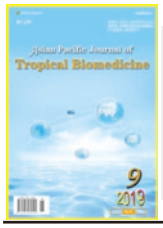

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Antidiabetic effect of *Opuntia dillenii* seed oil on streptozotocin−induced diabetic rats

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ABSTRACT

Objective: To assess the antidiabetic effect of *Opuntia dillenii* seed oil on rats with diabetes mellitus.

Methods: A rat diabetes model was established by intraperitoneal injection of rats with 50 mg/kg streptozotocin. Thirty albino Wistar rats were divided into five groups: the diabetic control group and normal control group were treated only with distilled water, two diabetic groups received 1 and 2 mL/kg of oil per day, respectively, for 30 days and one diabetic group received 2 mg/kg of glibenclamide. In addition, blood glucose was determined weekly. Body weight, average daily food, water intake and urinary volume of each animal were determined before and after the treatment period. After the treatment period, hepatic glycogen was determined using the anthrone reagent, and glycosuria, total cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, urea, creatinine and uric acid were estimated using common clinical diagnostic kits.

Results: Oral intake of the oil at 1 and 2 mL/kg for the diabetic animals significantly diminished blood glucose, glycosuria, total cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, urea, creatinine and uric acid, accompanied by a noticeable elevation in the amount of hepatic glycogen in comparison with the diabetic control group. Similarly, *Opuntia dillenii* seed oil significantly increased the food intake and decreased the urinary volume per day in treated rats of the same groups in comparison with the period before the treatment intervention and attenuated body weight loss in the diabetic rats. Moreover, this effect of the oil was dose dependent. On the other hand, the oil did not affect their need for water.

Conclusions: The results show that *Opuntia dillenii* seed oil has a very important antidiabetic effect on streptozotocin-induced diabetic rats. Hence, we suggest it as a preventive control of diabetes mellitus.

1. Introduction

Diabetes mellitus (DM) is a malady produced by a metabolic disorder of sugars, and it is usually related to an abnormal insulin levels in the blood or the insensitivity of target organs to insulin. Moreover, no control of glycaemia in diabetic patient causes the hyperglycemia. In addition, the persistence of hyperglycemia in diabetic patients causes the increase of oxidative stress due to the auto-oxidation of glucose[1], finally leading to significant mortality

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and morbidity induced by microvascular (nephropathy, retinopathy, and neuropathy) and macrovascular (stroke, peripheral vascular disease and heart attack) complications in diabetics[2]. The number of diabetics worldwide is rising and estimates proposed that there would be 592 million diabetics in the year 2035, with remarkable rises in developing states[3]. The interaction of environmental risk, behavioral and genetic predisposition factors can cause this disease. Therefore, the increasing prevalence of DM requires preventive interventions[4]. Until now, there is no cure for this disease. Insulin therapy is used to control blood sugar levels in diabetics. Nevertheless, there are several disadvantages, including insulin resistance after long-term treatment. However, the oral antidiabetics used to treat this disease are expensive or have unwanted side effects or contraindications[5]. That is why a large part of the population come to using herbal medicine to treat diabetes to avoid these problems[6]. As a result, the search for best performing and safer agents to treat this disease is becoming an active area of research around the world[7]. The Cactus plant belongs to the Cactaceae family[8], it is of Mexican origin, and it has been introduced in North Africa in the 16th century[9]. In Cactaceae family, about 1 500 species have been cited and are grouped in the *Opuntia* genus, it is distributed in several regions such as Europe, Mediterranean countries, Africa and other regions[10]. This plant develops in arid and semiarid regions[11]. Most species of *Opuntia* have edible fruits and are very fragrant[12]. *Opuntia dillenii* (*O. dillenii*) is a species of cactus, growing in western and northeastern Morocco. It plays a great role in subsistence agriculture. It is characterized by an acid taste and the presence of a large number of seeds. The stem and fruit of this plant are used in conventional medicine for the treatment of diabetes[13], gastric ulcers, inflammation[12], analgesic[14] and antihyperglycemic effect[15]. *O. dillenii* seed oil (ODSO) is an oil that is characterized by a great level of unsaturation fatty acids, wherein linoleic acid is the significant fatty acid, β-sitosterol is the sterol marker and vitamin E is represented by only γ-tocopherol[16]. Antioxidant[17] and anti-inflammatory[18] activities are the only studies that have been done on this oil. So far, very few studies have been carried out on ODSO and no studies have been carried out with regard to the antihyperglycemic and antidiabetic activities of this oil. The goal of the current study was to evaluate the antidiabetic effect of ODSO on streptozotocin (STZ) provoked diabetic rats.

