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Antihyperglycemic, Antihyperlipidemic and Antioxidant effect of *Atriplex farinosa* and *Atriplex nummularia* in Streptozotocin-induced Diabetes in rats

Gamal A. Soliman[1,2] and Abd El Raheim M. Donia[3,4]
[1]Pharmacology Department, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, KSA.
[2]Pharmacology Department, College of Veterinary Medicine, Cairo University, Egypt.
[3]Pharmacognosy Department, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj, KSA.
[4]Medicinal and Aromatic Plants Department, Desert Research Center, Cairo, Egypt.
* **Corresponding Author's e-mail**: donia22276@yahoo.com, a.donia@psau.edu.sa

ABSTRACT

The present study was designed to investigate the antihyperglycemic effect of Atriplex farinosa (A. farinosa) and Atriplex nummularia (A. nummularia) extracts in streptozotocin (STZ)-diabetic rats. Glibenclamide was taken as the standard drug. Diabetes was induced in adult male albino rats, weighing 160-175 g, by administration of STZ (45 mg/kg of body weight) intraperitoneally. Diabetic rats showed an increase in levels of fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c) in addition to serum levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL-C) and malondialdehyde (MDA) in their pancreas homogenates. They showed a decrease in levels of plasma insulin, hemoglobin (Hb), and serum level of high density lipoprotein (HDL-C)and activities of superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) and glutathione (GSH)in pancreas homogenates.Oral administration of A. farinosa and A. nummularia (200 and 400mg/kg) extracts and glibenclamide (0.6 mg/kg) decreased the FBGand elevated insulin levels after 4 and 8 weeks of treatment in STZ-diabetic rats in a dose-dependent manner. A meaningful reduction in the concentrations of HbA1c, TG, TC, LDL-C in serum and elevations in the activities of SOD, GPx, CAT and GSHin pancreas homogenates were observed in diabetic animals medicated with A. farinosa and A. nummularia extracts. Levels of HDL-Cin serum and MDA in pancreas homogenates were recovered significantly in A. farinosa and A. nummularia-medicated diabetic rats. Thus, our results show that A. farinosa and A. nummularia (200 and 400 mg/kg) possesses a promising antihyperglycemic effect that is comparable with glibenclamide.
Key words: Chenopodiaceae, Insulin, HbA1c, Pancreas, Streptozotocin.

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INTRODUCTION

Diabetes mellitus (DM) is a common and serious disorder throughout the world with prevalence of 246 million people in 2007 and forecasts to rise to 300 million by 2025 [1].It is a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbance of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both [2].Diabetes is strongly associated with both microvascular and macrovascular complications, including retinopathy, nephropathy, and neuropathy (microvascular) and ischemic heart disease, peripheral vascular disease, and cerebrovascular disease (macrovascular), resulting in organ and tissue damage in approximately one third to one half of people with diabetes [3]. In the year 2000, death from diabetes-associated complications accounted for approximately 6% of worldwide mortality [3]. Treatment of DM by insulin and/or oral drugs fails to prevent diabetes-associated complications in many patients indicating that additional treatment would be helpful.

The species of the genus *Atriplex* belonging to family Chenopodiaceae are partly spontaneous in the WANA (West Asia and North Africa) area and have partly been introduced to determine their adaptability for use as fodder species [4]. *Atriplex farinosa* is a tall shrub of yellow white appearance with large, naked panicles, but leaf base cordate with long, obtuse auricles, fruit bracts entire, longer than broad [5].Two flavonol glycosides; isorhamnetin-3-*O*-rhamnosyl (1-6) glucopyranoside and isorhamnetin-7-*O*-

glucopyranoside were isolated from *A. farinosa* [6]. *A. nummularia* Lindl. is a species of saltbush known by the common names old man saltbush, blue-green saltbush, and giant saltbush. The plant is generally palatable to grazing animals, but the palatability can be limited by the concentration of salt in the plant tissues as the plant takes in water from saline soils [7]. It is widely used as a forage crop in Tunisia. Australian Aborigines used the seeds as a traditional food source.

Many oral antihyperglycemic agents are available along with insulin for the treatment of diabetes, but these agents have significant side effects, and some are ineffective in chronic diabetes patients [8]. Thus, there is an increasing need of new natural antihyperglycemic products with less side effects and high antihyperglycemic potential.

