Chronic Administration of *Rosa canina* Hydro-Alcoholic Extract Attenuates Depressive-Like Behavior and Recognition Memory Impairment in Diabetic Mice: A Possible Role of Oxidative Stress

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Significance of the Study

- In this study, *Rosa canina* showed attenuated impairment of recognition memory and depressive-like behavior probably through modulation of oxidative stress in a streptozotocin model of diabetes in the mouse brain, which could make it a potential choice as a complementary strategy for reducing secondary diabetes complications.

Keywords

Diabetes · Depression · Recognition memory · *Rosa canina*

Abstract

Objective: This study was designed to evaluate whether chronic *Rosa canina* (RC) extract administration could improve recognition memory and depressive-like behavior in diabetic mice. **Materials and Methods:** Seventy-five male albino mice (25–30 g) were randomly divided into 5 groups (15 in each group). A single intraperitoneal injection of 200 mg/kg streptozotocin (STZ) was administered to the mice to induce diabetes. The control group received normal saline, and the diabetic groups received normal saline or 50, 250, and 500 mg/kg of RC extract for 28 days. The mice were weighed each week. Recognition memory and depressive-like behavior were assessed using forced swimming and novel object recognition (NOR) tests, respectively. Malondialdehyde (MDA) levels and total antioxidant capacity (TAC) were measured in the mouse brain homogenate to evaluate

oxidative stress. Statistical analysis was conducted using SPSS, version 22. **Results:** The groups receiving 250 or 500 mg/kg RC had significantly lower immobility time (159.4 ± 4.7 and 150.1 ± 3.1 s) compared to the sham control group (192.1 ± 7.8 s) in the forced swimming test, and a higher discrimination index (0.39 ± 0.02 and 0.48 ± 0.03) was seen in diabetic animals in the NOR task compared to the sham control group (0.2 ± 0.01). Also, the groups receiving treatment with RC (250 and 500 mg/kg) had significantly higher TAC (0.92 ± 0.04 and 0.96 ± 0.05 mmol/L) and lower MDA (0.76 ± 0.02 and 0.67 ± 0.03 nmol/mg protein) levels in the brains in comparison to the model group. In the 3rd and 4th weeks of study, the RC-treated mice (250 and 500 mg/kg) gained more weight (31.2 ± 0.3 and 32.4 ± 0.3 g, and 31.3 ± 0.2 and 33.7 ± 0.3 g, respectively) than the diabetic group (30 ± 0.2 and 29.6 ± 0.3 g). **Conclusion:** This study showed that RC attenuated impairment of recognition memory and depressive-like behavior probably through modulation of oxidative stress in an STZ model of diabetes in mouse brains.

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Introduction

According to the definition of American Diabetes Association, “Diabetes is a group of metabolic diseases characterised by hyperglycemia resulting from defects in insulin secretion, insulin action, or both” [1]. This disease is associated with a broad spectrum of complications such as neuropathy, retinopathy, nephropathy, and atherosclerosis [2]. In addition, psychiatric comorbidities such as dementia, depression, and anxiety are experienced by the majority of diabetic patients [3], resulting in a reduction of quality of life, poor treatment outcomes, and increase in the cost burden of medical care [4].

There is evidence that the majority of these complications result from overproduction of reactive oxygen species, including superoxide anion (O_2^-), which induce oxidative stress and reduce antioxidant capacity [5]. Free radicals trigger biologic mechanisms that cause memory impairment and depressive-like behavior in animal models [6]. Also, diabetes is associated with a decline in circulating levels of antioxidants, which is a risk factor for the appearance of dementia and depression [7].

The depressive-like behavior has been observed in diabetic animals using different behavioral tasks such as tail suspension and forced swimming tests [8, 9]. Also, evidence has shown that inhibition of hippocampal oxidative stress can exert antidepressant-like effects on diabetic animal models [9]. The recognition memory impairment had been reported using different cognitional tasks such as novel object recognition (NOR) or placement tests in rodent models of diabetes [10, 11]. The reduction of brain oxidative stress has been shown to induce significant improvements in the recognition memory indexes in models [12]. Supplementation with antioxidant molecules including ascorbic acid, vitamin E, carotenoids, flavonoids, and tannins has been shown to ameliorate oxidative stress in diabetes and therefore could be considered as a supplementary therapeutic option [13].

Medicinal herbs are used mostly in developing countries for primary health care purposes [14, 15]. Some of these medicinal herbs contain ascorbic acid, flavonoids, alkaloids, phenolic compounds, and carotenoids, which show antidiabetic, antioxidant, and hypoglycemic effects. They have been shown to effectively reduce diabetes complications such as cataract, diabetic nephropathy, and vascular dysfunction, as well as retinopathy [16].