2. Materials and methods

2.1. Collection of plant material

The fresh fruits of *O. dillenii* used in this study were collected in February 2016 from regions in Essaouira, Morocco. The specimen was deposited at Mohammed First University, Oujda, Morocco under the reference number HUMPOM 351, after its identification by the expert botanist Mohammed Fennan, from the scientific institute of the university Mohammed 5.

2.2. Preparation of O. dillenii seeds

Fruits of *O. dillenii* were peeled, then the seeds were separated from the fruit. After that, the seeds were washed with distilled water, dried in the oven at 37 ℃ until the stabilization of their weight, and then ground with a blender until a fine and homogeneous powder was obtained and stored at -20 ℃ until use.

2.3. Oil extraction

An amount of 100 g of seeds powder was added in 500 mL of petroleum ether and the mixture was stirred under ambient temperature for 24 h. After filtration, the organic solvent was removed on a rotary evaporator under temperature 40 ℃. The resulting oil was dried and stored at 4 ℃.

2.4. Chemicals

STZ was purchased from Sigma-Aldrich (Hamburg, Germany), and glibenclamide obtained from Sigma chemicals (USA). All other reagents and chemicals utilized were of analytical grade.

2.5. Animals and housing

Male and female albino Wistar rats (150-200 g) were employed in this work. Animals were housed in macrolon cages under standard laboratory prescriptions [12 h darkness /12 h light, (21 ± 2) ℃]. The rats received standard pellets diet and water *ad libitum* during the experimental period. In this study, rats were used and treated by reviewing the International Guide to the Use and Care of Laboratory Animals, published by the National Institutes of Health in the United States (NIH Publication No. 85-23, revised 1985). The experiment was approved by Faculty of Sciences of Oujda, Mohamecl First University (Oujda Ie 04/12/2018).

2.6. Induction of diabetes

STZ recently prepared in citrate buffer (0.1 mol/L phosphate, 0.1 mol/L citrate, pH 4.5) was injected intraperitoneally to rats (fasted overnight) by a single dose (50 mg/kg) to induce experimental diabetes. Rats with fasting blood glucose higher than or equal to 1.8 g/L on day 7 after injection, and with indication of polydipsia and polyuria were regarded diabetic and incorporated in the study.

2.7. Grouping of animals

The rats were randomized into 5 groups with 6 animals in each

group: Normal control and diabetic control rat groups received distilled water alone, two diabetic groups received 1 and 2 mL/kg of ODSO, respectively, and one diabetic group received 2 mg/kg of glibenclamide. The treatment product was administered orally once per day for 30 d. In addition, blood glucose was determined weekly, body weight, average daily food, water intake and urinary volume of each animal were determined before and after the treatment period. After the experimental period, rats were fasted for 12 h. Rats were then given ether anesthesia and sacrificed to collect the blood samples for biochemical estimations.

2.8. Hepatic glycogen

The amount of hepatic glycogen was determined according to the protocol described by Ong and Khoo[19]. Liver fragments (0.3-0.5 g) were first milled, mixed with 2 mL of 30% KOH and boiled at 100 ℃ for 30 min. The mixture was treated twice with 4 mL of 95% ethanol to precipitate glycogenesis. The resulting pellet was hashed with 8 mL of 95% ethanol and solubilized in 1 mL of distilled water. Glycogen concentration was determined using the anthrone reagent. The optical density was read at 625 nm.

2.9. Biochemical assays

Separated plasma samples were used for the assessment of glucose, glycosuria, total cholesterol (TC), triglycerides (TG), urea, uric acid, creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), using common clinical diagnostic kits and following protocols from the manufacturer.

