Attenuation of Oxidative Stress and Inflammation by *Portulaca oleracea* in Streptozotocin-Induced Diabetic Rats

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Abstract

The present study was designed to investigate the protective effect of the aqueous extract of *Portulaca oleracea* against hyperglycemic, oxidative damage and inflammation in the serum of streptozotocin (STZ)-induced diabetic rats. In the present study, the rats were divided into the following groups of 8 animals each: control, untreated diabetic, 3 *Portulaca oleracea* (100, 200, 400 mg/kg/d)–treated diabetic groups. At the end of the 4-week period, glucose, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), glutathione (GSH), and total antioxidant status (TAS) levels were measured. STZ caused an elevation in the serum levels of glucose, MDA, IL-6, and TNF-α with reduction in the levels of GSH and TAS ($P < .01$). *Portulaca oleracea* ameliorated glucose, MDA, IL-6, TNF-α, GSH, and TAS levels in diabetic groups versus to the untreated groups ($P < .05$). Taken together, *Portulaca oleracea* prevented hyperglycemia by preventing the oxidative stress and inflammation.

Keywords

Portulaca oleracea, diabetes, rat, streptozotocin, oxidative indices, inflammation

The metabolic syndrome is characterized by insulin resistance, dyslipidemia, and hypertension and is associated with type 2 diabetes and cardiovascular disease.[1]

Diabetes is a complex metabolic disorder that consists of progressive hyperglycemia in the context of insulin resistance, which precedes insulin deficiency as a result of β-cell failure.[1] Accumulating evidence shows that β-cell loss in diabetes due to the combination of oxidative stress and inflammation. Oxidative stress is caused by imbalance between oxidant-antioxidant systems, which could be because of elevated free radical generation and decreased activity of antioxidants.[2] Involvement of oxidative stress in the pathogenesis of diabetes is suggested not only by the generation of free radicals especially reactive oxygen species (ROS) but also because of nonenzymatic protein glycosylation, auto-oxidation of glucose, impaired glutathione metabolism, modification in antioxidant enzymes and lipid peroxides formation.[3] On the other hand, oxidative stress induces overproduction of ROS, which activates several inflammatory signaling cascades that will contribute to inflammation.[4] Expression of pro-inflammatory molecules might attract local inflammatory cells, which may further exacerbate the local inflammation, causing β-cell apoptosis and type 2 diabetes.[5] Therapeutic approaches were designed to improve oxidative stress and inflammation and prove new drugs for the prevention of diabetes.[6] In the past

decade, there is a growing interest to evaluate biological and medical properties of herbal remedies against diabetes.[6] *Portulaca oleracea* L (*Portulaceae*, common name purslane) is a warm-climate annual, used traditionally for alleviating pain and swelling.[7] It has been shown a wide range of pharmacological effects including antibacterial,[8] antioxidant,[9,10] anti-inflammatory,[11] skeletal muscle relaxant,[12,13] and wound healing[14] activities. It is also serves as a vegetable, widely sold in shops in China, United Arab Emirates, and Oman[15] and has been reported to be rich in α-linolenic acid and β-carotene.[16] In addition, purslane consists of flavonoids[17], coumarins[18] and monoterpene glycoside, in particular, contain dopamine, *N-trans*-feruloyltyramine,[19] high concentration of noradrenaline,[20] adenosine,[21] and ferulic acid.[22] The protective effect of purslane against type 2 diabetes remains uncertain. Hence, the present study was conducted to find the effect of purslane as antidiabetic agent in

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streptozotocin (STZ)-induced diabetic rats by measuring glucose, interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), malondialdehyde (MDA), glutathione (GSH), and total antioxidant status (TAS) levels in the serum.

Materials and Methods

Reagents

All purified enzymes, coenzymes, substrates, standards, buffers, kits, and other chemicals were purchased from Sigma-Aldrich Chemical (St Louis, MO, USA). Glucose kit was purchased from Pars Azmoon kit (Iran).

Animals

Wistar albino rats (2 months; 200 ± 13 g) were bred at the university experimental animal care center. Animals were maintained under standard environmental conditions and had free access to standard rodent feed and water.