Rosa canina (RC) is one of the Iranian traditional medicinal herbs which has potential to prevent and alleviate conditions such as rheumatic diseases, urinary tract infections, biliary complaints, sciatica, fever, and colds [17].

Recently, the antioxidant activity of RC fruits has been reported in different antioxidant systems to contain significant amounts of ascorbic acid, which justifies its high radical scavenging activity [18]. Hence, this study was designed to evaluate whether chronic supplementary RC administration improves recognition memory and depressive-like behavior by modulating oxidative stress-related factors in diabetic mice.

Materials and Methods

Plant Collection and Extraction

The herb fruits were collected over the postflowering phase (during autumn) from East Azerbaijan Province (northwest region of Iran) and approved for genus and species by the Herbarium of Tabriz University of Medical Sciences, Tabriz, Iran. The material was dried at room temperature and powdered. The dried fruit powder was added to 300 mL of methanol and water (1:1, v/v) in a Soxhlet apparatus for 10 h [18]; the solvent was evaporated and the dried extract was reconstituted to prepare a solution of 50 mg/mL in distilled water.

Animals

Male albino mice ($n = 75$) weighing 25–30 g were obtained from the Animal Facility of Tabriz University of Medical Science. The mice were kept in separate plastic cages ($n = 5$) in a well-ventilated room at $21 \pm 2^\circ\text{C}$ under a 12:12 h light/dark cycle with free access to water and food.

The experimental procedures were carried out in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health) and approved by the Ethics Committee of Tabriz University of Medical Sciences.

Study Design

The mice were randomly divided into 5 groups of 15 mice each: the control and diabetic groups. The control group received only normal saline (NS) (0.5 mL/animal; NS group). For the diabetic groups, streptozotocin (STZ) was administered to induce diabetes. They were then divided into 4 groups; the diabetic control was given NS (0.5 mL/animal; STZ+NS). The other diabetic groups were administered 50, 250, or 500 mg/kg of RC extract (STZ+RC 50, 250, or 500). NS and treatments were administered to the animals by oral gavage once a day for 28 days. The mice were weighed each week.

Diabetes Induction

To induce diabetes, a single intraperitoneal injection of 200 mg/kg STZ (Sigma-Aldrich, St. Louis, MO, USA) prepared in 5 M sodium citrate; pH 4.5 was administered to the mice [19]. Fasting blood glucose levels were measured periodically, from the 3rd day of STZ injection, using a portable glucometer (Accu-Chek, Germany). Blood was obtained by lancet from tail veins. Mice with a glucose concentration exceeding 300 mg/dL were considered diabetic.

Forced Swimming Test

A Plexiglas cylinder (height: 30 cm, diameter: 22.5 cm) filled with water ($23\text{--}25^\circ\text{C}$) to a depth of 15 cm was used for the test. The cylinder was placed inside a black enclosure. The enclosure made a

Table 1. The effect of diabetes and treatment on body weight

Groups	Weeks				
	0	1	2	3	4
NS	26.8±0.3	28±0.2	29.3±0.1	31.8±0.2	34.3±0.1
STZ+NS	27.1±0.3	28.1±0.2	28.6±0.3	30±0.2**	29.6±0.3**
STZ+RC 50	27.5±0.2	28.6±0.4	29.1±0.3	30.3±0.1	29.7±0.2
STZ+RC 250	27.1±0.5	28.3±0.3	29.1±0.3	31.2±0.3##	32.4±0.3##
STZ+RC 500	27.2±0.3	28.2±0.3	29±0.2	31.3±0.2##	33.7±0.3##

Each value represents the mean ± SEM ($n = 15$). ** $p < 0.01$ vs. NS group; ## $p < 0.01$ vs. STZ+NS group. NS, normal saline; STZ, streptozotocin; RC, *Rosa canina*. Groups: NS, normal saline only; STZ+NS, streptozotocin + normal saline; STZ+RC 50, streptozotocin + 50 mg/kg *Rosa canina*; STZ+RC 250, streptozotocin + 250 mg/kg *Rosa canina*; STZ+RC 500, streptozotocin + 500 mg/kg *Rosa canina*.

high contrast between the black background and a white mouse and prevented the cylinder from mirroring the image of the room. A video camera (Visionite, VCS-E740H, South Korea) was placed between the tank and one of the walls. Immobility time was analyzed using a computer-assisted video analysis system (EthoVision, Noldus). Mice were dropped individually into a cylinder; after an initial vigorous activity of 2 min, the mice acquired an immobile posture which was defined as the duration of time when the velocity of mice movement decreased below 2 cm/s. The duration of immobility (s), was recorded during the last 4 min of the 6 min test. The mice were subjected to the same training session, 24 h before the test.