MATERIALS AND METHODS

Plant material

Atriplex farinosa Forssk was collected from the South Eastern corner of Egypt, during autumn season 2012, while *Atriplex nummularia* was collected from North Western Desert of Egypt during summer 2013. The collected plant samples were kindly identified by Prof. Dr. Ahmed Morsy Ahmed, Prof. of plant ecophysiology, Desert Research Center, Cairo, Egypt. A specimen from each plant has been deposited in the Herbarium of the DRC, Cairo, Egypt (No. 11073 HDRC,11074HDRC).The plant was dried under shade and then grinded to fine powder. The dried powder (one kg) was extracted with 70% aqueous ethanol by percolation in the solvent with occasional shaking for 48 h and the process was repeated three times. The ethanol extract was combined and concentrated under vacuum to obtain a dry crude extract (75 g). The dry crude extract yield was 7.5% (7.5 g extract/100 g raw material).

Preparation of the extracts

About one kg of the dried powder of the aerial parts of each plant was percolated in70% aqueous ethanol with occasional shaking for 24hour. The process was repeated for three times. The combined ethanol extracts were concentrated under reduced pressure at a temperature not exceeding 35ºC.

Animals

Adult male albino rats weighing 160-175 g were used. Animals were obtained from Lab Animal Care Unit, Pharmacy College, Prince Sattam bin Abdulaziz University, Al-Kharj, KSA. All animals were housed under standard conditions of natural 12 h light and dark cycle with free access to food and water and were allowed to adapt to the laboratory environment for one week before experimentation.

Acute toxicity study

Acute toxicity study for the ethanol extracts of *A. farinosa* and *A. nummularia* was carried in adult male albino rats according to OECD-423 guidelines (OECD, 2001). Two groups of rats (*n=6*) were fasted overnight then received *A. farinosa* and *A. nummularia* extracts, respectively at a dose of 2000 mg/kg by the oral route. The control rats treated with the vehicle (3% v/v Tween 80 in distilled water) and kept under the same conditions. Each animal was observed for symptoms of toxicity and/or mortalities for every 15 min in the first 4 h after medication, then every 30 min for the successive 6 h and then for 48 h. Since, there was no mortality at this level; the dose of both extracts was increased to 4000 mg/kg and animals were observed for another 48 h.

Induction of diabetes in experimental rats

Diabetes was induced by a single intraperitoneal injection of a freshly buffered (0.1 M citrate, pH 4.5) solution of STZ(Sigma, Germany) at a dosage of 45 mg/kg body weight. After 72 h of STZ administration, the tail vein blood was collected to determine blood glucose level. Only rats with blood glucose over 250 mg/dL were considered diabetic and included in the experiments. Treatment with glibenclamide and *A. farinose* and *A. nummularia* extracts started 72 h after STZ injection.

Experimental protocol

The diabetic rats were randomly divided into seven groups (n=6). The vehicle was administered to rats of the 1st (normal control) and 2nd(diabetic control) groups at 5 mL/kg. The 3rd group (reference group) was diabetic rats given glibenclamide at a dose of 0.6 mg/kg. Diabetic rats of the 4th and 5th groups received *A. farinosa* extract at doses of 200 and 400 mg/kg, respectively. Diabetic rats of the 6th and 7th groups received *A. nummularia* extract at doses of 200 and 400 mg/kg, respectively. Vehicle, glibenclamide and extracts were given orally by gavage as single daily treatments, for 8weeks.

Biochemical evaluation

At 4 and 8 weeks after treatment, a blood sample was withdrawn through the retro-orbital venous plexus of each rat under sodium pentobarbital anesthesia (40 mg/kg, intraperitoneally) into sampling tubes containing EDTA and used for estimation of total Hb [9] and HbA1c [10]. Two other samples were collected from the overnight fasted animals. The first samples were collected in sampling tubes containing sodium fluoride and centrifuged at 3500 rpm for 15 min to separate plasma. FBG levels were measured in plasma according to [11].The second samples were collected in sampling tubes without

anticoagulants and centrifuged at 3500 rpm for 15 min to separate serum. Serum levels of insulin [12], TG [13], TC [14], HDL-C [15] and LDL-C [16] were evaluated. At the end of the experiment, the *in vivo* antioxidant activity was estimated by measuring the activities of SOD, GPx and CAT enzymes and levels of GSH and MDA in the pancreatic tissue homogenates using the specified kits from Biodiagnostic Chemical Company (Egypt) according to the instructions of the supplier.

