed as mean \pm standard deviation. Student T-test was used to compare treatments ($p < 0.05$) while differences in group treatments was analyzed by one-way analysis of variance (ANOVA) with tukey post-hoc test using instant 3 software ($p < 0.05$). Spearman's Correlation was conducted to show relationship between blood glucose and lipid profile as influenced by treatments administered.

RESULTS

Table 1 shows the Fasting Blood Glucose (FBG) levels of experimental animals treated with methanol root extracts of *M. jalapa*. The untreated diabetic group (DU) had a sustained hyperglycemia throughout the experimental period. No significant difference ($p < 0.05$) in the

blood glucose levels of the treated diabetic groups DTM and DTS when compared with the untreated diabetic group (DU) on day 1 (before treatment). By day 4 however, a significant drop in fasting blood glucose (5.46 ± 0.04 mmol/L) was observed in the DTM group which was not significantly different ($p > 0.05$) from the healthy control groups (HU and HTM). Results of 2 hour postprandial (2HPP) blood glucose show that treatment with methanol root extract of the plant significantly lowered ($p < 0.05$) blood glucose levels postprandial as treatment progressed. The values recorded for the diabetic treated group DTM (8.60 ± 2.20 mmol/L) compared with that observed for the healthy treated group (5.78 ± 0.39 mmol/L) as at day 10.

Differences in average values of FBG and 2HPP treatments on days 4 and 7 (Figure 1) were significant ($p < 0.05$) in diabetic animals (DTM) treated with the extract. The untreated diabetic group (DU) however had elevated blood sugar levels for both treatments throughout the experimental period ($p > 0.05$).

Table 1: Effect of oral administration of methanol extracts of *Mirabilis jalapa* roots on fasting blood sugar (FBS) levels of experimental animals.

Groups	FBS (mmol/L)				
	Before alloxan induction	Day 1 (No treatment)	Day 4	Day 7	Day 10
DU	5.30 \pm 0.65 ^a	15.90 \pm 2.45 ^a	15.10 \pm 1.37 ^b	15.40 \pm 4.74 ^a	10.42 \pm 2.97 ^b
HU	5.34 \pm 0.63 ^a	5.34 \pm 0.63 ^b	5.00 \pm 0.98 ^a	4.78 \pm 0.47 ^b	4.70 \pm 0.36 ^a
HTM	5.10 \pm 0.60 ^a	5.10 \pm 0.60 ^b	3.32 \pm 1.06 ^a	5.60 \pm 0.26 ^b	4.98 \pm 0.13 ^a
DTM	6.50 \pm 0.17 ^a	15.60 \pm 3.81 ^a	5.46 \pm 0.40 ^a	6.62 \pm 1.10 ^b	6.28 \pm 1.29 ^a
DTS	6.02 \pm 0.39 ^a	19.60 \pm 4.34 ^a	13.78 \pm 4.53 ^b	11.80 \pm 3.28 ^a	6.82 \pm 0.40 ^a

Data are expressed as mean \pm standard deviation, n=5. Values bearing different superscript within a particular column differ significantly ($p < 0.05$).

Key: DU: Diabetic untreated rats (diabetic control); HU: Healthy untreated rats (normal control); HTM: Healthy rats treated with *M. jalapa* extract; DTM: Diabetic treated with *M. jalapa* extract; DTS: Diabetic treated with standard drug.

Table 2: Effect of oral administration of methanolic extracts of *Mirabilis jalapa L.* roots on 2 hours post-prandial blood glucose (2HPP) of experimental rats.

Groups	2HPP(mmol/L)				
	Before alloxan induction	Day 1 (No treatment)	Day 4	Day 7	Day 10
DU	5.30±0.65	15.90±2.45 ^a	17.62±2.82 ^a	19.80±5.37 ^a	24.24±2.96 ^a
HU	5.34±0.63	5.34±0.63 ^b	6.00±0.50 ^b	5.96±0.27 ^b	5.88±0.14 ^b
HTM	5.10±0.60	5.10±0.60 ^b	6.38±1.46 ^b	6.28±0.10 ^b	5.78±0.39 ^b
DTM	6.50±0.17	15.60±3.81 ^a	12.36±1.43 ^{a,b}	11.02±1.42 ^{b,c}	8.60±2.20 ^{b,d}
DTS	6.02±0.39	19.60±4.34 ^a	18.10±4.08 ^a	14.24±3.12 ^{a,c}	12.26±3.93 ^{c,d}

Data are expressed as mean ± standard deviation, n=5. Values bearing different superscript within a particular column differ significantly (p<0.05)

Key: DU: Diabetic untreated rats (diabetic control); HU: Healthy untreated rats (normal control); HTM: Healthy rats treated with *M. jalapa* extract; DTM: Diabetic treated with *M. jalapa* extract; DTS: Diabetic treated with standard drug metformin