Study Design

Forty male Wistar albino rats were randomly allotted to 5 experimental groups (n = 8 per group) as follows: group 1, control (C); group 2, diabetic (D); group 3, diabetic and *Portulaca oleracea*–treated (100 mg/kg/d) (D + PO1); group 4, diabetic and *Portulaca oleracea*–treated (200 mg/kg/d) (D + PO2); and group 5, diabetic with *Portulaca oleracea*–treated (400 mg/kg/d) (D + PO3). Rats were kept in their own cages at constant room temperature (21°C ± 2°C) under a normal 12-hour light/dark cycle with free access to food and water. The animals were housed according to regulations for the welfare of experimented animals. The study was conducted in Mashhad Medical University Experimental Animal Research Laboratory. Protocols were approved by the Ethical Research Committee of Mashhad University of Medical Sciences. On the first day of the study, the diabetic groups were given STZ in a single intraperitoneal injection at a dose of 60 mg/kg for induction of diabetes. Blood was extracted from the tail vein for glucose analysis 72 hours after STZ injection. Rats with blood glucose levels higher than 250 mg/dL were accepted as being diabetic. In the control groups (C), physiological saline (intraperitoneally) was injected as vehicle. *Portulaca oleracea* was injected (intraperitoneally) to the treatment groups from 3 days after STZ administration for 4 weeks. Blood glucose level was recorded at weekly intervals. At the end of the 4-week period, animals were anesthetized by ether and blood was subsequently collected from the retro orbital sinus. Blood and sera were separated by centrifugation at 3000 rpm for 10 minutes for glucose, IL-6, TNF-α, MDA, GSH, and TAS.

Biochemical Analysis

During the experiment, the serum glucose concentration was measured with the Ames One Touch glucometer (One-Touch Basic; Lifescan, Johnson & Johnson, New Brunswick, NJ, USA) in rat tail vein blood. At the end of experiment, blood glucose was estimated using the diagnostic kits (Pars Azmoon kit, Iran) on an automatic analyzer (Abbott, model Alcyon 300, Dallas, TX, USA). TNF-α and IL-6 was measured by enzyme-linked immunosorbent assay method according to the manufacturer's instructions. The serum MDA was estimated by TBARS (thiobarbituric acid reactive substances) method.[23,24] The whole blood reduced GSH was measured using
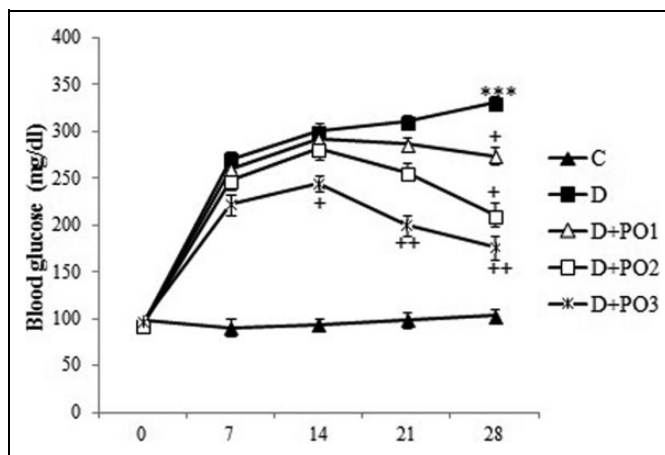

Figure 1. Effect of purslane on blood glucose level (mg/dL). Control (C), untreated diabetic rats (D), *Portulaca oleracea* (PO)–treated (100 mg/kg/d) diabetic rats (D + PO1), PO-treated (200 mg/kg/d) diabetic rats (D + PO2), and PO-treated (400 mg/kg/d) diabetic rats (D + PO3) during 4 weeks of study (n = 8, for each group). Values are the means ± standard error of the mean (SEM) for 8 rats in each group. Significantly different from normal control (group C) rats (***P < .001). Significantly different from streptozotocin (STZ)-treated (group D) rats (+P < .05, ++P < .01).

Ellman's reagent (5,5′-dithio-bis-2-nitrobenzoic acid,) as described by Beutle et al.[25] The TAS was measured by FRAP (ferric reducing antioxidant power) method.[26,27]

Statistical Analysis

All experiments were carried out at least in duplicate. Each group consisted of 8 rats. One-way analysis of variance was performed and Tukey's post hoc test was used for multiple comparisons. Statistical analyses were performed using the InStat 3.0 program. The results are expressed as mean ± standard error of the mean. The results originated from analysis of serum. Linear correlation tests were also performed. Differences of P < .05 were considered significant.

Results

After the experimental period (4-week), STZ-diabetic rats exhibited significant (P < .001) hyperglycemia compared with the control rats (Figure 1). Purslane decreased blood glucose level in the diabetic rats compared to the untreated diabetic rats in a dose-dependent manner (P < .001) (Figure 1). Purslane (200 and 400 mg/kg/d) significantly decreased glucose in STZ diabetic rats only at the fourth week of the study (P < .05 and P < .01, respectively), while the highest dose of purslane (80 mg/kg/d) was significantly reduced blood glucose in diabetic rats in the beginning of the first week of treatment (P < .05 and P < .01, respectively) (Figure 1).

