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Original Article

Comparative Histopathologic Evaluation of the Effects of *Portulaca oleracea*, Omega-3, and Combination of Sodium Selenite and Vitamin E on Hepatic Enzymes of Experimental Diabetic Rats

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ABSTRACT

Introduction: *Portulaca oleracea* (PO) plant, Omega 3, and Sodium Selenite plus Vitamin E exert antidiabetic effects by compensating for the deficiency in insulin release and enhancing antioxidant status. The purpose of the present study was to comparatively assess the effect of *Portulaca oleracea*, omega-3, and a combination of Sodium Selenite and Vitamin E on hepatic enzyme activities in streptozotocin-induced diabetic rats.

Materials and methods: A total of 48 adult male Wistar rats (weighing approximately 220 ± 10 g) were injected by a single intraperitoneal injection of streptozotocin (60 mg/kg body weight.) and were randomly assigned to 4 groups, and 4 replicates for each group. Group 1 served as diabetic control, groups 2, 3, and 4 received *Portulaca oleracea* extract (1.5 mg/kg/day, orally), Omega-3 (500 mg/kg/day, orally), and Sodium Selenite (0.5 mg/kg/day, orally) plus Vitamin E (400 Iu/kg/day, orally), respectively, for 28 days. At the end of the study, blood samples were taken for biochemical investigations.

Results: The levels of blood glucose, AST, ALP, and GGT enzymes in all treatment groups were less than those of the control group. The ALT enzyme activity in rats treated with *Portulaca oleracea* and Vitamin E plus Selenium was less than in control and omega-3 treatment groups.

Conclusion: Results indicated that *Portulaca oleracea* is more effective in hepatic enzyme activities of diabetic rats, compared to other treatment groups.

1. Introduction

Diabetes mellitus is a pathologic condition that causes extensive and non-physiological metabolic imbalance disorders, including an increase in blood glucose, and changes in carbohydrate, lipid, and protein metabolism in different body tissues, such as liver and pancreas[1,2]. An increase in blood glucose initiates a series of cascade reactions, which leads to an increase in the production of free radicals (including oxygen free radicals) in various body tissues[3,4]. The high potency of these compounds for chemical reactions damages cells and tissues. Several reports have been published concerning the involvement of Reactive Oxygen Species (ROS) in tissue damages[5] among which the high level of ROS in pancreatic islets and changes in oxidative stress markers in laboratory animals can be noted[6]. Aerobic cells can be protected against free radicals, particularly ROS, by antioxidants compounds, such as glutathione, vitamins E and C, as well as super Oxide Dismutase (SOD), glutathione Peroxidase (GPx), and catalase enzymes[7,8]. Studies have also shown a significant decline in both non-enzymatic antioxidants, including rehabilitated glutathione (GSH) and Vitamin E as well as enzymatic antioxidants, such as SOD, catalase, and GPx in diabetic rats)[9,10]. It has also been

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indicated that free radicals can cause diabetic damage in different organs, such as the pancreas and liver, by declining SOD, catalase, and antioxidant activities[10,11]. Free radicals can also damage the unsaturated fatty acid in cell membranes[12]. The combination of fatty acids in cell membranes can affect cell membrane-related phenomena, such as the interaction between insulin and its receptors[13]. In addition, it has been indicated that the fatty acid composition of membrane phospholipids in insulin targets tissues, such as the liver and skeletal muscles, affecting both insulin secretion and its biological activity[14]. Red blood cells are also susceptible to oxidative damage due to the presence of fatty acid in their membrane and high concentration of oxygen and hemoglobin[11]. Hence, it is beneficial to use antioxidant compounds (particularly natural antioxidants) and omega-3 fatty acids to prevent oxidative damage.

Vitamin E plus Selenium is one of the important food compounds with high antioxidant properties and can also affect different biological processes of the body. Shamsi et al.[15] have indicated that Vitamin E decreases blood glucose in diabetic rats and reduces diabetic disorders. It has been reported that Vitamin E declines Malondialdehyde and increases GSH and SOD in diabetic rats[16].

Vitamin E prevents lipid peroxidation and protects cells against peroxide radicals; thus, it is the most important antioxidant in the biological membrane, which can neutralize free radicals[17]. Selenium is the only trace element that enters the genetic code as selenocysteine. This element can be extensively found in selenoproteins, namely the GPx enzyme, through which the Selenium antioxidant effect can be activated[18]. Reports available on the efficacy of Selenium in diabetes have indicated a decline in the effectiveness of streptozotocin (STZ) and enhancement of positive effects on GPX enzyme activity in laboratory rats[19,20].

