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The effect of oral administration of eggplant hydroalcoholic extract on avoidance memory retrieval in streptozotocin-induced diabetic male rats

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ABSTRACT

Introduction: Diabetes is caused by defects in insulin secretion or function. Diabetes causes structural and functional damage in the central and peripheral nervous system, including degeneration of the memory system. The present study is an attempt to determine the effect of eggplant extract on memory retrieval in diabetic rats.
Methods: Mature male Wistar rats (200-250 g) are divided into five groups (n = 7): 1) healthy (control), 2) untreated diabetic, 3, 4 and 5) diabetic rats treated by the hydroalcoholic extract of eggplant (25, 50 and 100 mg/kg). Rats with streptozotocin (STZ) (60 mg/kg) became intraperitoneally diabetic. On the fifth day after receiving the STZ, the animals with blood glucose higher than 200 mg/dL, were considered diabetic. The control group only received saline and the treated diabetic group received eggplant extract orally for two weeks. The healthy group did not receive any medication or extract. Shuttle box was used to assess the spatial memory of the rats.
Results: Eggplant extract in higher doses (50 and 100 mg/kg) significantly reduced blood glucose levels in diabetic rats ($P < 0.001$). The spatial memory in diabetic rats was weakened ($P < 0.01$). Eggplant extract at a dose of 50 mg/kg significantly improved the paramnesia in diabetic group ($P < 0.05$).
Conclusion: STZ increased blood glucose, resulting in spatial memory deficits, And this has probably occurred through the production of free radicals in the brain tissue. It seems that, in addition to reducing blood glucose levels, eggplant, due to containing compounds with antioxidant properties, can reduce free radicals and thereby improve memory deficits caused by diabetes.

Implication for health policy/practice/research/medical education:
Diabetes is an important factor in the loss of memory. Eggplant can reduce blood sugar in people with diabetes and reduces the symptoms of memory disorders caused by diabetes.
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Introduction

Diabetes mellitus is a disease caused by defects in insulin secretion or function which leads to increased blood glucose. In this disease, the metabolism of carbohydrates, fat and protein is impaired (1). Progression of diabetes is associated with more complex disorders and complications including retinopathy, nephropathy, neuropathy and microvascular disorders (2). Diabetic neuropathy is considered as an important complication of diabetes. It is known that in diabetes, the sensitivity to painful stimulus is increased and the motor nerve conduction velocity (MNCV) in peripheral nerves including the sciatic nerve is reduced (3,4). According to the previous studies, chronically high blood glucose in diabetes causes structural and functional damage in the peripheral and central nervous system including degradation of the memory system (5). Memory and learning disorders as well as complex information processing disorders are reported in patients with type 1 and 2 diabetics (6,7). Oxidative stress is involved in the pathogenesis of many central nervous system disorders (e.g. neurodegenerative diseases) or in the physiological process of aging (8). Studies have shown the brain is very vulnerable to oxidative stress resulting from the high content of unsaturated fatty acids and is particularly sen-

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sitive to the destruction of reactive oxygen species (ROS) (9,10). Based on previous findings, the incidence of diabetes mellitus in laboratory animals (e.g. rats) and human is associated with disorders in cognitive and memory processes, brain atrophy and increased risk of dementia. Although the structure of these disorders is not well-known in the diabetes community, it has been found that cortex and hippocampus are the main areas associated with these trends, and are significantly affected by diabetes. For example, diabetes mellitus has led to exacerbation of oxidative stress and lipid peroxidation in some brain regions, including the hippocampus (11,12).

Phenolic compounds or phenolic phytochemicals are secondary metabolites with herbal origin which form an important part of diets (13) and provide the potential antioxidant advantages to manage the oxidations associated with stress in chronic diseases such as diabetes and cardiovascular disease (14). Vegetables such as eggplant, pepper and tomato from the Solanaceae family have a high phenolic content and eggplant in particular, is a source of phenolic phytochemicals with high antioxidant activity in removal of the free radicals (15-18). In fruits, antioxidant and phenolic compounds can be found in both meat and skin (19). Therefore, eggplant that can easily be included in people's diets, was used in the present study. Hence, the aim of this study was to introduce eggplant plant which is rich in antioxidants and can be useful in controlling diabetes and its complications.

