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β-Islet cell regeneration potential of *Mirabilis jalapa* in hyperglycemic rats

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ABSTRACT

Objective: To investigate the role of *Mirabilis jalapa* root extracts in restoration of glucose homeostasis in alloxan-induced hyperglycemic Wistar albino rats.

Methods: Experimental hyperglycemic rats were treated daily with 200 and 400 mg/kg of *Mirabilis jalapa* extracts after initial fasting for 6 h. Two-hour postprandial glucose and changes in body weight were monitored during treatment. After 14 d, the rats were sacrificed and blood was collected for biochemical assessment of serum glucose and insulin levels, lipid profile, and oxidative stress markers. Histopathological examinations of harvested pancreas were also carried out.

Results: *Mirabilis jalapa* root extracts at 200 and 400 mg/kg increased the body weight of hyperglycemic rats. Postprandial glucose levels of the extract-treated hyperglycemic groups progressively declined during treatment compared with the untreated hyperglycemic control group (P<0.05). The lipid profile indices of the untreated negative control group were significantly elevated (P<0.05), which were reversed by treatment with *Mirabilis jalapa* extracts. The remarkable increases in antioxidant enzyme activities and a significant decrease in malondialdehyde levels were observed in the hyperglycemic group treated with *Mirabilis jalapa* extracts. *Mirabilis jalapa* extracts also significantly increased serum insulin levels (P<0.05). In addition, histopathological examinations of the pancreas revealed a significant cell population within the islet nests of the extract-treated hyperglycemic groups.

Conclusions: *Mirabilis jalapa* extract can restore glucose homeostasis and show hypoglycemic and hypolipidemic effects in hyperglycemic rats. Further studies are needed to verify the active components of the plant and the underlying mechanism of action in the future.

KEYWORDS: *Mirabilis jalapa*; Glucose toxicity; Diabetes mellitus; Hyperglycemia; β-Islet cell; Antioxidant; Rat

1. Introduction

Diabetes mellitus can be devastating to the well-being of an individual. The short and long-term complications of the disease impose significant economic consequences on individuals and their families. This disease is also a leading cause of death[1] and a global estimate indicates about 462 million or 6.28% of world's population are living with type 2 diabetes mellitus (T2DM) with a projected prevalence of 5 821-9 904 per 100 000 by 2040[2,3]. According to Manne-Goehler *et al*.[4], the total unmet need for diabetes care in low and middle-income countries was 77% indicating poor performance in hospital-based treatment/management of the disease. The pathophysiology of diabetes mellitus centers on derangement of

Significance

Mirabilis jalapa is known in Chinese and African traditional medicine for its hypoglycemic effect. Several studies have demonstrated its potential as a treatment for type 2 diabetes mellitus. This paper shows that *Mirabilis jalapa* extract improves peripheral utilization of blood glucose, acts as an antioxidant, and stimulates regeneration of islet cells of the pancreas.

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glucose metabolism and other dietary energy molecules. A prevailing feature of this disease is the apparent hyperglycemic state amid a high ADP:ATP ratio which signals a low energy charge in cells and as a response, mobilization of stored forms of biofuels is triggered to avert cellular starvation. The resulting increase in concentration of biofuels and their metabolites within the vascular space precipitates toxic conditions including glucose toxicity, acidosis, oxidative stress, and electrolyte imbalanc[5]. The elevation of plasma total cholesterol and triglycerides, as well as other dyslipidemic effects that are characteristics of chronic T2DM, have been identified as risk factors for onset of coronary artery disease in T2DM[6,7]. A major link to the biochemical changes as described is the insufficiency of secreted insulin and/or insulin resistance. Glucose toxicity in insulin insufficiency induces the generation of excessive levels of reactive oxygen species (ROS) that continually bombard and damage β-cells[8,9]. Interventions that eliminate oxidative stress are thought to initiate mechanisms that promote β-cell functionality thereby addressing the underlying cause of hyperglycemia.

