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Original Article

Memory and Learning Improvement by Resveratrol and Probiotics via the Gut-brain Axis and Antioxidant Activity in Diabetic Rats

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Abstract

Background and Objective: Diabetes affects the central nervous system associated with cognition, especially memory and learning. The present study aimed to investigate the effects of probiotics (living microorganisms that provide health benefits) and resveratrol (a polyphenol with potential antioxidant activity) combination on oxidative stress, glucagon-like peptide-1 (GLP-1), memory, and learning in diabetic rats.

Materials and Methods: Male Wistar rats were randomly divided into five groups (six animals per group) of control, diabetic, probiotic-treated diabetic (50×10^9 CFU/kg in drinking water), resveratrol-treated diabetic (10 mg/kg, oral gavage), as well as probiotics and resveratrol-treated diabetic. The treatment procedures lasted for four weeks, and a Shuttle Box test was then performed to evaluate memory and learning. At the end of the study, animals were sacrificed, and the hippocampus was removed to perform biochemical studies.

Results: The levels of malondialdehyde and total oxidative status significantly decreased in the diabetic group treated with combined resveratrol and probiotics ($P<0.05$). Furthermore, the levels of superoxide dismutase, catalase, and glutathione peroxidase significantly increased in the hippocampus of the diabetic group treated with combined resveratrol and probiotics ($P<0.05$). According to the results, the combined therapy improved memory and learning ($P<0.05$). In addition, the level of GLP-1 increased in the treatment groups ($P<0.05$).

Conclusions: Treatment with resveratrol and probiotics significantly normalized pyramidal cell densities in the hippocampus of diabetic rats. This combination also reduced oxidative stress and activated the gut-brain axis in diabetic animals.

Keywords: Diabetes, Glucagon-like peptide-1, Memory and learning, Oxidative stress probiotics, Resveratrol

Background

Diabetes is a chronic metabolic disease and is characterized by insulin resistance and loss of pancreatic β-cell function [1, 2]. Hyperglycemia is one of the central factors for the development of oxidative stress that induces important complications in diabetic patients [3]. These complications typically include microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (cardiovascular and cerebrovascular) diseases [4].

Diabetes affects the central nervous system (CNS) associated with cognition, especially memory and learning; moreover, it increases the risk of developing dementia by up to 60% [5]. Hyperglycemia enhances the formation of reactive oxygen species (ROS) through glucose autoxidation, polyol pathways, and non-enzymatic glycation of proteins. These free radicals can have significant effects on carbohydrates, proteins, and DNA [6].

The hippocampus is a part of the limbic system of the brain, and it is the consolidation center for cognitive functions, such as memory and learning that are affected in diabetes [7]. The gut-brain axis (GBA) has been introduced as a novel therapeutic target in neurological disorders and other diseases that function through glucagon-like peptide-1(GLP-1) [8]. Additionally, GLP-1 and its analogs can cross the blood-brain barrier and improve memory and learning [9].

Studies have indicated that probiotics can suppress the production of oxidative stress by increasing the levels of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [10,11]. Previous studies also revealed that probiotics were beneficial for brain function and had therapeutic effects for various CNS disorders [12]. Another way to treat metabolic disorders is the

use of natural compounds rich in phenols and flavonoids [13-16]. Resveratrol is a polyphenol that can cross the blood-brain barrier in the areas of the brain that are involved in learning and memory and may be involved in modulating message transmission in CNS [17]. Consequently, it has been suggested as a potential compound in the treatment of diabetes and neurodegenerative disorders [18]. Probably, the concurrent administration of these compounds can have potent neuroprotective effects.

Objectives
The present study aimed to investigate the therapeutic effects of probiotics and resveratrol combination on oxidative stress, memory, learning, as well as GLP-1 levels in Streptozotocin (STZ) induced diabetic rats.

Materials and Methods
Animals
This experimental study was conducted on 30 healthy 8-week-old Wistar rats (weight range: 250-300) that were purchased from Hamadan University of Medical Sciences, Hamadan, Iran. The rats were kept under a conditioner at 50%-60% humidity and a controlled temperature of 22±2°C within the animal room under a 12:12-h light/dark cycle. Subsequently, the rats were randomly divided into five groups of six animals per group and kept in separate cages. The experimental groups included: 1) control rats, 2) diabetic rats, 3) diabetic rats receiving probiotic supplements ($50×10^9$CFU/kg), 4) diabetic rats receiving resveratrol (10 mg/kg), and 5) diabetic rats receiving the combined probiotic and resveratrol supplements.