2.10. Statistical analysis

Data were presented as mean ± SEM and subjected to statistical analysis using Graph Pad Prism 5 Software, San Diego, CA, USA. Multiple-group comparisons were analyzed by one-way analysis of variance (ANOVA). Statistical significance was agreed as $P < 0.05$.

3. Results

3.1. Effect of ODSO administration on food intake, water intake and urinary volume in diabetic rats

The intraperitoneally injection of rats with STZ (50 mg/kg) increased their water requirement and urination frequency. On the other hand, it did not affect the need for food in comparison with the normal control rats. After treatment, the difference in water intake was not significant between diabetic rats with treatment (ODSO at 1 mL/kg and 2 mL/kg, and glibenclamide) and diabetic rats without treatment. Moreover, oral intake of ODSO at 1 mL/kg and 2 mL/kg did not affect daily water intake compared to that before treatment. The same result was obtained in diabetic rats treated with glibenclamide (Figure 1A). The

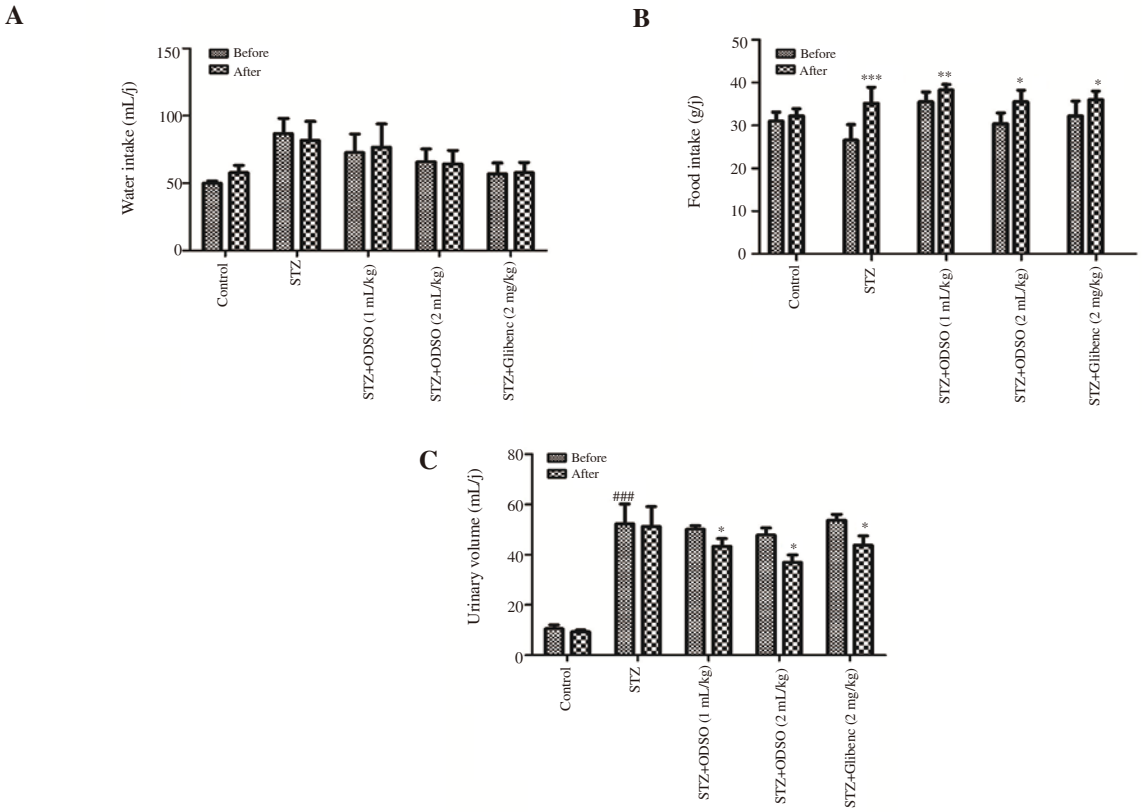

Figure 1. Effect of oral intake of *Opuntia dillenii* seed oil (ODSO) at 1 and 2 mL/kg on water intake (A), food intake (B) and urinary volume (C) in diabetic rats. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ different from before treatment. $^{###}P < 0.001$ different from the normal control group after treatment. STZ: streptozotocin.