Materials and Methods

Male Wistar rats weighing 200-250 g obtained from animal reproduction center in Ahwaz University of Medical Sciences were used in this experimental study. The rats were kept in a special room for animals with standard conditions, temperature of 22± 2°C. and humidity of 55%-60%. Four animals were kept in each cage and exposed to 12-hour cycles of light and darkness together with enough food and water. Before starting the experiment, the rats were kept in individual cages for one week to become familiar with the laboratory. Then, the animals were randomly divided as follows:

1) The control group (intact), 2) untreated diabetic, 3, 4 and 5) the group of diabetic rats treated with different doses of eggplant.

In this study, the diabetes was induced to the rats through intraperitoneal injection of streptozotocin (STZ) (60 mg/kg). After 72 hours, blood samples were taken from the rats' tail, and using urine strips and blood glucose measuring device (Bionime Rightest GM110, developed by Iran KMT), the glucose of blood samples was measured. The rats with blood glucose greater than 200 (mg/dL), were considered diabetic. Twenty-four hours after the last administration, glucose levels were measured again and memory testing was performed as below.

Preparation of eggplant hydroalcoholic extract

An adequate amount of fresh eggplant which is deep purple was prepared for extraction. These eggplants were washed, and peeled after their species were determined. Then the prepared eggplants were cut into 2-4 cm pieces and dried at room temperature. After drying, the pieces were grinded, and a certain amount of alcohol ethanol 80% was added to them until their surface was completely covered by alcohol. The resulting mixture was kept at 30 to 35 degrees for 72 hours and stirred periodically. After that, the mixture was passed through a clean cloth until coarse particles were separated, then the resulting solution was screened by Whatman filter paper. The resulting solution which was free of suspended particles was then concentrated by rotary, and dried at temperature of 25-30°C. The obtained dry extract was kept frozen at -20°C before it was used. Each time, the required amount of the dry matter was taken and gavaged after being dissolved in saline.

Avoidance memory test

Using a shuttle-box apparatus consisting of two compartments, one dark and the other bright, whose floor was covered with 1-2 mm stainless steel wire with one centimeter intervals as well as an electrical power generation device, a slight 75-volt, 0.3 mA Shock was applied to the rats' sole in the dark compartment. First, the animals were individually placed in the shuttle box with open guillotine doors for 3-5 minutes to move freely between the inside and outside of the compartment in order to learn about the education apparatus. Then the animal was placed in a bright box and the delay in movement to the dark box was recorded (training). Once the animal entered the dark compartment, the guillotine door closed and electric shocks were applied to the rats' sole. Twenty four hours later, the delay of rats entrance into the dark compartment (this time without any shock) as passive avoidance memory was measured in seconds and the ration of delay in entering the dark compartment on the memory day was measured by the equation: Inflection ratio (IR)=($L1$-$L0$/L0) that L0 shows initial low latency into dark room on the learning day and L1 shows low latency into dark room on the memory test day.

Statistical methods

Results are expressed as mean ± SEM. Data was analyzed using SPSS (version 21). To evaluate the results of tests in different groups ANOVA, one-way and post hoc, LSD was used. In all cases, the differences between the groups at P <0.05 were considered significant.

Results

Evaluation of blood glucose levels

Figure 1 shows blood glucose levels in the untreated diabetic rats and diabetic rats treated by different dosages of eggplant extract on the first day of treatment. As can be seen, the blood glucose levels were not significantly different between untreated diabetic and diabetic treated groups.