Induction of Type 2 diabetes
To induce type 2 diabetes, single doses of STZ (65 mg/kg) (Sigma-Aldrich, USA) and nicotinamide (110 mg/kg) were administered intraperitoneally (dissolved in 0.1 M citrate buffer, pH=4.5)[3]. Furthermore, blood glucose levels were measured by glucometer seven days after STZ injection and regarded as type 2 diabetes if their blood glucose was above 250mg/dl.

Animal treatments
Probiotics contain lyophilized bacteria, including eight different strains (*Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei,* and *Lactobacillus bulgaricus*) with a dose of $50×10^9$CFU/kg in drinking water for four weeks according to previously published studies [3]. Totally, 10 mg/kg of resveratrol powder was daily mixed in 1ml sterile distilled water per rat and maintained on ice until complete gavage [19]. The animals received probiotics and resveratrol once a day for four weeks. It should be noted that the behavioral tests were performed at the end of the treatment. Furthermore, the probiotics and resveratrol were purchased from Genuine Health (Canada) and Natural Fact Companies (USA), respectively.

Behavioral tests
Evaluation of passive avoidance learning
The passive avoidance learning (PAL) test was performed at the end of the experiment using a Shuttle Box. This plexiglass box is divided into both dark and light compartments with a dimension of 30×20×30 cm. The two compartments are interconnected by a single (20×50 cm) valve connected by a guillotine door. In total, three mm metal bars with a distance of 10 mm were installed on the floor of the plexiglass box. A dark chamber was considered during testing, and the guillotine door was closed between the two compartments during the training. When the rat was placed in the light compartment, the guillotine door was opened, and the delay time was measured by a chronometer. After the entrance of the rat to the dark compartment, the guillotine door was closed, and an electric shock was applied to the animals during the training phase through bars attached to the stimulator device. At this stage, the rats were placed in the light part to be acquainted with the device, and after 30 sec, the door was opened between the two parts. After the rat entered the dark area, the door was closed and after 30 sec, the animal was taken out and returned to the cage. Subsequently, these steps were repeated after 30 min, and following the second stage, the rat was placed in a bright environment for 30 sec, and then the guillotine door was opened between the two parts. The delayed entry time (step-through latency) (STLa) was recorded for each rat at that stage. After the rat had fully entered the dark chamber, the guillotine door was closed, and an electric shock was applied through the metal rods of the chamber floor for a second. The animal was then removed from the dark chamber after 30 sec and returned to the cage. This step was repeated after 2 min, and the retention test was performed according to a previously conducted study [20]. The rats were placed in a light chamber (the same as PAL training), and 5 sec later, the guillotine door was opened, and the STLa in the retention trial (STLr), as well as the time spent in dark compartment (TDC), were recorded for up to 300 sec. If the rat did not enter the dark chamber within 300 sec, the retention test was terminated and a ceiling score of

300 s was assigned.

Tissue measurement of GLP-1
The ELISA Kit was used to determine the GLP-1 levels according to the manufacturer's instructions (ZellBio, Germany).

Determination of total antioxidant capacity, total oxidative status, and malondialdehyde
Total antioxidant capacity (TAC) was determined by ferric-reducing antioxidant power assay [21,22]. Furthermore, the total oxidative status (TOS) of the sample was determined by the oxidation of ferrous iron to ferric in the samples with moderate acidity [21,22]. Malondialdehyde (MDA) level was measured according to the manufacturer's instructions (ZellBio, Germany) [21,22].

Measurement of antioxidant enzyme activity
The activity of catalase (CAT), SOD, and GPX enzymes was measured using a kit (ZellBio, Germany).

Histology of hippocampus
Hippocampus were fixed in 4% formaldehyde, immersed in paraffin, and then stained with hematoxylin and eosin according to previously conducted studies [23,24].

Statistical analysis
The results were analyzed using SPSS software (version 20) through ANOVA and Tukey's post hoc test in case of significant results. A p-value less than 0.05 ($P<0.05$) was considered statistically significant.

Results
Findings of passive avoidance memory test using the Shuttle Box test
The result showed no significant difference among

the animals regarding the latency to enter the dark box during the adaptation phase (Figure 1).