Portulaca oleracea is a rich source of omega-3 polyunsaturated fatty acids (alpha-linolenic acid), different vitamins (A, C, and E), and minerals with different pharmacological properties (such as antioxidant, anticancer, anti-inflammatory, and antimicrobial)[21]. However, bioactive compounds of *Portulaca oleracea* can have beneficial effects against diabetes[22]. Few studies have addressed the antidiabetic effects of *Portulaca oleracea* in previous years[23,24]. Thus, the present study aimed to compare the effect of Portulaca oleracea, omega-3, and Sodium Selenite plus Vitamin E on hepatic enzyme activities in streptozotocin-induced diabetic Rats.

2. Materials and Methods

2.1. Ethical approval

All procedures were approved by the Animal Care Committee of Veterinary Medicine, Islamic Azad University, Tabriz Branch, Iran. The principles of laboratory animal care were followed, and specific international laws were observed.

2.2. Animals

A total of 48 male Wistar rats aged 2-3 months, with an average weight of 220 g were bought from Razi Institute, Iran, and kept in laboratory conditions with *ad libitum* water and food intake. Experimental animals were kept in standard cages with a minimum of 50% humidity, 24°C temperature, and 12 hours dark/light cycle with appropriate ventilation in a particular cage. The rats were divided into 4 main groups of 10, and 8 rats randomly remained as a control group. The groups contained the control group of diabetic rats, which received the standard ration daily, the second group of diabetic rats was fed the standard ration plus *Portulaca oleracea* extract (1.5 mg/kg/day) via gastric feeding tube daily. The third group of diabetic rats was fed a standard ration plus omega 3 (500 mg/kg/day) via gastric feeding tube daily, the fourth group of diabetic rats was fed standard plus Vitamin E (400 iu/kg/day) and Selenium (0.5 mg/kg/day) via gastric feeding tube daily.

2.3. Extraction of Portulaca oleracea

The aforementioned atmospheric parts of *Portulaca oleracea* were prepared at the farm of Islamic Azad University, Tabriz, Iran, and kept in a dark glass bottle at 10°C temperature away from direct sunlight. Then, 250 g of the intended powder was extracted by ethanol-water solvent (70% ethanol-30% water) three times at normal laboratory temperature based on the method of Abdullah and Kusumaningtyas[25]. The extracts were mixed and condensed with reduced pressure so that their volume reached 500 ml, equal to 0.5 g of the powder per milliliter. The extract was divided into equal volumes (25 ml) and stored at -20°C temperature for further investigation.

2.4. Diabetes infusion

The rats were diabetic via IP Injection of STZ solution at a dosage of 60 mg/kg dissolved in buffer citrate 0.1 at pH=4.5. On the second day, blood samples were collected from animals under anesthesia with chloroform through a tail vein. Rats with fasting blood glucose higher than 250 mg/dl were considered diabetic and were used in the present study.

2.5. Blood sample

One day after the last gavage, blood samples were taken from all mice through a tail vein under chloroform anesthesia conditions once before receiving the medication (fasting) and once an hour after receiving the medication. The serum was extracted by centrifugation device for 15 minutes at a speed of 3000 rpm. Then, serum levels of blood glucose and liver enzymes, such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and alpha-glutamyl transpeptidase (GGT) were measured and recorded by standard kits of Pars Azmoon Company (Iran).

2.6. Statistical analysis

The obtained data were collected and recorded in Excel software. The statistical analysis was performed with SAS

version 19 using the mean comparison with Duncan's multi-domain test with 95% confidence level ($p < 0.05$)[26].

3. Results

3.1. Fasting blood glucose levels

Blood glucose levels in all treatment groups were significantly lower than the diabetic control group ($p < 0.05$), but indicated a higher blood glucose level than the control group ($p < 0.05$, Table 1). The lowest blood glucose levels were observed in the omega-3 (244 mg/dl), *Portulaca oleracea* (253 mg/dl), and Vitamin E + Selenium (283 mg/dl) groups although the difference was not significant ($p > 0.05$).

3.2. Blood glucose levels an hour after the last treatment

Blood glucose levels in all treatment groups were significantly lower than the diabetic control group ($p < 0.05$). The results indicated a significant difference between the *Portulaca oleracea* and the control groups ($p < 0.05$, Table 1). The lowest blood glucose levels were observed among the treatment groups as 136, 146, and 163 mg/dl in Vitamin E + Selenium, omega-3, and *Portulaca oleracea* groups, respectively, although the difference between them was not significant ($p > 0.05$).

3.3. AST activity levels

The activity of AST enzyme in all treatment groups was significantly lower than in the diabetic control group ($p < 0.05$), but still showed a higher difference in enzyme activity than the control group ($p < 0.05$, Table 2). The lowest AST enzyme activity among the treatment groups was observed in the groups of *Portulaca oleracea* (164 U/L), Vitamin E + Selenium (183 U / L), and omega-3 (236 U/L). However, this enzymatic activity in the groups consuming *Portulaca oleracea* and Vitamin E + Selenium showed a significant decrease, compared to the group consuming omega-3 fatty acids ($p <0.05$).