The role of medicinal plants in the management of T2DM is gaining a renewed focus on finding novel anti-diabetic agents with the potential to delay or prevent progression to chronic complications of the disease. The plant *Mirabilis jalapa* (*M. jalapa*) (Clavillia or 4 O' Clock flower in English, *Tanaposo* in Yourba Language) has been shown to have hypoglycemic and hypolipidemic effects, suppress postprandial hypoglycemia and delay the onset of dyslipidemia in rats[10,11]. Therefore, this study was designed to investigate the role of *M. jalapa* root extract in restoration of glucose homeostasis in alloxan-induced hyperglycemic Wistar albino rats.

2. Materials and methods

2.1. Reagents and chemicals

Cayman kits (Cayman, USA) were purchased for assessment of the antioxidant enzymes including superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase. Lipid profile was determined using Randox Kits while insulin level was estimated using ELISA kits (Pars Biochem). Alloxan monohydrate was donated by the Department of Biochemistry and Molecular Biology, Usmanu Danfodiyo University, Sokoto.

2.2. Plant material

The roots of *M. jalapa* (voucher specimen number: UDUS/ANS/0241) were donated from the botanical garden of the Usmanu Danfodiyo University, Sokoto for this research. The roots were cut into small pieces, shade dried, then pulverized using a pestle and mortar. The powder (500 g) was macerated with methanol for 72 h, concentrated using a rotavapor (Cole-Parmer 115VAC), and finally freeze-dried to a constant weight. The dried methanol extract was stored at −4 ℃ for further analysis.

2.3. Experimental animals

Wistar albino rats used were bred at the animal house facility of the Department of Biochemistry and Molecular Biology, Usmanu Danfodiyo University Sokoto, and were kept in well-ventilated plastic cages and maintained according to the OECD[12] guidelines for experimental procedures involving animals. The rats were fed with commercial pelletized broiler grower's mash and allowed access to water *ad libitum*.

2.4. Induction of hyperglycemia

Hyperglycemia was induced in healthy rats (180-200 g) by intraperitoneal administration of a single dose of 120 mg/kg bodyweight of freshly prepared alloxan monohydrate in normal saline after fasting animals for 6 h. Animals with sustained elevated blood glucose >200 mg/dL (11.0 mmol/L) that were monitored for a week using a glucometer strip test (Finetest, model number IGM-0017B, Infopia Co Ltd, Korea) were considered hyperglycemic and were selected for the study.

2.5. Animal grouping and experimental design

The experimental animals were grouped according to their body weight into six groups of five animals per group as follows: Group 1 served as the normal control for baseline comparison while group 2 served as the hyperglycemic group that received no treatment. Group 3 received 400 mg/kg of the plant extract. Groups 4, 5, and 6 were hyperglycemic groups that received 200 and 400 mg/kg of plant extract, and 5 mg/kg of glibenclamide, respectively. The doses were selected according to literature[10,11]. The rats fasted for 6 h, then allowed access to feed after which each treatment was administered as described. Postprandial blood glucose was monitored using a glucometer. Treatment lasted for 14 d during which changes in body weights were recorded on the 7th and 14th day. Thereafter, rats were humanely sacrificed and blood was collected and pancreases were harvested for further studies.

2.6. Biochemical analysis

Collected blood samples were assayed for the following biochemical parameters: blood glucose concentration was determined using the glucose oxidase method while lipid profile was

determined using Randox Kits following the procedures described by the manufacturer. The antioxidant status was determined using commercial kits (Cayman, USA) for assessment of SOD, GPx, and catalase activities. The method of Hartman (1983) was adopted for estimation of thiobarbituric acid reactive substances to measure malondialdehyde concentrations in serum. Circulating insulin level was estimated using ELISA kits (Pars Biochem).

2.7. Histological examination of pancreatic tissues

Harvested pancreas of sacrificed rats was initially washed with chilled normal saline, then preserved in 10% formaldehyde. The tissues were then processed using an automated tissue processing machine (Liaca TP 1020) and sections of 5 µm thickness were obtained. The prepared thin sections were then stained with hematoxylin and eosin, mounted, and viewed under a microscope at 100× and 400× magnification.