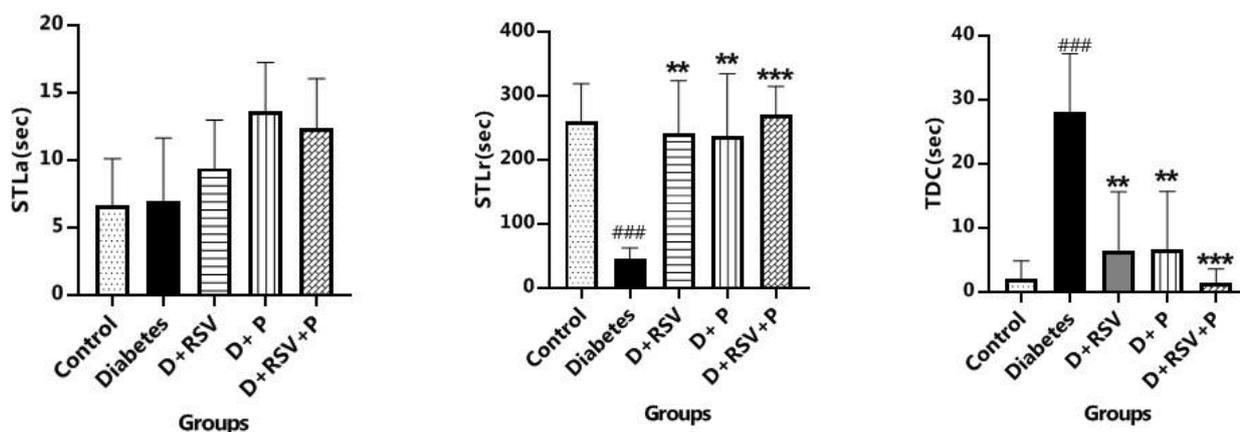### Comparison of the time of "first dark entry" in the step-through latency in the retention test
A significant decrease was observed in the time of "first dark entry" in the avoidance memory test in the diabetic group, compared to the control group ($P<0.001$). Moreover, the time of "first dark entry" in the probiotics alone and resveratrol alone groups indicated a significant increase ($P<0.01$). Furthermore, a comparison of the diabetic with the diabetic group treated with probiotics and resveratrol indicated a significant decrease in this regard ($P<0.001$) (Figure 1).

### Comparison of the duration of stay in the dark room of the Shuttle Box
After comparing the duration of stay in the dark room of the Shuttle Box in the avoidance memory test, the results indicated a significant decrease in the control group, compared to the diabetic group ($P<0.001$). Furthermore, the duration of stay in the dark room of the Shuttle Box in probiotics alone and resveratrol alone groups indicated a significant decrease in this regard ($P<0.01$). In addition, the combined probiotics and resveratrol group, compared to the diabetic group, showed a significant decrease in dark room stay ($P<0.001$) (Figure 1).

Effect of treatment with probiotics and resveratrol on malondialdehyde concentration
The level of MDA was significantly higher in the diabetic group, compared to the control group ($P=0.0034$). Moreover, the level of MDA was significantly decreased in the probiotic-treated diabetic group, compared to the diabetic group (39% decrease) ($P=0.093$). However, there was no