STZ injection produced significant changes in oxidative stress and inflammatory parameters in the serum of diabetic rats 4 weeks after diabetes induction, as shown by increased lipid peroxidation product (MDA) (P < .001), TNF-α (P < .01), IL-6 (P < .001) and decreased GSH (P < .001) and TAS (P < .01) compared with the control group (Table 1). The highest

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Table 1. Effect of PO on Serum MDA, GSH, TAS, IL-6, and TNF-α in Control, Untreated Diabetic Rats, and PO-Treated Diabetic Rats During 4 Weeks of Study (n = 8 for Each Group).[a]

	C	D	D + PO1	D + PO2	D + PO3
MDA (nmol/mL)	1.66 ± 0.26	4.45 ± 0.40***	4.02 ± 0.34***	3.21 ± 0.35*####	2.47 ± 0.29++#
GSH (nmol/mL)	2.78 ± 0.19	1.06 ± 0.11***	1.56 ± 0.18***	1.97 ± 0.22*+++	2.36 ± 0.15+++#
TAS (nmol/mL)	4.55 ± 0.70	1.78 ± 0.35**	2.37 ± 0.38*	3.11 ± 0.52	1.87 ± 0.35+
IL-6 (pg/mL)	2.12 ± 0.13	5.34 ± 0.54***	4.56 ± 0.45***	4.00 ± 0.32*	3.45 ± 0.36+
TNF-α (pg/mL)	9.82 ± 0.60	15.11 ± 1.13**	13.21 ± 0.90	11.54 ± 0.49+	10.26 ± 1.05++

Abbreviations: PO, *Portulaca oleracea*; MDA, malondialdehyde; GSH, glutathione; TAS, total antioxidant status; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.
[a]C denotes controls; D, denotes untreated diabetic rats; D + PO1 denotes PO-treated (100 mg/kg/d) diabetic rats; D + PO2 denotes PO-treated (200 mg/kg/day) diabetic rats; and D + PO3 denotes PO-treated (400 mg/kg/day) diabetic rats. Significantly different from normal control (group C) rats (*P < .05, **P < .01; ***P < .001). Significantly different from streptozotocin-treated (group D) rats (+P < .05, ++P < .05, +++P < .001). Significant difference between D + PO1 group versus D + PO3 group (#P < .05).

Table 2. Effect of PO on Serum MDA, GSH, and Total Protein in in Control, Untreated Diabetic Rats, and PO-Treated Diabetic Rats During 4 Weeks of Study (n = 8 for Each Group).[a]

	C	D	D + PO1	D + PO2	D + PO3
MDA (nmol/mg protein)	1.66 ± 0.26	4.45 ± 0.40***	4.02 ± 0.34***	3.21 ± 0.35*####	2.47 ± 0.29++#
GSH (nmol/mg protein)	2.78 ± 0.19	1.06 ± 0.11***	1.56 ± 0.18***	1.97 ± 0.22*++	2.36 ± 0.15+++#
Total protein (mg/g)	4.55 ± 0.70	1.78 ± 0.35**	2.37 ± 0.38*	3.11 ± 0.52	1.87 ± 0.35+

Abbreviations: PO, *Portulaca oleracea*; MDA, malondialdehyde; GSH, glutathione.
[a]C denotes controls; D, denotes untreated diabetic rats; D + PO1 denotes PO-treated (100 mg/kg/d) diabetic rats; D + PO2 denotes PO-treated (200 mg/kg/day) diabetic rats; and D + PO3 denotes PO-treated (400 mg/kg/day) diabetic rats. Significantly different from normal control (group C) rats (*P < .05, **P < .01, ***P < .001). Significantly different from streptozotocin-treated (group D) rats (+P < .05, ++P < .05, +++P < .001). Significant difference between D + PO1 group versus D + PO3 group (#P < .05).

dose of purslane (400 mg/kg/d) decreased the serum MDA (P < .01), IL-6 (P < .05), TNF-α (P < .01) and increased GSH (P < .001), and TAS (P < .05) content versus the untreated diabetic groups (Table 1). Dosage of 200 mg/kg/d of purslane decreased the serum levels of TNF-α (P < .05) and increased GSH (P < .01) versus the untreated diabetic groups (Table 1). A significant difference was observed between MDA and GSH levels in rats that received the lowest dose (100 mg/kg) and the highest dose (200 mg/kg) (P < .05) (Table 2).