Figure 2 shows blood glucose levels in the control group, untreated diabetic rats and diabetic rats treated by different dosages of eggplant extract on the seventh day of treatment. As can be seen, the blood glucose levels in all groups have significantly increased compared to the control group. However, in diabetic groups treated with doses of 50 and 100 mg/kg eggplant extract significantly decreased compared with diabetic group ($P<0.001$) but have not reached the level of the control group.

Figure 3 shows blood glucose levels in the healthy rats (control), untreated diabetic rats and diabetic rats treated by different dosages of eggplant extract on the fourteenth day of treatment. As can be seen, the blood glucose levels in the diabetic group and those treated with 25 mg/kg eggplant has significantly increased compared to the control group ($P<0.001$) while in diabetic groups receiving 50 and 100 mg/kg of eggplant extract significantly decreased compared to the diabetic group ($P<0.001$).

Avoidance memory assessment using shuttle box

Figure 4 shows the ratio of delay in entering the dark compartment in the control group, untreated diabetic and diabetic groups receiving 25, 50 and 100 mg/kg dosages of eggplant extract on the fourteenth day of treatment. As you can see, 50 mg/kg of eggplant extract dosage has been able to significantly improve memory deficiency resulting from diabetes ($P<0.05$). However, the 100 mg/kg of eggplant extract dosage, despite being effective in memory impairment improvement, did not prove to be as significantly effective as the former dosage and the 25 mg/kg dosage had no significant effect on memory impairment caused by diabetes.

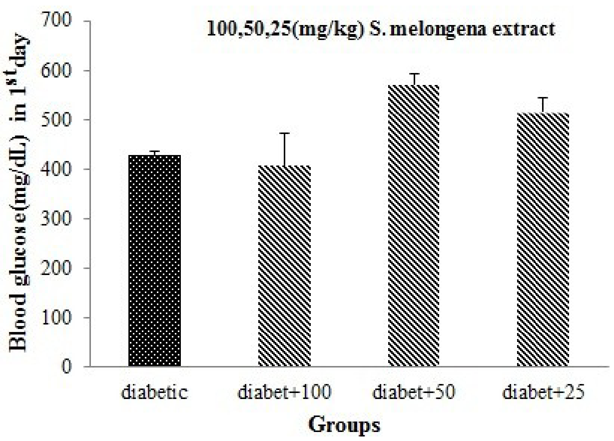

Figure 1. Comparison of blood glucose in the untreated diabetic rats and diabetic rats receiving different dosages of eggplant extract on the first day of treatment.

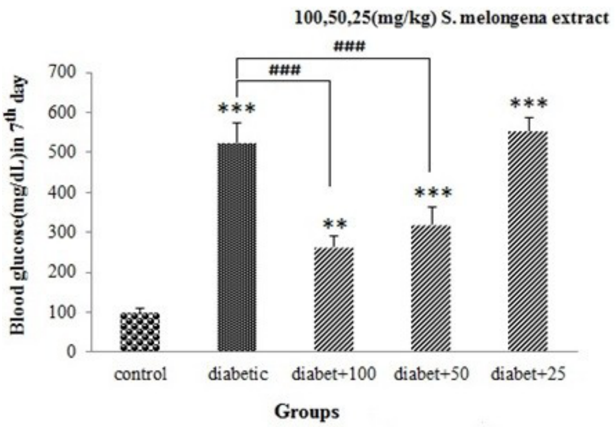

Figure 2. Comparison of blood glucose in untreated diabetic rats, diabetic rats receiving different dosages of eggplant extract and the control group, on the seventh day after the treatment. (* is the sign of comparison between the control group and other groups and # is the sign of comparison between eggplant extract-treated groups and untreated diabetic groups).