administration of oil at 1 and 2 mL/kg and glibenclamide at 2 mg/kg significantly increased the food intake compared to that before treatment ($P < 0.01$, $P < 0.05$ and $P < 0.05$, respectively). However, after treatment, there was no significant difference in food intake between diabetic rats with treatment (ODSO at 1 mL/kg and 2 mL/kg, and glibenclamide) and diabetic rats without treatment (Figure 1B). The intake of ODSO at 1 and 2 mL/kg and glibenclamide at 2 mg/kg substantially decreased the amount of urinary volume in diabetic rats compared to the period before the treatment; while the urinary volume of diabetic rats with treatment (ODSO at 1 mL/kg and 2 mL/kg, and glibenclamide) was decreased compared to diabetic rats without treatment, but the difference was not significant (Figure 1C).

3.2. Effect of ODSO administration on body weight in diabetic rats

The variation in body weight gain in normal and diabetic rats was demonstrated in Figure 2. Untreated diabetic rats lost significantly ($P < 0.001$) their body weight in comparison with healthy rats. However, oral intake of ODSO prevented loss of body weight at a dose of 1 mL/kg and significantly ($P < 0.01$) raised body weight gain at an amount of 2 mL/kg in diabetic rats. In addition, glibenclamide substantially ($P < 0.01$) raised body weight gain at an amount of 2 mg/kg in diabetic rats.

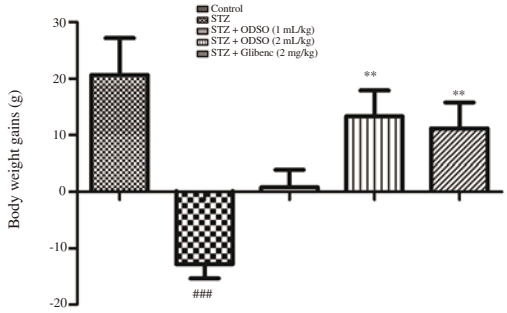

Figure 2. Effect of oral intake of *Opuntia dillenii* seed oil (ODSO) at 1 and 2 mL/kg on body weight gains in diabetic rats. ###$P < 0.001$ different from normal control group; **$P < 0.01$ different from control diabetic group. STZ: streptozotocin.

3.3. Effect of ODSO administration on plasma glucose in diabetic rats

The intraperitoneally injection of rats by STZ at a single concentration (50 mg/kg) provoked a substantial rise ($P < 0.001$) in fasting glycemia in rats for 30 d, compared with normal control rats (Table 1). In addition, the oral intake of diabetic rats with an amount of 1 mL/kg of ODSO induced a diminution in their fasting blood glucose at the end of four weeks, and this effect was significant ($P < 0.05$) in the second and fourth week, whereas diabetic rats received 2 mL/kg of ODSO showed a significant decrease in fasting glucose during treatment period in comparison with diabetic control rats. Diabetic rats received glibenclamide (2 mg/kg) also showed a substantial decrease in fasting blood glucose that was similar to that of rats treated with 2 mL/kg ODSO.

3.4. Effect of oral intake of ODSO on glycosuria level in diabetic rats

The action of the ODSO on the glycosuria amount in diabetic rats was demonstrated in Figure 3. The results demonstrated that the glycosuria in diabetic control rats was substantially ($P < 0.001$) increased in comparison with normal rats. The intake of the ODSO (1 and 2 mL/kg) and glibenclamide (2 mg/kg) substantially decreased glycosuria levels ($P < 0.001$; $P < 0.001$; $P < 0.01$) which were different from diabetic control rats.

3.5. Effect of oral intake of ODSO on hepatic glycogen amount in diabetic rats

The action of the ODSO on the hepatic glycogen amount in diabetic rats was shown in Figure 4. The results showed that the hepatic glycogen amount in diabetic rats was substantially ($P < 0.001$) lower, in comparison with normal rats. Moreover, the administration of the ODSO (1 and 2 mL/kg) and glibenclamide (2 mg/kg) significantly increased hepatic glycogen level ($P < 0.01$; $P < 0.01$; $P < 0.001$, respectively), compared with diabetic control rats.

Table 1. Effect of ODSO on blood glucose levels in diabetic rats.