NOR Test

A NOR test was performed in 3 sessions (habituation, training, and retention) with small modifications. Briefly, the Plexiglass-open-field box (33 × 33 × 20 cm) and common objects (different in shape and texture) were used for the test. The direction of mouse nose to the object (distance of ≤2 cm) and rearing up against the object for investigation was considered as exploration. After each trial, the arena and objects were cleaned with 70% ethanol. The total locomotor activity (in habituation session) and time spent with each object were recorded by a video camera fixed above the center of the task apparatus and scored using fully automated EthoVision XT video tracking software.

The habituation session of the NOR task started 1 day before the training step. Then, each mouse was placed in the box for habituation in the absence of objects for 10 min. Locomotor activity was recorded during this session. Twenty-four hours later, the mice were subjected to a training session in which 2 identical objects (A and A') were placed in the box and the total time spent to explore both objects was recorded over 10 min. In the retention session, the next day after the training trial, the mice were returned to the same task, but one of the familiar objects was replaced by a novel object named as B. The recognition memory was measured by discrimination index (DI): $DI = (N - F)/(N + F)$, where N is time spent to explore the new object and F is time spent to explore the familiar object in retention sessions.

Sampling and Processing

The mice were anesthetized with an injection of ketamine (80 mg/kg, i.p.) and xylazine (8 mg/kg, i.p.). Brain tissue was removed

from the skull and washed in NS and homogenized in 1.15% KCl solution. The homogenates were centrifuged at 1,000 rpm for 1 min at 4 °C, and the supernatant was used for biochemical evaluations.

Biochemical Assessments

Malondialdehyde (MDA) levels as a lipid peroxidation indicator were measured using the thiobarbituric acid reactive substances method and spectrophotometrically at a 523-nm wavelength and compared with a standard curve. Total antioxidant capacity was measured using a Randox (Crumlin, UK) total antioxidant status kit.

Statistical Analyses

Descriptive data were expressed as means ± SEM. Comparison of different groups was carried out by 1-way ANOVA followed by post hoc Tukey test. All analyses were performed using IBM SPSS Statistics software (version 22; SPSS Inc., USA). In all comparisons, $p < 0.05$ was considered significant.

Results

Body Weight and Serum Glucose Level

Baseline and 1st and 2nd week body weights in the groups were not significantly different ($p > 0.05$). One-way ANOVA analysis showed that in the 3rd and 4th weeks of study, the body weights of mice in STZ+NS group (30 ± 0.2 and 29.6 ± 0.3 g) were considerably lower than the NS group (31.8 ± 0.2 and 34.3 ± 0.1 g) ($p < 0.01$). Further analysis showed that in the 3rd and 4th weeks of study, the RC-treated mice (in 250 and 500 mg/kg doses) gained more weight (31.2 ± 0.3 and 32.4 ± 0.3 g as well as 31.3 ± 0.2 and 33.7 ± 0.3 g, respectively) than the diabetic group ($p < 0.01$) (Table 1).

Diabetic groups receiving STZ administration had significantly higher levels of glucose levels (580 ± 24 mg/dL) compared to the control group (108 ± 17 mg/dL) ($p <$

Fig. 1. The effects of diabetes and treatments on immobility time in 15 mice (mean $\pm$ SEM). ** $p < 0.01$ vs. NS group; ## $p < 0.01$ vs. STZ+NS group. NS, normal saline; STZ, streptozotocin; RC, *Rosa canina*.

0.01). However, the glucose levels did not show a significant difference among diabetic groups during the study days (in a range of 510 to >600 mg/dL) ($p > 0.05$).

Forced Swimming Test

One-way ANOVA revealed a significant difference in the duration of immobility among the study groups ($p < 0.01$). The Tukey post hoc comparison showed a statistically significant immobility time in the STZ+NS group (189.1 ± 2.9 s) as compared to the control group (155.4 ± 4.2 s) ($p < 0.01$). Also, immobility time in the STZ+RC (250 and 500) groups (159.4 ± 4.7 and 150.1 ± 3.1 s) was significantly lower than in the STZ+NS group ($p < 0.01$); however, for STZ+RC 50 group (183 ± 4.3 s) it was not significant (Fig. 1).

NOR Test

None of the treatments with the doses used had a significant effect on locomotor activity in the different groups. The effects of diabetes and treatment with RC on the DI of mice are shown in Figure 2. One-way ANOVA revealed a significant difference in the DI among study groups in the retention phase of the NOR task ($p < 0.01$). Also, the Tukey post hoc comparison showed a significant lower DI index in the STZ+NS group (0.19 ± 0.02) as compared to the NS group (0.45 ± 0.02) ($p < 0.01$). Further, treatment with RC (250 or 500) (0.39 ± 0.02 or 0.48 ± 0.03) significantly increased the DI compared to the STZ+NS group ($p < 0.01$).