Figure 1. Average latency time to enter the dark compartment (A), time of "first dark entry" in the avoidance memory test (B), and duration of stay in the dark room of the Shuttle Box (C).
Data are presented as means±SEM. **$P<0.01$ and ***$P<0.001$ were set as significant, compared to diabetes; ###$P<0.001$ compared to controls. D: diabetes, RSV: resveratrol, P: probiotic, STLr: step-through latency, RSV: resveratrol, P: probiotic.
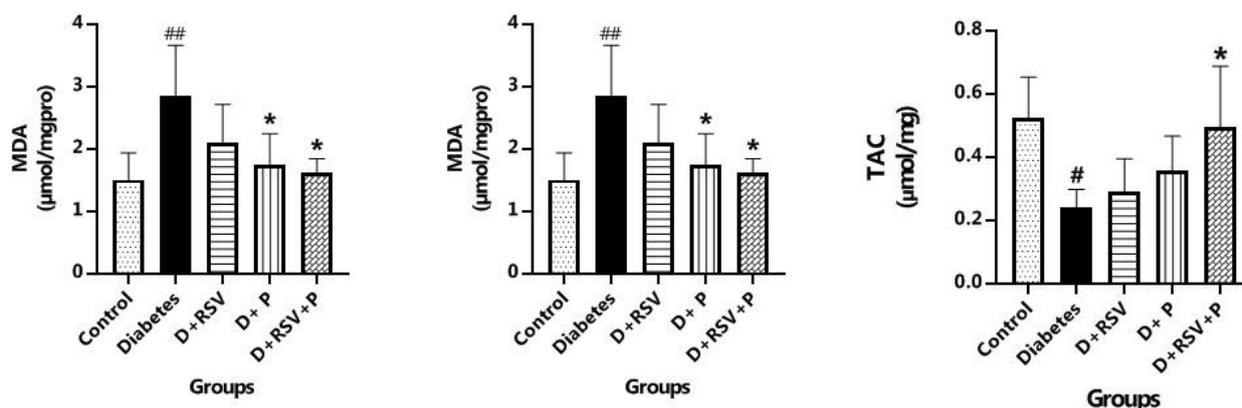
Figure 2. Malondialdehyde, total oxidative status, and total antioxidant capacity levels in different treated groups.
Data are presented as means±SEM. *P<0.05 and **P<0.01 were set as significant, compared to diabetes; ##P<0.01, compared to controls.
D: diabetes, RSV: resveratrol, P: probiotic, MDA: Malondialdehyde, TOS: total oxidative status, TAC: total antioxidant capacity.

significant decrease in the resveratrol-treated diabetic group, compared to the diabetic group. On the other hand, there was a significant decrease in the diabetic group treated with resveratrol and probiotics, compared to the diabetic group (44% decrease) (P=0.0185) (Figure 2).

Effect of treatment with probiotics and resveratrol on total oxidative status
The level of TOS as a marker of oxidant showed a remarkable increase in the diabetic group, compared to the control group (P=0.0036). The level of TOS was significantly decreased in the resveratrol-treated diabetic group, compared to the diabetic group (45% decrease; P=0.0062). Combined probiotics and resveratrol treatment reduced the level of TOS significantly (52% decrease; P=0.0015), which indicated the effect of oxidant decrease in response to combined therapies (Figure 2).

Effect of treatment with probiotics and resveratrol on total antioxidant capacity
The level of TAC was significantly (P=0.0192) lower in the diabetic group, compared to the

control group. Moreover, the increase in the level of TAC was not significant in the diabetic group receiving resveratrol alone and probiotics alone; however, the combined probiotics and resveratrol treatment increased TAC significantly (105% increase; P=0.04) (Figure 2).

Effect of treatment with probiotics and resveratrol on superoxide dismutase, activity of catalase, and glutathione peroxidase activity
The level of SOD activity significantly reduced in response to the combined probiotics and resveratrol treatment (47% decrease; P <0.001). The level of enzyme activity in the combined probiotics and resveratrol treatment group was similar to that of the control group, indicating that this combination therapy was effective (Figure 3). The decrease in CAT enzyme activity was significant in the combined treatment group (45% decrease; P=0.01). Furthermore, the level of enzyme activity in the combined probiotics and resveratrol treatment group was similar to that of the control group, indicating the positive effect of the combined treatment (Figure 3). Furthermore, the combined
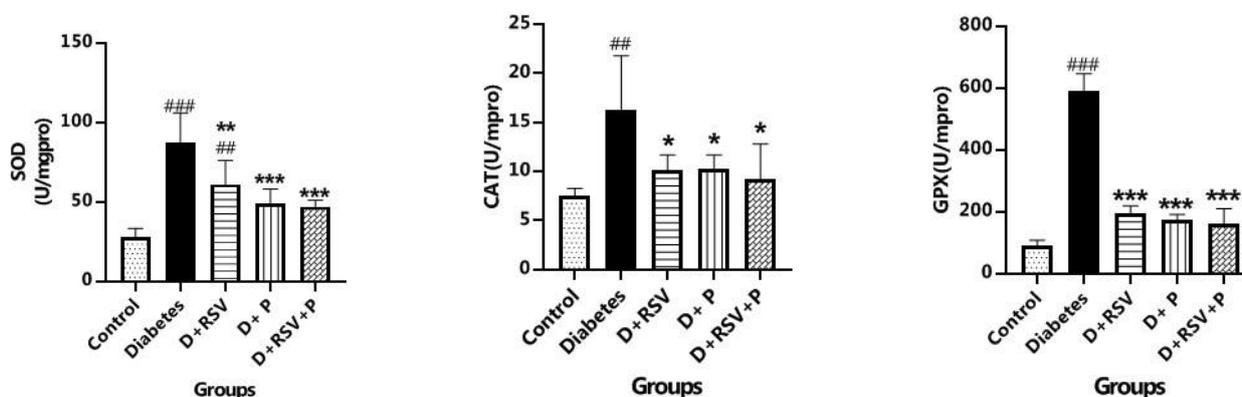
Figure 3. Dismutase, catalase, and glutathione peroxidase levels in different treated groups.
Data are presented as means±SEM. **P<0.01 and ***P<0.001 were set as significant, compared to diabetes; ##P<0.01 and ###P<0.001, compared to controls. D: diabetes, RSV: resveratrol, P: probiotic, SOD: dismutase, CAT: catalase, GPX: glutathione peroxidase.