Discussion

The results of the present study indicate that intraperitoneal injection of purslane significantly ameliorated the adverse metabolic effects in the serum of rats treated with STZ. Purslane injection after STZ treatment resulted in lower serum glucose level when compared with rats treated with STZ alone. In addition, purslane treatment of diabetic rats recovered decreased GSH and TAS levels as well as increased MDA, TNF-α, and IL-6 levels. The results confirmed the previous findings showed by others using STZ to induce diabetes in rats and enhance the susceptibility to lipid peroxidation.[28,29] Oxidative stress pays an essential role in the complications and pathogenesis of diabetes. Hyperglycemia induces extra production of oxygen free radicals, which is involved in the development of diabetes and its complications.[28] Several investigations have indicated that STZ disrupts balance between plasma oxidant and antioxidant system, causes the progression of diabetes

mellitus and its complications.[29,30] STZ enters the pancreatic β cell by the low-affinity glucose protein-2 transporter, making the selective damage of the insulin-producing islet β cells and, in turn, a significant decrease in insulin secretion.[29] Therefore, diabetes progressed in the STZ-treated rats via damage to the pancreas due to induction of oxidative stress both locally and systemically.[29] These results may be the important mechanism in STZ-induced hyperglycemia complications.[30]

Oxidative stress is associated with the activation of a cascade of inflammatory signaling pathways and characterized by abnormal cytokine production (TNF-α and IL-6).[31] TNF-α has been shown to enhance adipocyte lipolysis, which further increases free fatty acids and also elicits its own direct negative effects on the insulin signaling pathway by altering the tyrosine/serine phosphorylation of insulin receptor substrate.[32]

In our experimental model of diabetes mellitus, it was seen that STZ administration led to a significant decrease in plasma GSH and TAS accompanied by a significant increase in MDA, TNF-α and IL-6 in serum. MDA is an aldehydic product of lipid peroxidation that combine quickly with biomolecules and contributes to cellular disturbance, including β-pancreatic cell, thus, deregulating glucose metabolism.[33,34] The amelioration of variable measurements in STZ-diabetic rats after purslane treatment might indicate a protective effect of purslane against STZ function that could be mediated via reduction of oxygen free radicals. Purslane treatment of the diabetic rats restored oxidative stress indices. This may be due to a reduction in free radical production and also elevation in antioxidant content. In

the current study, GSH and TAS levels were increased in purslane-treated diabetic rats versus the untreated diabetic rats. Purslane may also decrease lipid peroxidation by increasing the antioxidant content.

It is also presumed that the reduction of pro-inflammatory mediators by purslane treatment might have improved insulin signaling pathways and glucose uptake process. This observation perfectly agrees with those of Lee et al[35] who demonstrated hypoglycemic and anti-inflammatory activity of purslane in diabetic mice. Their work showed that purslane treatment to diabetic mice could make helpful effects by reducing blood glucose, ameliorating renal function via decreasing inflammation in diabetes. Similarly, El-Sayed[36] observed that purslane seed may effectively control hypoglycemic, hypolipidemic, and insulin resistance in diabetic patient; possibly due to its contents of polyunsaturated fatty acids, flavonoids, and polysaccharides. In addition, it was demonstrated that aqueous extract of purslane could markedly alleviate high fat diet-induced oxidative injury by enhancing blood and liver antioxidant enzyme activities.[37] Another study indicated that purslane leaves had a protective effect against oxidative stress caused by vitamin A deficiency.[38] It was shown that betacyanins from purslane ameliorated cognition deficits and attenuate oxidative damage induced by D-galactose in the brains of senescent mice.[38]

In our study, prooxidant-antioxidant balance was evaluated by measuring MDA, GSH, and TAS levels in the serum of the diabetic rats. Elevated MDA and reduced GSH and TAS levels pointed out that the balance changed toward pro-oxidation in STZ-induced diabetic rats. Purslane treatment of diabetic rats improved GSH and TAS levels due to reduction in free radical production and enhancement antioxidant defenses. Purslane consists of ingredients with its antioxidant activity such as flavonoids, amino acids, proteins, and enzymes. Flavonoids are a group of phenolic compounds with its hydrogen donating activity[39] and a scavenger of free radicals. In biological systems, Purslane showed its antioxidant impact via hydrogen donating antioxidant activity[39] and a scavenger of free radicals.

Purslane modulates oxygen radical production, which may be responsible at least in part for the amelioration hyperglycemia, inflammation, and oxidative stress seen in the present study in STZ-diabetic rats. Moreover, elevated GSH and TAS levels after Purslane treatment play an additional role in decreasing oxidative stress. In summary, the present study showed that the association between hypoglycemic effect of purslane with antioxidant and anti-inflammatory activities in STZ-diabetic rats. However, detailed studies are required for the evaluation of the exact protective mechanism of purslane against diabetes and its complications in human and animal models.

Author Contributions

SS was involved with supervising this work, writing the manuscript, study conception and design, analysis and interpretation of data, and critical revision. AB performed the experiment, and was involved in analysis and interpretation of data. TF was involved with writing and editing the manuscript, helped design the manuscript, performed the experiment, and was involved with acquisition of data.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Ethical approval for this study was granted by the Ethical Research Committee of Mashhad University of Medical Sciences.

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