Histopathological study
Animals were euthanized; liver, kidneys, spleen and pancreas were collected and kept in 10% neutral buffered formalin for 48 h, then embedded within paraffin. Sections of 4 μm thickness were prepared using a rotary microtome. The sections stained with haematoxylin and eosin (H&E) and then observed by light microscopy for histopathological examination.

Statistical analysis
Results are expressed as mean± standard error (SE) of mean. Statistical analysis was performed, using a one-way analysis of variance (ANOVA). When the F-value was found statistically significant ($P < 0.05$), further comparisons among groups were made using Dunnett's multiple comparisons test. All statistical analyses were performed using SPSS software17.0 (Released Aug. 23, 2008), Chicago, USA.

RESULTS
Acute toxicity test
Oral administration of *A. farinosa* and *A. nummularia* extracts did not cause death in the highest dose of 4 g/ kgb. wt. No visible signs of toxicity were reported in the rats exposed to different doses of both extracts indicating their safety. Accordingly, the oral LD_{50} of *A. farinosa* and *A. nummularia* extracts was determined to be higher than 4 g/ kgb. wt which is the highest tested dose.

Effect on the plasma glucose and insulin levels
STZ-diabetic rats exhibited a significant increase in FBG at 4 weeks (307.2±6.62 mg/dL) and 8 weeks (310.4±5.62 mg/dL) of treatment as compared to normal control rats (88.7±3.28 and 85.2±2.96 mg/dL, respectively). The elevated FBG of diabetic rats showed a tendency toward normal levels after dosing of glibenclamide (0.6 mg/kg), *A. farinose* extract (200 and 400 mg/kg) and *A. nummularia* extract (200 and 400 mg/kg) at 4 and 8 weeks of treatment (Table 1). In parallel with the reduction of FBG levels, there was a significant decrease in serum insulin level in animals treated with *A. farinosa* and *A. nummularia* extracts at 200 and 400 mg/kg on both week 4 and week 8, compared to diabetic control rats.

Effect on total hemoglobin and HbA1c
Table 2 shows the HbA_1C and hemoglobin levels of normal and experimental animals. After 8 weeks, control diabetic animals showed a considerable reduction in the level of total hemoglobin (9.6±0.18 mg/dL) and a significant elevation in the level of HbA1c (8.8±0.11 % Hb) in comparison with normal controls (14.2±0.13 mg/dL and 3.6±0.05 % Hb, respectively). Administration of *A. farinosa* and *A. nummularia* extracts (200 and 400 mg/kg) to diabetic rats revert the levels of total hemoglobin and HbA1c to normal conditions (Table 2). Similarly, total hemoglobin and HbA1c contents were restored toward their normal values by the administration of the standard drug glibenclamide.

Effect on serum lipid profile
Our observation provides further support to the growing body of evidence showing that STZ-induced diabetescan also induce anomaly of serum TC, TG, HDLC, and LDL-C. Tables3 and 4showed the levels of serum TG,TC, LDL-C, and HDL-C of rats in different experimental groups after 4 and 8 weeks of treatment, respectively. Diabetic animals had increased contents of serum TG, TC and LDL-C and decreased level of HDL-C compared to normal control group. Similar with the glibenclamide-treated STZ group (except serum level of TG), *A. farinosa* and *A. nummularia* administration showed a significant decrease in the levels of serum TG, TC, and LDL-C and a significant increase in the level of HDL-C after 4 and 8 weeks treatment when compared with the diabetic control group. Glibenclamide did not significantly change the serum level of TG, when compared to diabetic control rats.

Effect on oxidative stress markers in pancreatic tissues
Table 5 clearly illustrate the effect of *A. farinosa* and *A. nummularia* extracts on the activities of antioxidant enzymes and levels of GSH and MDA in the pancreatic homogenates of different experimental groups. A significant decrease was observed in the antioxidant activity of SOD, GPx and CAT and level of GSH in the pancreas homogenates of diabetic animals along with elevation in the level of MDA. Glibenclamide and *A. farinosa* or *A. nummularia* extracts treatment for 8 weeks significantly raised antioxidant enzyme activity (SOD, GPx and CAT) and antioxidant level (GSH) and inhibited the formation of MDA in a dose-dependent manner.