Fig. 2. The effects of diabetes and treatments on discrimination index in 8 mice. Each value represents the mean $\pm$ SEM. ** $p < 0.01$ vs. NS group; ## $p < 0.01$ vs. STZ+NS group. NS, normal saline; STZ, streptozotocin; RC, *Rosa canina*.

Brain Lipid Peroxidation Level and Antioxidant Activity

The effects of STZ and treatment with RC on the TAC and MDA levels in the mice are shown in Figure 3. One-way ANOVA revealed a significant difference in the MDA levels and TAC in the brain among the study groups ($p < 0.01$). Also, the Tukey post hoc comparison showed significantly higher MDA (0.94 ± 0.05 nmol/mg protein) levels and lower TAC (0.72 ± 0.02 mmol/L) in the STZ+NS group compared to the control group (0.75 ± 0.02 nmol/mg protein and 0.92 ± 0.06 mmol/L) ($p < 0.01$). Further, treatment with RC (250 and 500) significantly increased TAC (0.92 ± 0.04 and 0.96 ± 0.05 mmol/L) and decreased MDA (0.76 ± 0.02 and 0.67 ± 0.03 nmol/mg protein) levels in the brain in comparison to the STZ+NS group ($p < 0.01$).

Discussion

The present work showed that RC decreased cognitive performance impairment, depression, and oxidative stress in STZ-induced diabetes in mice. Further, the diabetes modelling in mice using STZ increased lipid peroxidation, decreased TAC, and disturbed oxidative stress steady state in the mouse brain, similar to previous studies [5, 9] in which it was reported that diabetes induction using STZ increased lipid peroxidation and decreased

Fig. 3. The effects of diabetes and treatments on TAC and MDA levels in the brain in 12 mice (mean $\pm$ SEM). * $p < 0.05$ vs. NS group; # $p < 0.05$, ## $p < 0.01$ vs. STZ+NS group. NS, normal saline; STZ, streptozotocin; RC, *Rosa canina*; TAC, total antioxidant capacity; MDA, malondialdehyde.

TAC in the rodent brain. A probable explanation could be that insulin signaling systems are turned off in a diabetic state, leading to distortion of glucose metabolism and changes in mitochondrial energy production, reduced ATP production, and increased reactive oxygen species in the brain as reported previously [20]. It has been suggested that oxidative stress induces cytosolic acidification, which consequently increases neuronal apoptosis, excitotoxicity, and protein misfolding, and results in neurodegeneration and cognitive decline [21].

The finding that STZ-induced diabetes decreased DI and thus impaired recognition memory in the NOR task in mice confirmed previous studies [21, 22] in which Butterfield et al. [21] reported that STZ decreased DI and novel object exploration time in the NOR test.

In this study, diabetes increased immobility time in the forced swimming test in mice similar to findings of previous studies [19, 23], probably because immobility time is an indicator of despair which is an important symptom of depression [9].

In this study, oral administration of higher doses of RC modulated the MDA level and TAC in the brain of diabetic mice, similar to other antioxidant effects of RC reported in previous studies [17, 18]. It is assumed that the antioxidant activity of RC could be attributed to its different amounts of vitamin C, polyphenol, and flavonoid content [24].

In this study, higher doses of RC improved recognition memory in the NOR task in the diabetic mice similar to a previous study [22] in which it was reported that RC could significantly improve learning and memory in an aged mice model through activation of neuroprotection pathways. Equally important, other medicinal herbs such

as *Lepidium meyenii*, *Prunella vulgaris*, and *Cyperus rotundus* have also been reported to improve learning, memory, and hippocampal neurogenesis in animal models [25]. Park et al. [26] reported that the administration of PMC-12, a traditional medicinal herb, decreases the latency time and improves memory and learning in the Morris water maze task [27, 28]. Further, Meena et al. [29] demonstrated that the procognitive effects of *Bacopa monnieri* and *Centella asiatica* are mediated through their antioxidant activity.

In STZ-induced diabetes in mice, RC attenuated depressive-like behavior in the forced swimming test, similar to a study by Jafari et al. that showed RC extract has antidepressant activity in normal mice as proved by the forced swimming stress model [25]. Equally important, it has been revealed that other medicinal herbs such as *Panax ginseng* have antidepressant activity which could be due to their antioxidant activity. It has been proven that supplementation with these herbs exerts a positive impact on the severity of symptoms in depression [30].

Conclusion

This study revealed that RC attenuated impairment of recognition memory and depressive-like behavior possibly due to modulation of oxidative stress in the STZ model of diabetes in the mouse brain, which could make it a choice as a possible complementary strategy for reducing secondary diabetes complications.

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Disclosure Statement

No conflicts of interest are reported.

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