Groups	Blood glucose (g/L)				
	0 week	1st week	2nd week	3rd week	4th week
Control	0.95 ± 0.05	0.94 ± 0.04	0.97 ± 0.03	1.03 ± 0.04	1.03 ± 0.05
STZ	2.22 ± 0.11$^{###}$	2.47 ± 0.13$^{###}$	2.58 ± 0.13$^{###}$	2.64 ± 0.17$^{###}$	2.61 ± 0.13$^{###}$
STZ + ODSO (1 mL/kg)	2.28 ± 0.23	2.13 ± 0.25	1.98 ± 0.23*	2.12 ± 0.43	1.64 ± 0.31*
STZ + ODSO (2 mL/kg)	1.95 ± 0.07	1.94 ± 0.13*	1.88 ± 0.09**	1.78 ± 0.05**	1.71 ± 0.11***
STZ + Glibenclamide (2 mg/kg)	2.09 ± 0.12	1.89 ± 0.22*	1.82 ± 0.15**	1.77 ± 0.13**	1.51 ± 0.13***

The data are expressed in mean ± SEM. ###$P < 0.001$ different from normal control animals; *$P < 0.05$ different from diabetic control animals; **$P < 0.01$ different from diabetic control animals; ***$P < 0.001$ different from diabetic control animals. ODSO: *Opuntia dillenii* seed oil. STZ: streptozotocin.

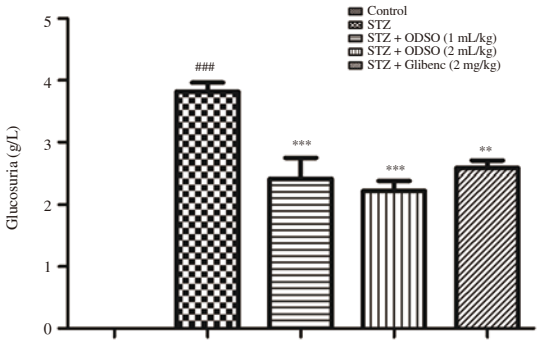

Figure 3. Effect of oral administration of *Opuntia dillenii* seed oil (ODSO) at 1 and 2 mL/kg on glycosuria levels in diabetic rats. The bar graph represents mean ± SEM. $^{###}P < 0.001$ different from the normal control group; $^{**}P < 0.01$, $^{***}P < 0.001$ different from the diabetic control group. STZ: streptozotocin.

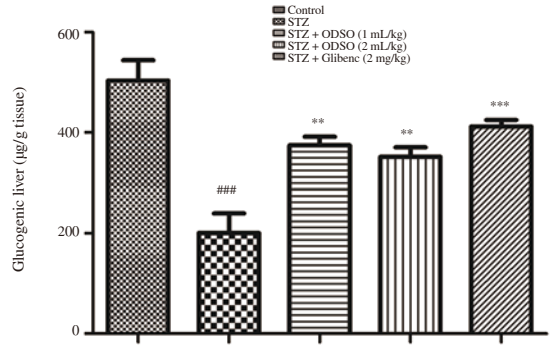

Figure 4. Effect of oral intake of *Opuntia dillenii* seed oil (ODSO) at 1 and 2 mL/kg on hepatic glycogen level in diabetic rats. The bar graph represents mean ± SEM. $^{###}P < 0.001$ different from the normal control group; $^{**}P < 0.01$, $^{***}P < 0.001$ different from the diabetic control group. STZ: streptozotocin.

3.6. Effect of oral intake of the ODSO on TG and TC amounts in diabetic rats

The action of ODSO on serum TC and TG levels in diabetic rats was shown in Figure 5. The data demonstrated that the plasma TC and TG in diabetic rats were significantly higher, compared to normal rats. The administration of the ODSO (1 and 2 mL/kg) significantly decreased serum TC ($P < 0.05$, $P < 0.01$) and TG ($P < 0.01$, $P < 0.001$). In addition, glibenclamide reduced serum TC and TG ($P < 0.001$) compared with diabetic control rats.