3.4. ALT activity levels

ALT enzyme activity was significantly lower in the groups treated with *Portulaca oleracea* and Vitamin E + Selenium and also in the healthy control group than the diabetic control group and omega-3 consuming group ($p < 0.05$, Table 2). The lowest ALT enzyme activity was observed among the treated groups in the groups consuming Vitamin E + Selenium (83 U/L), *Portulaca oleracea* (85 U/L), and omega-3 (117 U/L). *Portulaca oleracea* and Vitamin E + Selenium indicated enzymatic activity close to the healthy control group.

3.5. ALP activity levels

Alkaline phosphatase activity in all treated groups was significantly lower than in the diabetic control group, and the Vitamin E + Selenium group showed a significant decrease, compared to the omega-3 group ($p < 0.05$, Table 2). The lowest ALP enzyme activity was observed among the treatment groups in the groups consuming Vitamin E + Selenium (129 U/L), *Portulaca oleracea* (145 U/L), and omega-3 (184 U/L). *Portulaca oleracea* and Vitamin E + Selenium revealed enzymatic activity close to the healthy control group.

3.6. GGT activity levels

GGT activity was significantly lower in all treatment groups than in diabetic and control groups ($p < 0.05$, Table 2). The lowest activity of the GGT enzyme among the treatment groups was observed in the groups of *Portulaca oleracea* (14 U/L), Vitamin E + Selenium (16 U/L), and omega-3 (21 U/L). However, this enzymatic activity did not show a significant difference among the groups ($p > 0.05$).

Table 1. Fasting blood glucose levels in control and treatment groups of diabetic rats on day 28

Groups Blood glucose	Control group	*Portulaca oleracea* group	Omega-3 group	Vitamin E + Selenium group	Diabetic control group
Fasting blood glucose	125^{a}	253^{b}	244^{b}	283^{b}	550^{c}
One hour after the last treatment	114^{a}	163^{c}	146^{b}	136^{b}	466^{d}

^{a,b,c,d}: Different superscript letters in the same group mean significant differences ($p < 0.05$)

Table 2. Enzyme activity levels in control and treatment groups of diabetic rats on day 28

Groups Enzymes	Control group	*Portulaca oleracea* group	Omega-3 group	Vitamin E + Selenium group	Diabetic control group
AST	79^{a}	164^{c}	236^{d}	183^{c}	294^{b}
ALT	72^{a}	85^{a}	117^{b}	83^{a}	122^{b}
ALP	114^{a}	145^{a}	184^{c}	129^{a}	528^{b}
GGT	30^{a}	14^{b}	21^{b}	16^{b}	29^{a}

^{a,b,c,d} Different superscript letters in the same group mean significant differences ($p < 0.05$)

4. Discussion

Portulaca oleracea extract contains active pharmacological agents, such as alkaloids, glycosides, terpenoids, sterols, and flavonoids. It may be stated that some of these compounds can reduce the severity of autoimmune reactions and the inflammation process to the extent that leads to the destruction of beta cells. Consequently, the destruction of the remaining cells is prevented, which provides ample opportunity for the

proliferation of these cells and the regeneration of the pancreatic islets. It was found that the consumption of *Portulaca oleracea* extract caused the regeneration of pancreatic islets in diabetic rats with STZ due to the presence of flavonoids, such as quercetin, existing in the aerial parts of the plant, which can release insulin by changes in Ca++ metabolism[27]. The results of a study addressing the effect of *Portulaca oleracea* extracts on alloxan-induced diabetic rats have indicated a significant decrease in the Hemoglobin A1C (Hb A1C), serum levels of glucose, Tumor Necrosis Factor-alpha (TNF-α), and Interleukin 6 (IL-6) of *Portulaca oleracea* pre-treated diabetic rats confirming that *Portulaca oleracea* is a general tissue-protective and regenerative agent and also demonstrated the antidiabetic effect of the hydro-ethanolic extract of *Portulaca oleracea* seeds on diabetic animals[28]. *Portulaca oleracea* modulates radical oxygen production, which may be responsible at least in part for the amelioration of hyperglycemia, inflammation, and oxidative stress[29]. In an investigation by Dehghan et al. [30], it was indicated that 16 weeks of aerobic training or/and *Portulaca oleracea* seed consumption were effective in the regulation of diabetic parameters and biomarkers associated with atherosclerosis in women with Type 2 Diabetes (T2D). Another relevant study revealed that diabetes significantly impaired brain abilities and swimming training, and *Portulaca oleracea* synergistically reversed and ameliorated neurobehavioral dysfunction in type 2 diabetic rats[31]. *Portulaca oleracea* can keep blood glucose levels normal in three ways. Firstly, it reduces the transfer of glucose from the intestine to the bloodstream, secondly, increases cell access to glucose in the bloodstream; and finally, it modulates the sensitivity of cells to insulin[32].