treatment was also able to significantly decrease the activity of the GPX enzyme (P<0.001). The level of enzyme activity in the treatment groups was similar to that of the control group (Figure 3).

Effect of treatment with probiotics and resveratrol on glucagon-like peptide-1

The concentration level of GLP-1 in diabetic rats was significantly lower than that in the control group (P<0.001). Moreover, the level of GLP-1 significantly increased in the probiotics and resveratrol group, compared to the diabetic group (P<0.01). The combination of probiotics and resveratrol significantly increased the level of GLP-1(Figure 4).
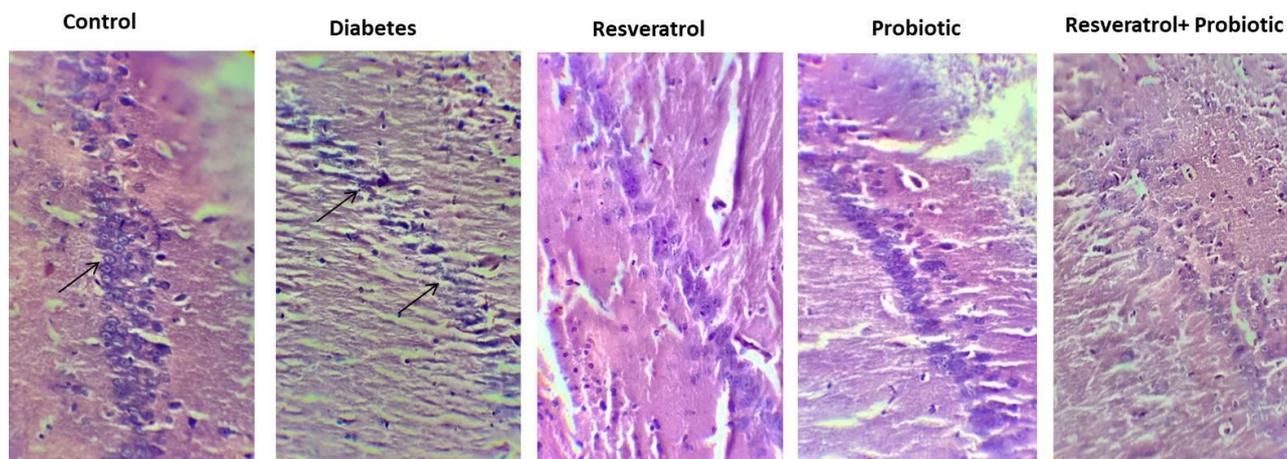
Histology of hippocampus

Hematoxylin and eosin-stained neuron densities showed that the diabetic rats showed a significant decrease in pyramidal cell densities, compared to the control group. However, treatment resveratrol

and probiotics significantly normalized these changes (Figure 5).
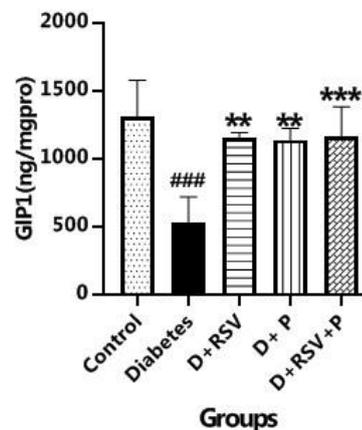
Figure 4. Glucagon-like peptide-1 levels in different treated groups.
Data are presented as means±SEM. **P<0.01 and ***P<0.001 were set as significant, compared to diabetes; ###P<0.001 compared to controls. D: diabetes, RSV: resveratrol, P: probiotic, GLP-1: glucagon-like peptide-1.