3.7. Effect of oral intake of the ODSO on plasma urea, creatinine and uric acid amounts in diabetic rats

The action of ODSO intake on plasma uric acid, creatinine and urea level in diabetic rats was shown in Figure 6. The results demonstrated that plasma uric acid, creatinine and urea amount in diabetic control rats were significantly higher, in comparison with normal rats. The intake of the ODSO (1 and 2 mL/kg) substantially diminished uric acid ($P < 0.05$), creatinine and urea ($P < 0.05$; $P < 0.001$) in comparison with diabetic control rats. The intake of the glibenclamide (2 mg/kg) also substantially diminished uric acid, creatinine and urea in comparison with diabetic rats.

3.8. Effect of oral intake of the ODSO on serum ALT and AST amounts in diabetic rats

The effect of intake of the ODSO on plasma AST and ALT level in diabetic rats was shown in Figure 7. The results showed that plasma ALT and AST amounts in diabetic control rats were substantially ($P < 0.001$) increased. The administration of ODSO (1 and 2 mL/kg) significantly decreased AST ($P < 0.01$; $P < 0.001$) and ALT ($P < 0.01$; $P < 0.001$) levels, in comparison with diabetic control rats. The administration of glibenclamide (2 mg/kg) also decreased ALT and AST amounts, in comparison with diabetic control rats.

4. Discussion

Our study has assessed the antidiabetic effect of ODSO on diabetic rats, based on the analysis of biochemical parameters related with DM. The experimental animal model used in this study is induced by STZ, which is a substance extracted from *Streptomyces achromogenes*. Currently, it is the most used to cause DM in rats, due to its cytotoxic and selective effect against pancreatic cells. Indeed, STZ induces the death of pancreatic β cells by inducing the alkylation of their DNA,

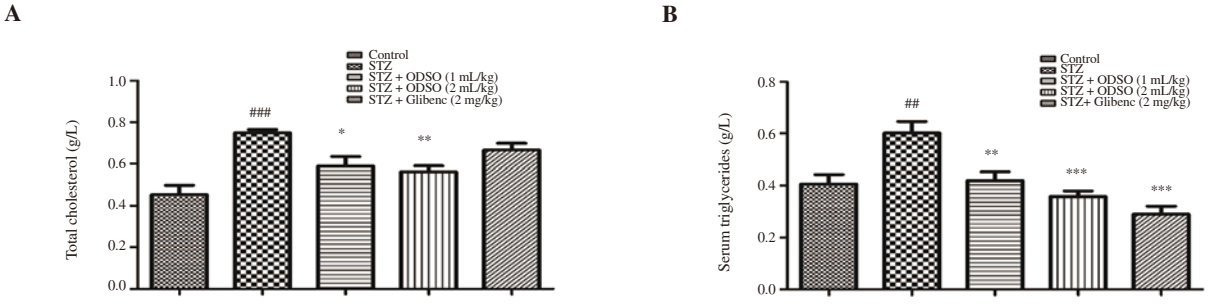

Figure 5. Effect of oral intake of *Opuntia dillenii* seed oil (ODSO) at 1 and 2 mL/kg on (A) total cholesterol (TC) and (B) triglycerides (TG) levels in diabetic rats. The bar graph represents mean ± SEM. $^{##}P < 0.01$, $^{###}P < 0.001$ different from the normal control group. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ different from the diabetic control group. STZ: streptozotocin.