Water, minerals, pectin, protein, carbohydrates, fatty acids, especially omega-3 unsaturated fatty acids, antioxidants, and numerous minerals (such as ferritin, copper, manganese, potassium, calcium, and cessation) are found in different parts of this plant[33,34]. *Portulaca oleracea* is the richest plant source with omega-3 fatty acids[33]. Its antioxidant compounds include Olefatoferol, Ascorbic acid, and Glutathione[4]. In addition, the antioxidant properties of the plant extract have been confirmed in laboratory studies[12]. In another study, it was found that aqueous and ethanolic extracts of *Portulaca oleracea* leaves can produce various antioxidants[35]. Moreover, isoquinoline, as the main alkaloid of *Portulaca oleracea* had a significant stimulating effect on insulin secretion and improved glucose uptake[36]. It should be noted that no significant toxic marks have yet been reported about *Portulaca oleracea* [37].

There are reports on the effectiveness of Selenium in diabetes as well as its significant role in reducing the effect of STZ, and enhancing the activity of GPx enzyme in rats[19,20]. However, Selenium has a narrow therapeutic index, and the increase in consumption can have toxic effects[38].

Vitamin E is known as the most important antioxidant of biological membranes that can neutralize free radicals[17]. Jamilian and Ravanbakhsh[39] reported that Vitamin E plus omega-3 fatty acid supplementation in gestational diabetes mellitus women had beneficial effects on biomarkers of inflammation and oxidative stress. Baburao Jain and Anand Jain[40] have demonstrated that Vitamin E supplementation has an important role in delaying the onset of diabetic complications as well as slowing down the progression of the complications. Another meta-analysis indicated that the supplementation of Vitamin E might be a valuable strategy for controlling diabetes complications and enhancing antioxidant capacity[41].

The essential fatty acids are reported to have a low level in different tissues of diabetic patients. Adding omega-3 fatty acids to the diet of diabetic patients can improve omega-3 fatty acid deficiencies[42]. The causes of low levels of essential fatty acids in diabetic patients are unclear, but some researchers assert that diabetics have less ability to convert linoleic acid into Eicosapentaenoic *acid* and Docosahexaenoic acid. In one of the latest studies on the antidiabetic effects of Vitamins C, A, and E, as well as omega-3 fatty acids, it was found that lipid peroxidation and malondialdehyde levels were reduced due to the decreased production of free radicals or inhibition of oxidative damage[43].

In a study, it was found that when the activity of ALT enzyme increases, injecting Vitamin E with Selenium, its activity is significantly closer to normal[44]. Contrary to the present results, another study indicated a significant increase in the activity of ALP enzyme due to Vitamin E + Selenium[45]. Similar to the results of the present study, Sousou et al.[46] indicated that *Portulaca oleracea* consumption could significantly increase the activity of liver enzymes (ALT, AST, and GGT) in rats with bile ducts closed, compared to rats with bile ducts. *Portulaca oleracea* extracts significantly increase serum total protein levels and decreases urea, uric acid, cholesterol, triglyceride LDL, and liver enzymes, including ALT and AST in diabetic rats[47]. A study by Zarei et al. [48] indicated that the extract of this plant could improve liver function due to the hypoglycemic and hypolipidemic antioxidant properties of *Portulaca oleracea* extract and its effect on reducing liver enzymes (ALT, ALP). In another study, Abdel et al. [49] revealed that consumption of fish (a source of omega-3) significantly reduced the activity of AST and ALT enzymes in diabetic rats.

5. Conclusion

Given the high content of ALA fatty acids (more than 3 times more than spinach) in *Portulaca oleracea* and their durability, as well as the presence of a rich source of Vitamin E (approximately 7 times more than spinach) along with other vitamins, minerals, and beneficial minerals, as well as the results of the current study, it can be concluded that *Portulaca oleracea* can be used as a food to prevent diabetes and control blood glucose during diabetes. Moreover, considering the effects of *Portulaca oleracea* and its compounds along with the combination of Vitamin E and Selenium on liver enzymes, it can be suggested that these two groups can strongly control the

destructive effects of diabetes on the liver cell function and even their activity proceeds to normal.

Declarations

Competing interests

The authors declare that they have no competing interests.

Authors' contribution

Daryoush Babazadeh designed the study and performed the sampling and practical procedures. Ali Shabestari Asl revised the draft of the manuscript, and checked the final version of the article, Alireza Sadeghi performed the statistical analysis, Muhammad Saeed revised the draft of the manuscript and removed the language errors, and Arman Moshavery wrote the draft of the manuscript. All authors check the final proof of the article and the statistical results.

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Availability of data and materials

All data and related findings of the thesis are prepared for publishing in the present journal.

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