2.8. Statistical analysis

Results are presented as mean±standard deviation (SD) where replicate analyses were conducted. The SPSS programme (IBM SPSS statistics for windows version 20.0 IBM Corp.) was used for one-way analysis of variance (ANOVA) followed by Tukey *post–hoc* test at a $P<0.05$ level of significance.

2.9. Ethical statement

The procedures conducted in this study were approved by the Usmanu Danfodiyo University Institutional Animal Care and Use Committee (IACUC-UDUS) with an approval reference number UDUS/IACUC/2018/AUP-R0-23.

3. Results

3.1. Effect of M. jalapa extract on body weight and serum biochemical changes in hyperglycemic rats

Figure 1 presents the changes in body weights of rats for 14 d. The body weight of the hyperglycemic group that received no treatment was significantly decreased on days 7 and 14, while the hyperglycemic groups given 200 mg/kg and 400 mg/kg of *M. jalapa* extract had increased body weight. In addition, the hyperglycemic group showed a significantly high level of postprandial blood glucose compared with the normal control group on day 3 (Figure 2). *M. jalapa* extract at both doses remarkably decreased postprandial blood glucose of hyperglycemic rats on days 7 and 14 ($P<0.05$), the effect of which was similar to that of standard drug glibenclamide. Moreover, 400 mg/kg of *M. jalapa* extract did not induce hypoglycemia in healthy rats.

The lipid profile indices of the untreated hyperglycemic group were significantly elevated ($P<0.05$) with a decreased level of high-density lipoprotein cholesterol and an atherogenic index of 0.79±0.62 when compared with the normal control group. *M. jalapa* extract at 400 mg/kg significantly modulated lipid profile indices with a lower atherogenic index of 0.43±0.17 (Table 1).

Table 1. Effect of *Mirabilis jalapa* extract on lipid profile in alloxan-induced hyperglycemic rats (mg/dL).

Groups	TC	TG	HDL-C	LDL-C	VLDL-C	AIX
Normal control	73.00±3.74^a	66.50±4.66^a	43.30±3.40^a	16.50±2.50^a	13.30±0.93^a	0.19±0.07^a
Alloxan	157.70±3.40^b	131.50±2.65^b	22.50±2.08^b	108.90±4.64^b	26.30±0.53^b	0.79±0.62^d
400 mg/kg *Mirabilis jalapa*	76.50±4.20^a	74.50±3.42^c	46.50±2.08^a	15.10±3.36^a	14.90±0.68^a	0.22±0.07^a
Alloxan+200 mg/kg *Mirabilis jalapa*	109.00±5.09^c	87.00±4.97^d	24.50±3.51^b	67.10±1.75^c	17.40±0.99^b	0.52±0.37^c
Alloxan+400 mg/kg *Mirabilis jalapa*	91.50±2.65^d	104.00±7.02^e	33.80±2.75^c	44.80±3.11^d	12.50±0.68^a	0.43±0.17^b
Alloxan+glibenclamide	71.00±4.16^a	80.50±6.25^c	35.80±4.57^c	19.20±3.69^a	16.10±1.25^b	0.35±0.16^b

Data are expressed as mean±standard deviation of pentaplicates. Different superscripts indicate significant differences ($P<0.05$) in the same column. TC: Total cholesterol; TG: Triglycerides; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; VLDL-C: Very low density lipoprotein cholesterol; AIX: Atherogenic index.

Table 2. Effect of *Mirabilis jalapa* extract on antioxidant status in alloxan-induced hyperglycemic rats.