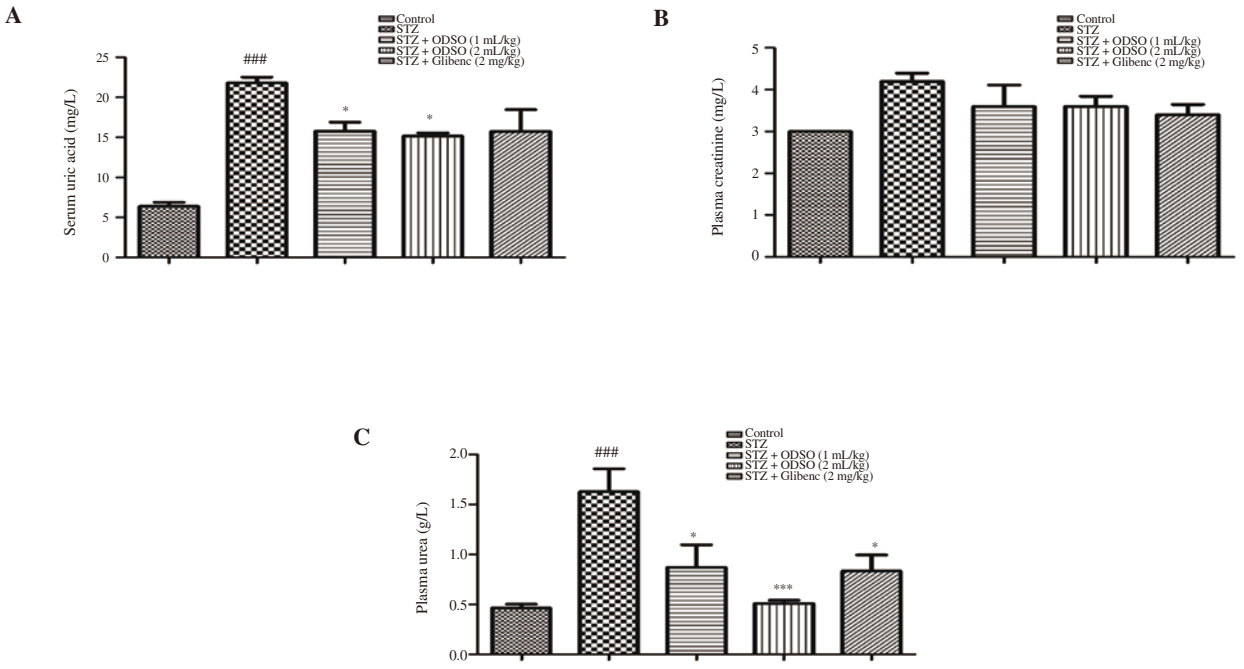

Figure 6. Effect of oral intake of *Opuntia dillenii* seed oil (ODSO) at 1 and 2 mL/kg on serum uric acid (A), creatinine (B) and urea (C) levels in diabetic rats. The bar graph represents mean ± SEM. $^{###}P < 0.001$ different from the normal control group. $^{*}P < 0.05$, $^{***}P < 0.001$ different from the diabetic control group. STZ: streptozotocin.

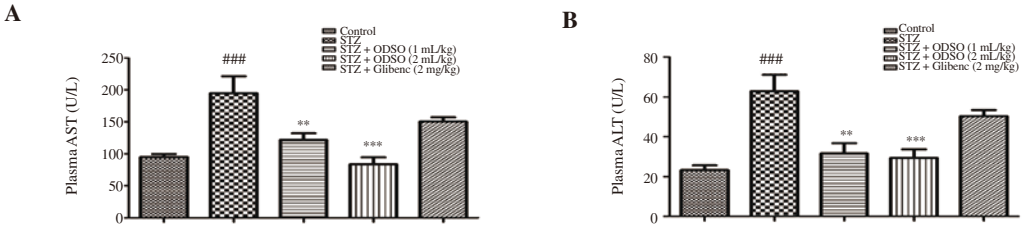

Figure 7. Effect of oral intake of *Opuntia dillenii* seed oil (ODSO) at 1 and 2 mL/kg on serum AST (A) and ALT (B) levels in diabetic rats. The bar graph represents mean ± SEM. $^{###}P < 0.001$ different from the normal control group. $^{**}P < 0.01$, $^{***}P < 0.001$ different from the diabetic control group. STZ: streptozotocin.

and thus reducing the release and synthesis of insulin. In addition, STZ has been shown to be involved in DNA fragmentation by producing reactive oxygen species[20,21].

The results of this study demonstrated that the intraperitoneal injection of STZ in rats induced significant hyperglycemia, which is the most important feature in DM patients[22]. In this work, 30 days of ODSO administration has significantly attenuated the increase of glycaemia. The study on chemical composition of ODSO has showed the richness of sterols[16], which are known to have ability to reduce the level of glucose in the blood[23]. Moreover, STZ has provoked noticeable decrease of hepatic glycogen, and substantial rise of glycosuria in rats, but this effect has been significantly reversed after the daily administration of ODSO in diabetic rats. According to the results, the oil has significant anti-hyperglycaemic effect on diabetic rats, which has been confirmed by the decrease in glycosuria and by glycogenogenesis. The restoration to normal state of hepatic glycogen by this oil is probably due to the activation of β cells to release the insulin that will activate the glycogen synthesis system[24].