Discussion

The findings of the present study showed that oral administration of eggplant extract for two weeks could signifi-

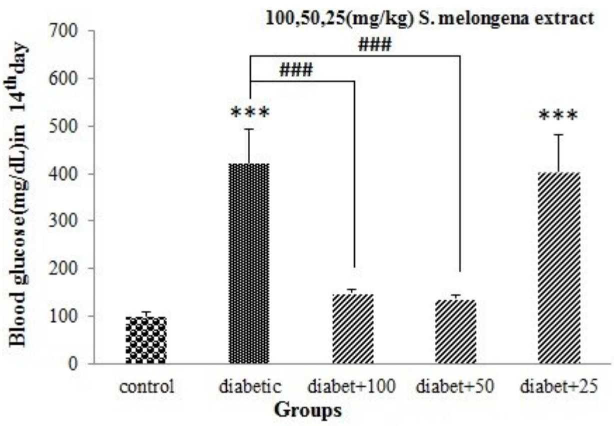

Figure 3. Comparison of blood glucose in the control group, untreated diabetic rats and diabetic rats receiving different dosages of eggplant extract and the control group, on the fourteenth day after the treatment. (* is the sign of comparison between the control group and other groups and # is the sign of comparison between eggplant extract-treated groups and untreated diabetic groups).

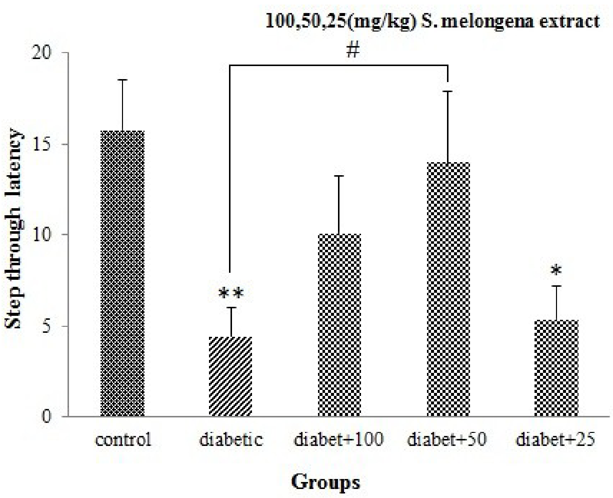

Figure 4. Comparison of delay in entering the dark compartment in the control group, untreated diabetic and diabetic groups receiving different doses of eggplant extract on the fourteenth day of treatment. (* is the sign of comparison between groups and the control group and # is the sign of comparison between eggplant extract-treated groups and untreated diabetic groups).