Figure 5. Histological changes of hippocampus determined by hematoxylin and eosin (magnification 400Ч). Diabetic animals showing reduced thickness of pyramidal cell layer in the CA1 with elevated apoptotic neurons irregular with chromatolysis. Treatment with resveratrol and probiotics normalizing these changes.

Discussion

Current medications used for the treatment of brain damage may have side effects. Therefore, there is an increasing demand for natural compounds with anti-hyperglycemic properties and fewer side effects [25]. The levels of GLP-1 were decreased in the brain of diabetic rats in the present study. Furthermore, the combination and alone treatment, compared to the diabetic group, increased the GLP-1 level. Isik et al. have shown that GLP-1 can protect neurons from oxidative stress damage and has a role in enhancing neurogenesis, as well as reducing apoptosis and inflammation [26]. According to this result, probiotics and resveratrol, as antioxidant compounds, release GLP-1 and probably bind to its receptors in the brain;

consequently, they reduce the free radicals and increase neuronal regeneration that in turn can increase memory and learning in diabetic rats.

The results of the present study revealed a decrease in TAC and an increase in TOS in the hippocampus of diabetic rats. The administration of resveratrol and probiotics alone or in combination improves antioxidant status and reduces oxidative stress biomarkers in the brain tissue. Moreover, the improvement in the antioxidant capacity is a major contributing factor in the prevention and treatment of neurological disorders [27]. Franco et al. showed that the injection of resveratrol in rats increased their serum TAC levels, compared to the untreated diabetic group [28].

In the present study, an increase was observed in

the total oxidant level. As a result, an increase was also noted in the activity of SOD, CAT, and GPX enzymes in the hippocampal tissue in untreated diabetic. In a study conducted by Tian et al., treatment with resveratrol increased the activity of SOD and CAT in the hippocampus of diabetic rats, compared to the untreated rats. Moreover, they showed that resveratrol enhanced learning and memory in STZ-induced diabetic rats by improving the activity of oxidative stress enzymes [18]. Similarly, Morshedi et al. showed that the administration of *Lactobacillus casei* for 12 weeks increased the GPX and SOD serum levels and reduced the level of ROS in diabetic rats [11], which was consistent with the findings of the current study.

The results of this study revealed that lipid peroxidation was higher in untreated diabetic rats, which was in line with the findings of previous studies. In this study, it was revealed that probiotic and resveratrol administration, especially their combined effect, reduced lipid peroxidation levels in the hippocampus of diabetic rats following the increased antioxidant enzyme activity. It is suggested that this combined therapy may be effective in improving the antioxidant system, enhancing MDA metabolism in the brain tissue, and reducing oxidative stress through its synergism effect that may improve memory and learning status in diabetic rats. In this study, the protective effect of probiotics and resveratrol against lipid peroxidation was consistent with the reports provided by previous studies [29].

This study evaluated the therapeutic effects of probiotics and resveratrol on memory and learning performance in diabetic rats. The findings revealed that the combination of probiotics and resveratrol could improve spatial memory and passive avoidance memory, and therefore, may be effective in improving memory and learning in diabetic rats. The results of this study are consistent with those obtained by Wang et al., which revealed that probiotics influenced memory-related behaviors, including spatial and non-spatial memory [30]. The impairment of memory and learning in diabetic rats is related to hippocampal oxidative stress induced by hyperglycemia [25]. Oxidative damage to the hippocampus of diabetic rats also results in the impairment of cognitive function. Therefore, antioxidants can be effective in preventing neuronal damage and cognitive function [25].

Conclusions
The present study suggests that these compounds can play important roles in reducing oxidative stress, enhancing antioxidant system activity,

decreasing lipid peroxidation, and increasing GLP-1 concentration in hippocampal tissue. Consequently, memory and passive avoidance learning are improved in STZ induced diabetic rats as a result of changes in the activity of hippocampal neurons.

Authors, contributions
EAO and IK designed the experiment and supervised the experiment. SM participated in animal handling, carried out laboratory tests, and prepared the manuscript. FM performed the pathological tests. IK, AK, and HT managed the analyses of the experiment.

Conflicts of Interest
The authors declare no conflict of interest.

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