The STZ induced diabetes in rats brings about several remarkable symptoms including polyphagia (after one month of STZ injection), polydipsia and loss of body weight, caused by the degradation and loss of structural proteins[25]. Likewise, all these symptoms have been found in STZ-induced diabetic rats in our study. Urinary volume, water intake and loss of body weight are increased compared with normal group. However, ODSO do not affect daily water intake and this could be explained by the fact that this model of diabetes is induced by a slight dose of streptozotocin (50 mg/kg), and the blood sugar does not exceed an average of 2 g/L. In addition, the STZ has provoked the elevation of the plasma TG and TC, and the elevation in these parameters has been reported in diabetic condition[26]. The restoration to normal levels of these parameters has occurred after the thirty days of ODSO administration. Studies have shown that phytosterols induce decrease in plasma TC levels, but their mode

of action is not completely understood[27]. Calpe-Berdiel *et al*. have shown that these compounds cause decrease in the solubility of cholesterol and its absorption across the intestinal barrier[28]. The prevention of diabetic complications as well as the improvement of lipid metabolism could be induced by the improvement of the lipid profile in diabetic animals treated with ODSO[29]. In diabetic animals, elevation in the plasma creatinine, urea and uric acid has been reported, which are considered as noticeable markers of renal dysregulation[30]. The daily intake of ODSO has ameliorated the renal function *via* the correction of plasma creatinine, uric acid and urea to normal levels. It has been reported that STZ causes the hepatotoxicity[31]. This hepatotoxicity induced by the STZ has also been noticed in our work by the elevation of AST and ALT. Therefore, increased ALT and AST may be induced by the release of these enzymes from the cytosol of liver to blood, which gives an explanation of the hepatotoxicity activity of STZ[20]. However, this effect of STZ has been corrected by the daily administration of ODSO. All these results agree with the study of Bouhrim *et al*, which explored the effect of ODSO on CCl_4-induced hepatotoxicity. Additionally, this study showed that this oil improved the metabolic function of the liver and excretory renal system[32].

It has been declared that ODSO contains a huge amount of unsaturated fatty acids, wherein linoleic acid is the principal polyunsaturated fatty acid and oleic acid is the main monounsaturated fatty acid. Besides, β-sitosterol is the sterol marker and the unsaponifiable fraction is represented by only γ-tocopherol[16,17].

Insulin resistance and insulin deficiency are the two major defects that cause hyperglycemia in patients with type 2 diabetes[33]. The pancreatic β cell increases its insulin secretion when it is stimulated by D-glucose under the effect of omega-3 fatty acids[34]. In addition, the fluidity of the cell membrane and the regulation of the GLUT4 transporter expression are improved by the polyunsaturated fatty acids[35]. The polyunsaturated fatty acids increase the amount of glucose absorbed by the insulin sensitive cells (3T3-L1 adipocytes) by rising the number of GLUT4 and GLUT1 transporters[36]. The β-sitosterol exhibits significant hypoglycemic effect in normal and hyperglycemic models[37].

A study that concerns the chemical composition of ODSO has shown that the ODSO is rich in phenolic compounds[16]. Compounds are a large group of natural antioxidants found in many foods and beverages, and involved in the prevention of several major chronic illnesses, such as diabetes[38]. Generally, diabetes is closely correlated with oxidative stress, and related to elevated ROS production or decrease in the antioxidant defense system[39]. Phenolic compounds, which are characterized by antioxidant activity, are known to have an antidiabetic activity by regulating the disturbed oxidative medium under diabetic conditions[40].

The preventative anti-diabetic effect of this oil could be due to the high insulin secretion, improved insulin sensitivity of the cells, and the capacity of glucose utilization. In summary, daily administration of ODSO for 30 d showed a significant preventive antidiabetic effect in diabetic rats. In addition, this effect was demonstrated by controlling dietary intake, urinary volume, body weight gain and biochemical parameters in relation to diabetes.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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