Groups	Catalase (U/mL)	SOD (U/mL)	GPx (U/mL)	MDA (mmol/L)
Normal control	1.65±0.11^a	16.66±1.35^a	21.613±2.050^a	18.60±2.63^a
Alloxan	0.45±0.02^b	2.01±0.05^b	5.173±0.507^b	57.10±3.81^b
400 mg/kg *Mirabilis jalapa*	1.81±0.09^a	16.58±2.07^a	19.853±1.748^a	20.20±1.69^a
Alloxan+200 mg/kg *Mirabilis jalapa*	1.53±0.28^c	8.00±1.94^c	11.505±2.858^c	38.90±5.90^c
Alloxan+400 mg/kg *Mirabilis jalapa*	1.31±0.05^c	9.63±1.63^c	14.283±1.306^c	28.70±5.18^d
Alloxan+glibenclamide	1.53±0.14^c	8.25±0.87^c	18.235±2.457^a	16.30±2.84^a

Data are expressed as mean±standard deviation of pentaplicates. Different superscripts indicate significant differences ($P<0.05$) in the same column. SOD: Superoxide dismutase; GPx: Glutathione peroxidise; MDA: Malondialdehyde.

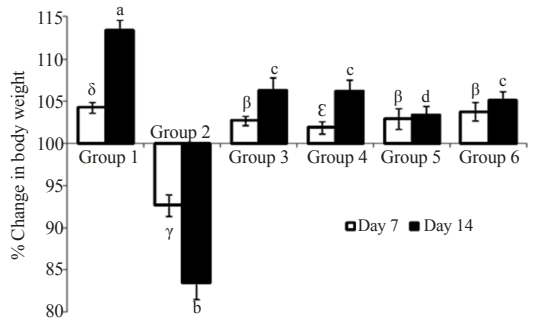

Figure 1. Effect of *Mirabilis jalapa* extract on changes in body weight of alloxan-induced hyperglycemic rats. Data are expressed as mean±standard deviation of pentaplicates. Bars with different Greek letters and alphabets are significantly different at $P<0.05$ on day 7 and 14, respectively. Group 1: Normal control; Group 2: Alloxan; Group 3: 400 mg/kg *Mirabilis jalapa*; Group 4: Alloxan+200 mg/kg *Mirabilis jalapa*; Group 5: Alloxan+400 mg/kg *Mirabilis jalapa*; Group 6: Alloxan+glibenclamide.

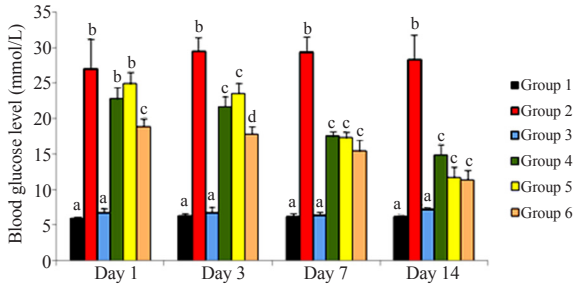

Figure 2. Effect of *Mirabilis jalapa* extract on 2 h postprandial blood glucose levels in alloxan-induced hyperglycemic rats. Data are expressed as mean±standard deviation of pentaplicates. Bars with different letters are significantly different at $P<0.05$. Group 1: Normal control; Group 2: Alloxan; Group 3: 400 mg/kg *Mirabilis jalapa*; Group 4: Alloxan+200 mg/kg *Mirabilis jalapa*; Group 5: Alloxan+400 mg/kg *Mirabilis jalapa*; Group 6: Alloxan+ glibenclamide.

3.2. Effect of M. jalapa extract on antioxidant status in hyperglycemic rats

The antioxidant status indicates the physiological capacity to compensate for rising levels of ROS responsible for oxidative damage in cellular processes. In the untreated hyperglycemic group, the antioxidant parameters including SOD, GPx, and catalase activities were significantly diminished and malondialdehyde level was significantly increased ($P<0.05$). The hyperglycemic rats treated with 200 and 400 mg/kg *M. jalapa* extract pronouncedly elevated the antioxidant parameters and decreased malondialdehyde level ($P<0.05$) (Table 2). In addition, treatment with 400 mg/kg *M. jalapa* extract alone did not cause any changes in these parameters (Table 2).