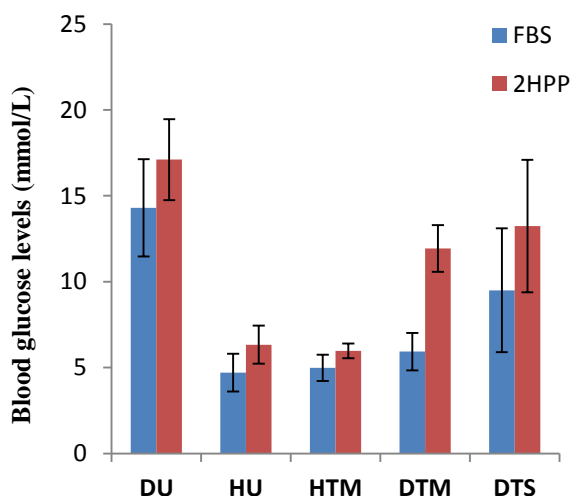


Figure 1: Comparison of FBS and 2HPP of experimental rats treated with methanol extracts of *Mirabilis jalapa L.* roots.

Key: DU: Diabetic untreated rats (diabetic control); HU: Healthy untreated rats (normal control); HTM: Healthy rats treated with *M. jalapa* extract; DTM: Diabetic treated with *M. jalapa* extract; DTS: Diabetic treated with standard drug metformin

Effects of administration of methanol root extract of the plant on indices of liver function indicated an elevation in total proteins in the diabetic untreated (DU) and all treated groups (HTM, DTM and DTS) in the range 42.36±3.10 –

43.74±2.67 g/dL when compared with the healthy control group HU (21.93±4.60 g/dL). Although albumin levels in all the groups were comparable, the AST and ALT levels in the DTM group were significantly different (p<0.05) from values observed for the DU and DTS groups (Table 3)

The lipid profile of experimental animals (Figure 2) shows the total glyceride levels (TAG) of treated groups DTM and DTS were significantly different (p<0.05) from the diabetic untreated group (DU). A similar trend was observed for the VLDL-C levels, where values observed for DTS and DTM were between 13.15±0.49 and 15.72±0.63 mg/dL as compared to 25.11±0.27 mg/dL recorded for the diabetic untreated group. A significant difference (p<0.05) was also observed for HDL-C levels between the diabetic untreated group and treated diabetic groups but HDL-C levels of treated diabetic groups were comparable to the healthy untreated groups (Figure 2). Fasting blood sugar levels (FBG) and lipid profiles were strongly correlated in the diabetic untreated group (DU) while FBG values of the methanol root extract treated group (DTM) correlated negatively with TC, TAG and VLDL-C (-0.65, -0.14 and -0.18) respectively (Table 4).

Table 3: Effect of oral administration of methanolic extract of *M. jalapa* roots on liver biochemical indices of experimental rats.

Groups	TP (g/dL)	Albumin (g/dL)	ALT (U/l)	AST (U/l)
DU	43.74±2.67 ^a	2.35±0.20 ^{ab}	43.63±3.20 ^a	149.62±4.71 ^a
HU	21.93±4.60 ^b	2.17±0.07 ^b	12.00±1.41 ^b	124.41±8.79 ^b
HTM	46.09±6.35 ^a	2.27±0.05 ^b	15.83±2.86 ^b	134.80±4.45 ^b
DTM	39.04±4.39 ^a	2.29±0.06 ^b	26.75±5.32 ^c	125.45±1.54 ^b
DTS	42.36±3.10 ^a	2.57±0.11 ^a	43.00±0.82 ^a	150.89±2.95 ^a

Data are expressed as mean ± standard deviation, n=5. Values bearing the same superscript within a particular column do not differ significantly (P>0.05) while values bearing different superscript within a particular column differ significantly (p<0.05).

Key: DU: Diabetic untreated rats (diabetic control); HU: Healthy untreated rats (normal control); HTM: Healthy rats treated with *M. jalapa* extract; DTM: Diabetic treated with *M. jalapa* extract; DTS: Diabetic treated with standard drug

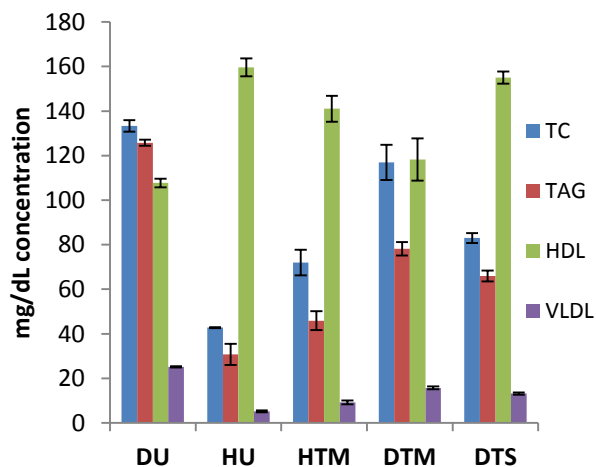


Figure 2: Lipid profile parameters of experimental animals treated with methanol root extracts of *M. jalapa*