Histopathological findings
The histological structure of the pancreas in normal control rats showed characteristic features of normal acini and normal cellular population in the islets of Langerhans (Figure 1-A). In contrast, the light

microscopic study of diabetic control rats revealed pathological changes of both exocrine and endocrine part of the pancreas represented by necrotic cells, vacuolation and marked decrease of β-cells (Figure 1-B). The severity of these injuries was alleviated markedly in all diabetic rats treated with *A. farinosa* (Figure 1-C) and *A. nummularia* (Figure 1-D) extracts in a dose-dependent manner.

Table 1: Levels of FBG and insulin in plasma of control and diabetic rats after 4 and 8 weeks of glibenclamide, *A. farinosa* and *A. nummularia* treatments.

Group	FBG (mg/dL)		Insulin (U/L)	
	4 weeks	8 weeks	4 weeks	8 weeks
Normal Control	88.7±3.28†	85.2±2.96†	17.7±0.16†	18.0±0.14†
Diabetic Control (STZ)	307.2±6.62*	310.4±5.62*	8.5±0.11*	8.5±0.10*
STZ + Glibenclamide(0.6 mg/kg)	119.5±3.26*†	110.5±3.31*†	15.8±0.12*†	15.9±0.12*†
STZ + *A. farinosa* (200 mg/kg)	167.4±5.38*†	165.3±5.14*†	10.4±0.10*†	11.3±0.13*†
STZ + *A. farinosa* (400 mg/kg)	145.5±5.11*†	134.8±5.23*†	13.3±0.15*†	13.6±0.16*†
STZ + *A. nummularia* (200 mg/kg)	185.2±5.25*†	178.9±5.17*†	9.6±0.11*†	10.1±0.11*†
STZ + *A. nummularia* (400 mg/kg)	173.8±4.50*†	172.4±5.55*†	10.0±0.14*†	10.8±0.14*†

Values represent the mean ± S.E. of six rats for each group.
* Significantly different from the values of normal control rats at P< 0.05.
†Significantly different from the values of diabetic control rats at P< 0.05.

Table 2: Levels of total hemoglobin and HbA1c in blood of control and diabetic rats after 4 and 8 weeks of glibenclamide, *A. farinosa* and *A. nummularia* treatments**.**

Group	Total hemoglobin (mg/dL)		HbA1c (% Hb)	
	4 weeks	8 weeks	4 weeks	8 weeks
Normal Control	14.3±0.18	14.2±0.13†	3.8±0.22	3.6±0.05†
Diabetic Control (STZ)	12.2±0.31	9.6±0.18*	4.7±0.37	8.8±0.11*
STZ + Glibenclamide(0.6 mg/kg)	13.1±0.29	12.9±0.17†	4.2±0.35	4.9±0.13*†
STZ + *A. farinosa* (200 mg/kg)	12.8±0.21	10.8±0.11†	4.7±0.46	5.6±0.12*†
STZ + *A. farinosa* (400 mg/kg)	13.0±0.27	11.1±0.13†	4.5±0.41	5.0±0.10*†
STZ + *A. nummularia* (200 mg/kg)	12.1±0.20	10.0±0.13†	4.9±0.45	6.6±0.11*†
STZ + *A. nummularia* (400 mg/kg)	12.6±0.24	10.5±0.15†	4.8±0.44	6.2±0.12*†

Values represent the mean ± S.E. of six rats for each group.
* Significantly different from the values of normal control rats at P< 0.05.
†Significantly different from the values of diabetic control rats at P< 0.05.

Table 3: Levels of TG, TC, HDL-C and LDL-C in serum of control and diabetic rats after 4 weeks of glibenclamide, *A. farinosa* and *A. nummularia* treatments**.**

Group	TG (mg/dL)	TC (mg/dL)	HDL-C mg/dL	LDL-C (mg/dL)
Normal Control	54.3±2.14†	55.7±2.61†	29.8±0.74†	23.6±0.63†
Diabetic Control (STZ)	98.7±3.45*	92.5±3.11*	20.1±0.27*	45.8±1.26*
STZ + Glibenclamide (0.6 mg/kg)	90.2±3.85*	71.6±2.50*†	25.8±0.29*†	29.5±1.25*†
STZ + *A. farinosa* (200 mg/kg)	81.3±2.34*†	80.7±2.74*†	24.1±0.66*†	35.7±1.15*†
STZ + *A. farinosa* (400 mg/kg)	72.3±2.77*†	75.0±2.35*†	23.5±0.25*†	32.7±1.66*†
STZ + *A. nummularia* (200 mg/kg)	86.7±3.15*†	82.7±2.62*†	23.4±0.20*†	37.4±0.83*†
STZ + *A. nummularia* (400 mg/kg)	77.8±2.38*†	77.3±2.48*†	22.8±0.37*†	33.9±0.35*†