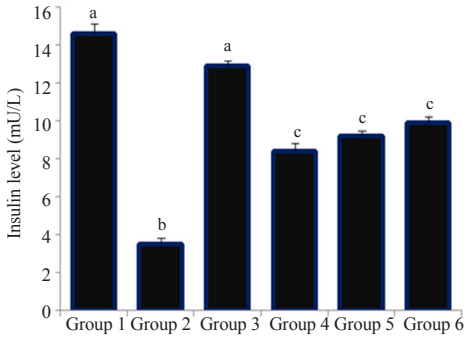

Figure 3. Effect of *Mirabilis jalapa* extract on serum insulin levels in alloxan-induced hyperglycemic rats. Data are expressed as mean±standard deviation of pentaplicates. Bars with different letters are significantly different at $P<0.05$. Group 1: Normal control; Group 2: Alloxan; Group 3: 400 mg/kg *Mirabilis jalapa*; Group 4: Alloxan+200 mg/kg *Mirabilis jalapa*; Group 5: Alloxan+400 mg/kg *Mirabilis jalapa*; Group 6: Alloxan+ glibenclamide.

3.3. Effects of M. jalapa extract on serum insulin levels and histology of damaged islet cells

Figure 3 presents the results of serum insulin levels in rats. The untreated hyperglycemic group showed a lower level of serum insulin compared with the normal control group. Treatment with 200 and 400 mg/kg of the extract elevated serum insulin levels [(8.40±0.40) and (9.20±0.26) mU/L, respectively] ($P<0.05$) in comparison with the untreated hyperglycemic group. Histopathological examination showed that the normal control group had normal pancreatic structure (Figure 4A) while the untreated hyperglycemic group showed significant reductions in nests of islets cells. In some areas, there was total depletion of islets nest and replacement with fibrous amorphous material (Figure 4B). Interestingly, the hyperglycemic groups that received 200 and 400 mg/kg of the extract had significant regeneration of islet cells with an increased number of nodular cells within the nests. Healing and regeneration of some nests of islets cells, reduced or no fibrosis, and minimal inflammation were also observed in the treated groups (Figure 4D and E).

4. Discussion

A major sign of metabolic derangement in diabetes mellitus is hyperglycemia. The inability of diabetics to effectively utilize glucose results in the mobilization of energy-rich molecules to sustain cellular metabolic function[13]. Biochemically, this is accompanied by elevation of lipid levels in the blood as well as ketone bodies due to overwhelming tricarboxylic acid cycle cycle[14]. The experimental animals induced with hyperglycemia in this study had elevated glucose levels, total cholesterol, triglycerides,