cantly reduce blood glucose levels in STZ-induced diabetic rats. Studies on alloxan-induced diabetic rats also showed that hydro-alcoholic eggplant extract could lead to significant reduction in blood glucose; however this effect was achieved in high doses and was dose-independent (20).
Alpha-glycosidase is an enzyme in the intestines that transforms oligosaccharides and disaccharides into monosaccharaides leading to absorption of carbohydrates and engagement in increasing the concentrations of blood glucose (21). Studies have shown that alpha-glycosidase inhibitors can delay the absorption of carbohydrates through competitive inhibition, and inhibit disaccharide hydrolysis and glucose absorption (22). In addition, acarbose which is well-known alpha-glycosidase inhibitor is clinically used as an anti-diabetic medicine. Natural sources of alpha-glycosidase inhibitors, including plants and micro-organisms, have attracted scientists' interest (23,24). Antioxidants, such as flavonoids, show significant anti-diabetic effect by inhibiting the activity of special enzymes such as aldose reductase (25). Eggplant contains important herbal materials such as phenolic compounds and flavonoids, which have high antioxidant capacity (26-28). This effect is also observed in the meat and skin of fruits (29). In vitro evaluation has also shown that eggplant extract has a positive effect on risk factors for hyperglycemia, hypertension, antioxidant activity and appropriate inhibition action against carbohydrate modulator enzymes such as alpha-glycosidase which is associated with glucose absorption in the intestines (30).
Eggplant is able to inhibit the starch hydrolysis enzymes such as α-amylase and α-glycosidase in a dose-dependent manner, where α-glycosidase is inhibited severely and α-amylase is inhibited moderately (31), which can reduce the glucose absorption from the intestine. It seems that by inhibiting these enzymes, eggplant extract can decrease glucose absorption and thereby reduce blood glucose.
In this experimental study, the effect of diabetes on learning and memory was evaluated. The results showed that diabetes could weaken the passive avoidance memory in rats and oral administered of eggplant extract can significantly improve memory in rats with diabetes.
Memory is a complex process of brain which includes information gain from the environment and consolidation of the obtained information and finally restoration of them for future uses. The studies have shown that progression of diabetes is associated with some disorders and complications such as retinopathy, nephropathy, neuropathy and microvascular disorders (32). In addition, chronically high blood glucose in diabetes causes structural and functional damage in the peripheral and central nervous system including degradation of the memory system (5, 33). The incidence of diabetes is one of the important risk factors for senile dementia, which is one of the Alzheimer symptoms (34). The findings of some researchers have shown that diabetes mellitus, especially type 1, can impair learning, memory and cognition in experimental models of disease. In addition, the findings show that there is a close relationship between diabetes mellitus and the emergence of disorders in learning and memory of laboratory animals, but the structures responsible for these disorders are not clearly known. However, there is a great deal of evidence for both microvascular and oxidative stress resulting from intensified formation of free oxygen radicals (35). It also has been proved that diabetes can structurally lead to significant reduction in neuronal density in the dentate gyrus area that plays an important role in spatial memory and learning (34). In addition, the diabetes mellitus reduces neuronal Nitric oxide (NO) synthase expression in the hippocampus, which plays an important role in synaptic plasticity, as well as learning and memory processes and this can partly justify the incidence of disorders in learning, memory, as well as LTP in diabetic animals (36,37).
Research has shown that cortex and hippocampus areas that are associated with learning and memory are significantly affected by diabetes. For example, diabetes mellitus causes exacerbation of oxidative stress and lipid peroxidation in some areas of the brain including the hippocampus (38,39) and reduce the insulin-like growth factor as well as brain-derived neurotrophic factor in some brain areas (40,41).
These findings justify the results of the present study on the effect of diabetes on learning and memory. According to the existing evidence, the changes in these inabilities can be attributed to changes in synaptic plasticity in the hippocampus area, and perturbations in the LTP process accordingly (42,43).
Epidemiological and biochemical studies suggest that common diabetic therapies cannot reduce the risk for development of these complications due to being unable to reduce the level of oxidative stress (44). Thus, the herbal compounds have been taken into considerations due to their properties, because these compounds reduce the level of oxidative stress and have lower side effects.
Eggplant is a plant which acts as one of the top ten vegetables in terms of oxygen free radicals cleansing capacity (45,46). The main constituents of eggplant include phenolic compounds, chlorogenic acid and caffeic acid that are all known as neuroprotective and antioxidant factors (46,47). The Most distinctive feature of all flavonoids is their antioxidant property. This feature is of particular importance because body cells are constantly exposed to damages by free radicals and reactive oxygen species that are produced during the metabolism of normal oxygen or external damages (48).
The studies on scopolamine–induced Amnesia model have shown that oral administration of eggplant extract can significantly improve avoidance memory impairment (49) which is consistent with the results obtained in the present study.

Conclusion

Diabetes impairs spatial memory retrieval and this is probably realized through oxidative reactions. In addition, due to containing compounds with antioxidant properties, the eggplant extract seems to be able to improve this impairment.

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Authors' contributions
SG: Design of the study and laboratory methods, preparation of eggplant extract and laboratory methods. SV: Preparation of the paper draft, statistical analysis and help to laboratory methods. HS: Help in design of the study and English editing of the paper.

Conflict of interests
The authors declared no competing interests.

Ethical considerations
The experiments were confirmed by Ethical Committee in Vice Chancellor of Research of Islamic Azad University. Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors.

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