Key: DU: Diabetic untreated rats (diabetic control); HU: Healthy untreated rats (normal control); HTM: Healthy rats treated with *M. jalapa* extract; DTM: Diabetic treated with *M. jalapa* extract; DTS: Diabetic treated with standard drug

DISCUSSION

A sustained hyperglycemic state has long been recognized as underlying cause of chronic disturbances often seen in diabetes. The mobilization of fuel molecules to compensate for

energy charge in insulin dependent cells signals failure in transport processes involved in cellular uptake of glucose. In response, cellular dynamics shift in favor of anabolic pathways leading to biosynthesis of glucose which complicates further, the blood glucose threshold. As demonstrated in this study, the methanol root extract of *M. jalapa* showed a blood glucose lowering effect (Table 1). A progression towards euglycemic state was observed following treatment with 200 mg/Kg body weight of the extract. The blood glucose lowering mechanism most probably differs from that observed for the standard drug metformin as shown in Table 2, where postprandial glucose remained elevated (12.26±3.93 mmol/L) in the diabetic group treated with metformin compared with that observed for diabetic group treated with the extract (DTM = 8.60±2.20 mmol/L) as at Day 10. Oral hypoglycemics lower blood glucose by different mechanisms (Bosenberg and Van Zyl, 2008). Metformin requires residual insulin activity but has minimal effect on postprandial glucose (Lund *et al.*, 2009). Zhou *et al.* (2012b) demonstrated ethanolic extract of *M. jalapa* roots had hypoglycemic and hypolipidemic effects in streptozotocin induced diabetes in mice and suggested further the compound trigonelline

present in the root of the plant most probably contributes to the observed effects (Zhou *et al.*, 2013). It was proposed that trigonelline influenced the GLP-1 receptor/p38 mitogen activated protein kinases signaling pathway (Zhou and Zhou, 2012b). The DPP4 and α -glucosidase inhibitory potentials of this compound in both plasma and small intestine have also been reported (Hamden *et al.*, 2013). The regulatory effects of the extract on postprandial glucose as demonstrated in this study support the insulinotropic and/or DPP4 inhibitory mechanisms, both of which are important in down regulating glucagon release. These mechanisms appear to be beneficial to diabetics with residual insulin activity which is typical of type 2 diabetes mellitus. Differences in the glucose levels postprandial (Table 2) and the observed marked difference ($p < 0.05$) between FBS and 2HPP (Figure 1) for all the groups except the diabetic untreated group (DU) suggests a mechanism of action of the extract different from that of metformin. The extract may have a stimulatory activity for insulin or enhance secretion or prolong the activity of GLP-1 peptide (Zhou *et al.*, 2012b).

One of the actions of the hormone glucagon is the stimulation of lipolysis as a carbon source in gluconeogenesis. The observed drop in TAGs of

diabetic group treated with the extract (78.18 mg/dL) when compared with untreated diabetic group (125.76 mg/dL) suggest an extract activity that promotes glucose utilization in meeting the energy needs of insulin dependent cells. FBS versus TAG and VLDL-C were observed to correlate negatively (Table 4). According to Khan *et al.* (2007), FBS exhibits a direct positive correlation with TC, TG, and VLDL but inverse HDL in diabetics. Similarly, a negative correlation of -0.14 (Table 4) between FBS and triglycerides indicates improvements in fuel molecule utilization thereby down regulating the need for lipolysis hence minimal TAGs mobilization. FBS of diabetic (DU) and healthy (HU) groups correlated positively with TGs, HDL and VLDL (Table 4). However, the correlation was stronger in the DU group due to derangements in hormonal regulatory mechanisms. Healthy animals are better able to regulate energy balance depending on metabolic needs. Although not demonstrated in this study, it is however evident that glucose uptake may play a role in the slow progression to dyslipidemia as observed in diabetic group treated with methanol root extract of *M. jalapa* suggestive of a balanced ATP : ADP ratio of individual insulin dependent cells.

Table 4: Correlation of effect oral administration of methanol extract of *M. jalapa* roots on FBS and Lipid profile of experimental animals

GROUPS	TC	TAG	HDL-C	VLDL-C
DU	0.81	0.83	0.86	0.84
HU	-0.13	0.23	0.69	0.47
HTM	0.53	0.95	-0.32	0.96
DTM	-0.65	-0.14	0.46	-0.13
DTS	-0.10	0.40	-0.02	0.31

Key: DU: Diabetic untreated rats (diabetic control); HU: Healthy untreated rats (normal control); HTM: Healthy rats treated with *M. jalapa* extract; DTM: Diabetic treated with *M. jalapa* extract; DTS: Diabetic treated with standard drug

CONCLUSION

Normo-glycemia and a generally slow progression to dyslipidemia were influenced by administration of *Mirabilis jalapa* root methanol extract to alloxan induced diabetic rats. The plant was also demonstrated to have postprandial hypoglycemic effect with a possible mechanism different from that of the standard drug metformin.

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