Values represent the mean ± S.E. of six rats for each group.
* Significantly different from the values of normal control rats at P< 0.05.
†Significantly different from the values of diabetic control rats at P< 0.05.

Table 4: Levels of TG, TC, HDL-C and LDL-C in serum of control and diabetic rats after 8 weeks of glibenclamide, *A. farinosa* and *A. nummularia* treatments**.**

Group	TG(mg/dL)	TC(mg/dL)	HDL-C(mg/dL)	LDL-C(mg/dL)
Normal Control	51.8±1.82†	59.3±2.40†	33.7±0.39†	24.8±0.37†
Diabetic Control (STZ)	104.7±3.79*	99.8±2.16*	17.9±0.23*	43.2±0.32*
STZ + Glibenclamide (0.6 mg/kg)	95.6±3.55*	78.8±2.73*†	28.7±0.28*†	29.2±0.58*†
STZ + *A. farinosa* (200 mg/kg)	75.3±2.16*†	83.2±2.27*†	22.8±0.22*†	37.7±0.32*†
STZ + *A. farinosa* (400 mg/kg)	70.2±2.51*†	77.4±2.28*†	25.2±0.36*†	33.5±0.66*†
STZ + *A. nummularia* (200 mg/kg)	82.7±2.78*†	85.8±3.22*†	21.5±0.38*†	38.1±0.73*†
STZ + *A. nummularia* (400 mg/kg)	73.5±2.27*†	81.2±2.15*†	24.4±0.50*†	35.0±0.49*†

Values represent the mean ± S.E. of six rats for each group.
* Significantly different from the values of normal control rats at P< 0.05.
†Significantly different from the values of diabetic control rats at P< 0.05.

Table 5: Activities of SOD, GPx and CAT and levels of GSH and MDA in pancreas homogenate of control and diabetic rats after 8 weeks of glibenclamide, *A. farinosa* and *A. nummularia* treatments

Groups	SOD (U/mg protein)	GPx (U/mg protein)	CAT (U/mg protein)	GSH (µmol/g tissue)	MDA (nmol/g tissue)
Normal Control	44.5±1.73†	4.1±0.09†	9.2±0.15†	9.7±0.10†	27.5±0.72†
Diabetic Control (STZ)	25.6±0.27*	1.5±0.05*	3.3±0.10*	4.8±0.07*	49.8±0.95*
STZ + Glibenclamide (0.6 mg/kg)	37.5±0.35*†	3.3±0.10*†	7.1±0.17*†	8.8±0.11*†	34.2±0.71*†
STZ + *A. farinosa* (200 mg/kg)	32.7±0.82*†	2.9±0.11*†	6.3±0.13*†	8.0±0.16*†	38.3±0.55*†
STZ + *A. farinosa* (400 mg/kg)	30.6±0.22*†	2.3±0.12*†	5.7±0.17*†	6.7±0.11*†	41.5±0.26*†
STZ + *A. nummularia* (200 mg/kg)	31.6±0.16*†	2.5±0.15*†	6.0±0.18*†	7.2±0.13*†	39.9±0.45*†
STZ + *A. nummularia* (400 mg/kg)	29.3±0.18*†	2.0±0.16*†	5.2±0.10*†	6.6±0.17*†	41.9±0.18*†