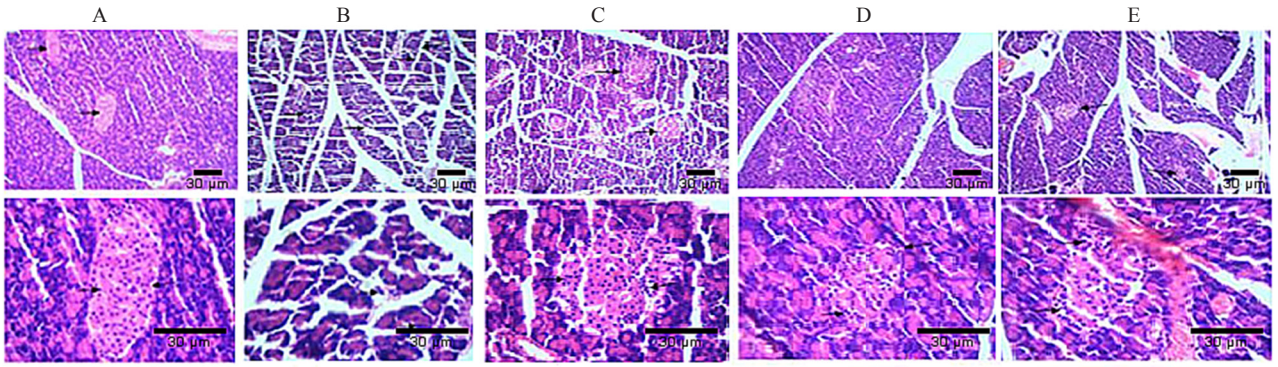

Figure 4. Photomicrographs of pancreatic tissues at 100× (upper panel) and 400× (lower panel) magnification. (A) Normal architecture of islet nest (black arrows) is observed in the normal control group. (B) The hyperglycemic group shows reduced nest of islets cells with an area of extensive fibrosis (black arrows). (C) The normal group that received 400 mg/kg of *Mirabilis jalapa* extract shows a normal architecture of islet nest. The black arrows indicate a normal islet cell population within several islet nests. (D) The hyperglycemic group treated with 200 mg/kg of *Mirabilis jalapa* extract shows mild regeneration of islet cells. The arrows indicate sparsely populated islet cells within the nest. (E) The hyperglycemic group treated with 400 mg/kg of *Mirabilis jalapa* extract has moderately dispersed islet nests (black arrow) when being viewed under 100× magnification.

low-density lipoprotein cholesterol, very-low-density lipoproteins, and decreased high-density lipoprotein cholesterol levels before commencement of treatment. Administration of 200 and 400 mg/kg of *M. jalapa* extract decreased progressively the postprandial blood glucose level of hyperglycemic rats during treatment. Treatment with the extract significantly reversed the changes observed in the hyperglycemic groups. Glycolytic oxidation of glucose inhibits lipolysis and promotes lipogenesis and subsequent gain in body weight. These changes were observed in the extract-treated hyperglycemic group with changes in body weight. Furthermore, the antehrogenic index of the treated hyperglycemic groups clearly indicates a reduced risk of dyslipidemia. The hypoglycemic and hypolipidemic effects of *M. jalapa* extracts have been similarly reported by Zhou *et al.* and Sadiq *et al*[10,11].

Prolonged hyperglycemia is accompanied by oxidative stress. The generation of free radicals initiates lipid peroxidation and consequent damage to exposed tissue[15]. The overproduction of free radicals, as the indicators of oxidative stress, depletes the function of endogenous antioxidant enzymes which play important roles in scavenging toxic intermediate of incomplete oxidation[16,17]. Our results show that 200 and 400 mg/kg of the extract elevated antioxidant enzymes activities including SOD, GPx, and catalase but decreased MDA levels when compared with the untreated hyperglycemic group, which suggests treatment may have influenced the peripheral utilization of glucose, and increase in synthesis of hepatic glycogen thereby preventing glucose toxicity and probably hindering the formation of ROS *via* activation of polyol pathway, glycation reactions, and hexamine pathway, all of which are reactions that deplete NADPH[18,19]. The flavonoids, alkaloids, and other phytoconstituents of the root extract of *M. jalapa* that have potent antioxidant activity probably influenced the rapid stabilization of the oxidant/antioxidant ratio in the experimental hyperglycemic rats[20,21].

Histopathological examinations of pancreatic islet cells show regeneration of islet cells in hyperglycemic rats administered with 200 and 400 mg/kg of *M. jalapa* extract. Similarly, the group that received 5 mg/kg glibenclamide, a sulfuryl urease categorized as an insulin secretagogue and useful in regulation of postprandial hyperglycemia also induced a significant increase in islet cells when compared to the untreated group[22–24]. The restoration of β-cell function in the extract-treated group was also evidenced by a consequent rise in circulating plasma insulin and this probably explains the observed progressive drop in postprandial hyperglycemia. Overall, we hypothesize from our results that *M. jalapa* root extract contains some bioactive components responsible for β-islet cell regeneration, which needs to be further verified in future studies. This mechanism of action of the plant extract is promising in the restoration of residual β-cell function which is a necessary step in the regulation of postprandial blood glucose.

Findings in this study illustrate the insulinotropic potential of *M. jalapa* root extract possibly through its revitalization effects on damaged pancreatic β islet cells and free radical quenching function. But the underlying mechanisms and the active components of the plant extract need to be further studied in future investigations.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

The work was conceived and designed by MES who also compiled the draft manuscript. Maintenance of experimental animals, specimen collection and biochemical analyses were conducted by CE. Preparation and microscopic examination of thin sections of the pancreas as well as interpretation of histopathological data were carried out by BU. Biostatistical analyses and data interpretation as well as review of draft manuscript were carried out by RSUW and UZU. Approval of final version of manuscript for publication was given by RSUW.

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