Values represent the mean ± S.E. of six rats for each group.
* Significantly different from the values of normal control rats at P< 0.05.
†Significantly different from the values of diabetic control rats at P< 0.05.
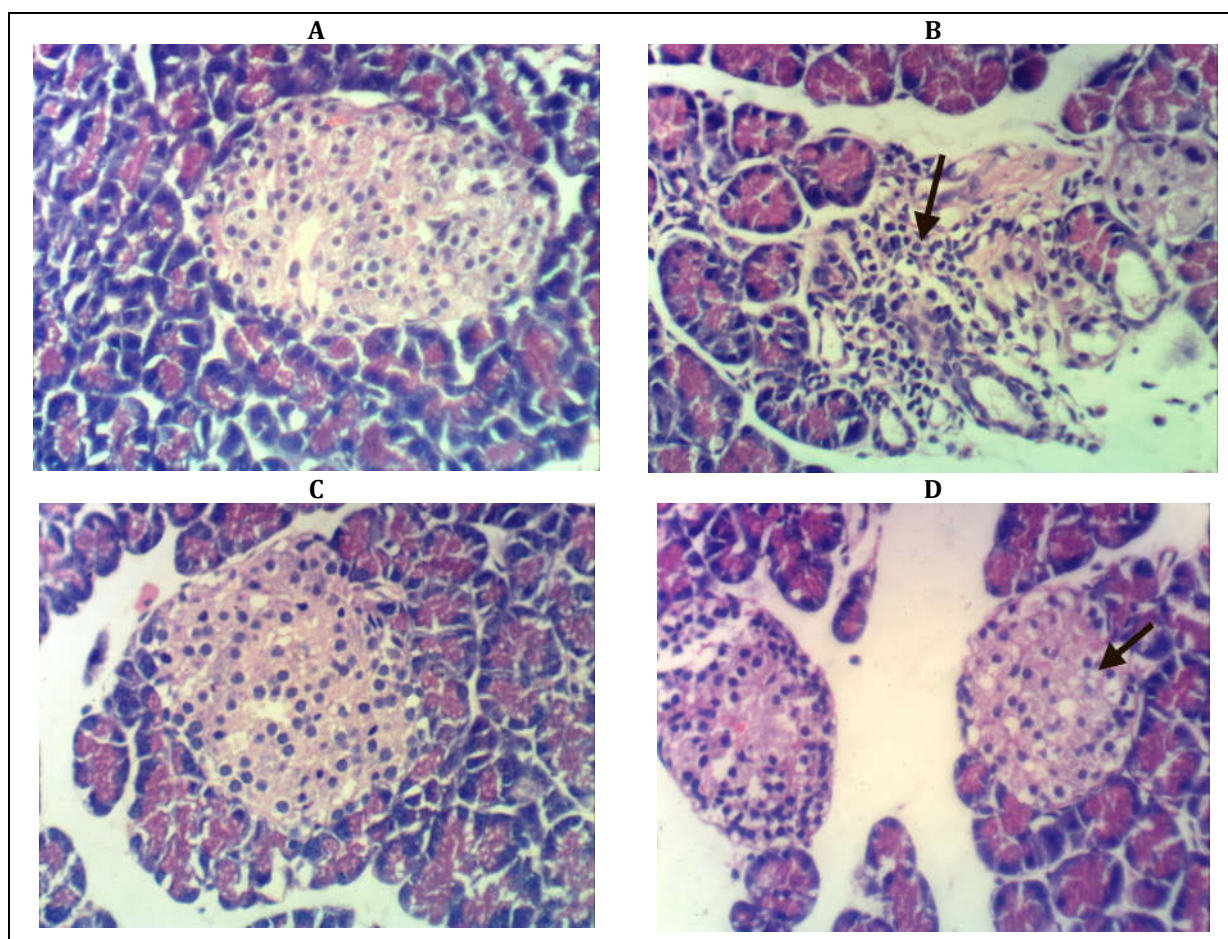

Figure 1: Photomicrographs of pancreas tissues of rats from different experimental groups. (A) Control rat pancreas showing characteristic features of normal acini and normal cellular population in the islets of Langerhans. (B) Diabetic control rat's pancreas shows pathological changes of both exocrine and endocrine parts represented by necrotic cells, vacuolation, disruption of normal endocrine architecture and marked decrease of β cells. (C) Pancreas of STZ-diabetic rats treated with *A. farinosa* (400 mg/kg), shows marked cellular restoration, reduced necrosis, reduced degeneration and normal endocrine and exocrine architecture. (D) Pancreas of STZ-diabetic rats treated with *A. nummularia* (400 mg/kg) showing

features similar to the control and most of the island of Langerhans cells were intact with no alteration except few vacuoles.(H & E, x400).

DISCUSSION

It is not constantly simple to determine if the consuming plant extracts are safe. In fact there are a large number of plant extracts with a wide range of adverse effect. In our study, oral administration of *A. farinosa* and *A. nummularia* extracts at doses up to 4000 mg/kg did not produce any sign of acute toxicity and none of animals died during 48 h of observation. Accordingly, it suggested that oral median lethal doses (LD50) of the tested extracts were higher than 4000 mg/kg. Therefore, *A. farinosa* and *A. nummularia* plants can be categorized as quietly safe since substances possessing LD50 higher than 50 mg/kg are non-toxic [17].

Diabetes is increasing at an alarming rate worldwide, which can mainly be attributed to the sedentary life style and calorie-rich diet. STZ-induced hyperglycemia in rodents is considered to be a good model for the preliminary screening of agents active against DM[18]. STZ, N-{methylnitrocarbamoyl}-D-glucosamine, is a potent DNA methylating agent and acts as a nitric oxide donor in pancreatic cells. β-cellsare particularly sensitive to damage by nitric oxide and free radicals because of their low levels of free radical scavenging enzymes [19].

Oral administration of glibenclamide and *A. farinosa* and *A. nummularia* extracts (200 and 400 mg/kg) showed significant increase in plasma insulin levels at the 4th and 8th weeks of treatment, compared to the control values of diabetic rats. In *A. farinosa* and *A. nummularia*-treated diabetic rats, the marked increase of plasma insulin may be due to the stimulation of insulin release from the existing β-cellsof the pancreas. On the other hand, daily administration of glibenclamide and *A. farinosa* and *A. nummularia* extracts (200 and 400 mg/kg) for 4 and 8 weeks abolished the blood glucose increase in the STZ-induced diabetic rats. This effect was dose dependent. The standard hypoglycemic drug; glibenclamide has been activating insulin release from pancreatic β-cellsmainly by inhibiting ATP sensitive K_{ATP} channels in the plasma membrane [20]. The antidiabetic effect following *A. farinosa* and *A. nummularia* treatments may be due to increased release of insulin from the existing β-cells of pancreas. Further, the antihyperglycemic activity of *both extracts* was associated with an increase in plasma insulin level, suggesting an insulinogenic activity of the plant extracts. The observed increase in the level of plasma insulin indicates that *A. farinosa* and *A. nummularia* stimulate insulin secretion from the remnant beta cells or from regenerated β-cells. In this context, a number of other plants have also been reported to exert hypoglycemic activity through insulin release stimulatory effect [21 and 22]. The maximum reduction in glucose levels was observed in rats receiving 400 mg/kg of *A. farinose* extract.

HbA_1C levels are monitored as a reliable index of glycemic control in diabetes [23]. During diabetes, the excess glucose of the blood reacts with hemoglobin and form HbA1c. The rate of glycosylation is directly proportional to that of FBG level. Studies have shown that HbA_1C comprises 3.4 to 5.8% of total hemoglobin in normal red cells, but is elevated in patients with DM [24].Koenig [23] also reported a 16% increase in HbA_1C levels in diabetic patients. Our results showed that, the low level of total hemoglobin and high level of HbA1c in diabetic rats at the 8th week was significantly improved by the administration of *A. farinosa* and *A. nummularia* (200 and 400mg/kg) extracts. This result was well correlated with an earlier report of decreased hemoglobin levels in experimentally diabetic rats [25]. Reduced HbA1c contents in the medicated diabetic rats could be related to the improvement in insulin release from the remnant pancreatic β-cells that resulting in improvement in glycemic state. In this context, several medicinal plants have also been reported to have the ability to reduce HbA_1C levels in diabetic rats [26].

As one of the complications that followed diabetic hyperglycemia is dyslipidemia [27], the serum lipid profile of rats was evaluated in this study. As expected, untreated diabetic animals showed a significant increase in serum TG, TC and LDL-C concentrations against low levels of HDL-C. This increase in serum lipids is mainly due to the increased fatty acid mobilization from adipose tissue. Since insulin has an inhibitory action on HMG-CoA reductase (3-hydroxy-3-methyl-glutaryl coenzyme A reductase), the key enzyme in cholesterol biosynthesis [28], insulin deficiency or insulin resistance may therefore be responsible for hyperlipidemia. Our results showed that *A. farinosa* and *A. nummularia* medication (200 and 400 mg/kg) brought back the increased levels of TG, TC and LDL-C of STZ-diabetic rats near to their normal levels. It could be suggested that this antihyperlipidemic effects of *A. farinosa* and *A. nummularia* pass through a decrease in the activity of cholesterol biosynthesis enzymes and/or the changed level of lipolysis, which are under the control of insulin [29].

Oxidative stress has been shown to play a key role in the causation of diabetes. STZ produces reactive oxygen species (ROS) in the body, which cause pancreatic injury and could be responsible for increased blood sugar as well as lipid peroxidation. As such, antioxidants may have a role in the alleviation of diabetes [30]. Scavenging or detoxification of excess ROS is achieved by an efficient antioxidative system

comprising of non enzymic as well as enzymic antioxidants [31]. The enzymic antioxidants include SOD, GPx and CAT. Reduction in the activity of these enzymes results in a number of deleterious effects due to the accumulation of superoxide anion radicals and hydrogen peroxide. In present study, reduced activities of SOD, GPx and CAT have been observed in the pancreatic homogenate of STZ-induced diabetic rats. The administration of *A. farinosa* and *A. nummularia* for 8 weeks increased the SOD, GPx and CAT activities and GSH level in the pancreas of diabetic rats. The capability of *A. farinosa* and *A. nummularia* extracts to restore the altered antioxidant enzymes in the pancreatic homogenate STZ-induced diabetic rats indicates their free radical scavenging potential. Robertson [32] demonstrated that antioxidants have been shown to brake the worsening of diabetes by improving β cellsfunction in animal models and suggested that enhancing antioxidant defense mechanisms in pancreatic islets may be a valuable pharmacologic approach to managing diabetes. In our study, a decrease was observed in GSH in pancreas during diabetes. Decreased GSH levels in diabetes have been considered to be an indicator of increased oxidative stress [33]. GSH depletion promotes generation of reactive oxygen species and oxidative stress with the subsequent cascade of effects affecting the functional and structural integrity of cell and organelle membranes. Administration of the extracts and glibenclamide increased the content of GSH in the pancreas of diabetic rats. High GSH levels protect cellular proteins against oxidation through the GSH redox cycle and also directly detoxify the reactive oxygen species generation induced by exposure to streptozotocin [34].

Further, lipid peroxidation measurement is a more practical and safer method to evaluate the factors causing cellular injury and the activation of the common pathway. Tissue MDA content, the final product of lipid breakdown caused by oxidative stress, is an important indicator of free radical-induced lipid peroxidation [35]. In present study, elevated MDA levels were induced in diabetic rats. This was significantly attenuated by treatment with *A. farinosa* and *A. nummularia* since plants has been reported to be rich in flavonoids and diterpenoids, well-known antioxidants [36] that scavenge the free radicals generated during diabetes.

The pancreas plays an essential role in the regulation of micronutrient metabolism. The diabetogenic effect of STZ may be due to destruction of β cells of the islets of Langerhans [37]. This is particularly apparent here with the islets shrinkage (atrophy), cellular degeneration, and clear decrease in the area occupied by β cells, in the diabetic animals due to the effect of STZ-induced pancreatic injury. The extensiveness of these injuries in STZ-diabetic rats was noticeably lessened by glibenclamide and *A. farinosa* and *A. nummularia* extracts. Both extracts significantly suppressed further damage to endocrine cells, evidenced by the decreased number of necrotic cells. This effect by *A. farinosa* and *A. nummularia* is of important significance because cell necrosis is an irreversible process, whereas cell degeneration is reversible. B cells regeneration by various plants in STZ-induced diabetic rats have been previously reported [38 and 39]. Regeneration of β cells is known as one of the four means by which remedial plants demonstrate antihyperglycaemic activity [40]. However, the effect of *A. farinosa* and *A. nummularia* extracts may be through the prevention of β cells death and recovery of the partly injured β cells.

CONCLUSION

From this study, we can conclusively state that, *A. farinosa* and *A. nummularia* extracts possess antidiabetogenic and antioxidant properties in addition to beneficial effects on diabetic hyperlipidemia. These beneficial effects could be attributedto the bioactive components in both extracts.The probable mechanism of the antihyperglycemic activity may be through a stimulation of insulin release from the remnant pancreatic βcells. Hence these plants may be considered as among the potential sources for the isolation of new oral anti hypoglycemic agents.

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