Orginal Article

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The Effect of Genistein on Spatial Memory in Ovariectomized Rat Model of Parkinson's Disease

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ABSTRACT

BACKGROUND AND OBJECTIVE: Impaired learning and memory are the complications of Parkinson's disease. Moreover, estrogen reduction during menopause may impair memory. Given that genistein has neuroprotective and estrogen effects, this study aimed to investigate the effect of genistein on learning and memory of ovariectomized rat model of Parkinson's disease.

METHODS: In this experimental study, 48 female Wistar rats were divided into six groups of eight, including a Parkinsonism group receiving dimethyl sulfoxide solvent, four ovariectomized groups of rats with Parkinson's disease receiving dimethyl sulfoxide solvent, genistein (10 mg/kg), tamoxifen (20 mg/kg), and a mixture of genistein (10 mg/kg) and tamoxifen (20 mg/kg) as pre-treatment for a week, as well as a control group. Nigrostriatal pathway was destroyed by 8 µg of 6-hydroxy-dopamine. Learning and spatial memory were evaluated by Morris water maze test.

FINDINGS: In training and assessment stages, there was a significant difference between the control group and the Parkinsonism and ovariectomized-Parkinsonism groups ($p<0.0001$). The mean times the ovariectomized-Parkinsonism and Parkinsonism groups remained in the target quadrant were 4.21±0.26 s and 5.94±0.61 s, respectively, which was less compared to the control group (12.15±0.33). In addition, ovariectomy prolonged acquisition ($p=0.002$) and reduced probe testing time ($p=0.034$) in the rats with Parkinson's disease. The genistein group spent more time in the target quadrant compared to the group receiving genistein and tamoxifen (11.85±0.46 s vs. 6.37±0.86 s, respectively; $p=0.0001$).

CONCLUSION: The results showed that genistein improves spatial learning and memory in the ovariectomized rat model of Parkinson's disease.

KEY WORDS: *Genistein, Learning, Memory, Ovariectomy, Parkinson.*

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Introduction

Parkinson's disease is a progressive neurodegenerative disease and is the second most common neurodegenerative disease following Alzheimer's across the globe. Neuropathology of this disease is characterized by the destruction of the midbrain dopaminergic neurons in the substantia nigra pars compacta (SNc) and reduced dopamine in the corpus striatum (1). One of the non-motor symptoms in advanced stages of the illness is decreased cognitive function (2, 3). Inflammation, apoptosis, mitochondrial dysfunction, and oxidative stress are the key factors associated with neuronal death of nigrostriatal pathway (4). Ovariectomy is the most common experimental animal model to investigate the effects of reduced estrogen production (5). *Glycine hispida* is a great source of phytoestrogens (6). Phytoestrogens act structurally and functionally similar to endogenous estrogen, but without the side effects, they also have neuroprotective effects (7).

Genistein, as one of the major components of *Glycine hispida*, is an isoflavonoid with estrogenic, anti-inflammatory, and neuroprotective effects and mitogenic properties (8, 9), which leads to decreased release of dopamine in corpus striatum (10, 11). Genistein can pass through the blood-brain barrier (10) and bond with α and β estrogen receptors; however, it has higher affinity to β receptors (11, 12). Genomic or non-genomic estrogenic signaling functions of genistein are applied through estrogen receptors (13-15). On the other hand, genistein has nitric oxide-releasing feature (16).

Genistein may exert agonist or antagonist effects on estrogen receptors (17, 18). Positive effects of flavonoid compounds including genistein on Parkinson's disease are demonstrated, and since one of the mechanisms of increased damage to substantia nigra of the brain is elevated oxidative stress, protective effect of genistein against this disease might be due to its antioxidant (19). Studies showed that high doses of genistein lead to reduced structural and behavioral disorders in rat model of Parkinson's disease (20). Sarkak et al. proposed that consumption of *Glycine hispida* could improve cognitive function in the ovariectomized rat model of Parkinson's disease in Morris water maze, which might be due to high neuronal density caused by this flavonoid compound (21). Given the side effects of the current drugs for Parkinson's disease treatment, including levodopa, it seems that *Glycine hispida* can have beneficial estrogenic effects without the side effects of estrogen in postmenopausal women, which leads to reduced severity of symptoms of Parkinsonism. Considering the positive effects of isoflavonoid compounds such as *Glycine hispida*, especially on memory in animal models of Parkinsonism, we aimed to evaluate the therapeutic effects of genistein on learning and memory in ovariectomized rat model of Parkinson's disease.

Methods

Animals: In this experimental study, 48 female Wistar rats in the weight range 170-200 g were randomly divided into six groups of eight including a control group receiving dimethyl sulfoxide (DMSO), a Parkinsonism group receiving DMSO, four ovariectomized groups of rats with Parkinson's disease receiving DMSO, genistein (27 mg of genistein in 1cc DMSO; 10 mg/kg; Laboratories LC, USA), tamoxifen (56 mg of tamoxifen in 1cc DMSO; 20 mg/kg; Iran Hormone Co., Iran), and a combination of genistein (10 mg/kg) and tamoxifen (20 mg/kg). In the ovariectomized animals, the drugs were administered seven days after ovariectomy. All the groups were intraperitoneally injected the solvent and drugs as pre-treatment. Then, on the seventh day, nigrostriatal pathway of all the animals was destroyed by injecting 6-hydroxy-dopamine hydrochloride (6-OHDA), except for the control group.

Hydroxy-dopamine hydrochloride (6-OHDA) injection: To destroy the nigrostriatal pathway, 6-OHDA (Sigma-Aldrich, USA) was employed. After anesthetizing the animals and fixing them in a stereotaxic instrument (Stoelting, USA), SNc with coordinates AP=5.3, DV=8, ML=1.6 (22) were marked on the surface of the skull, and a hole was created by a dental drill. Then, 8 µg of 6-OHDA in 4 ml of 0.9% saline solution containing 0.1% of ascorbic acid was injected bilaterally into the SNc. To confirm the injection site, methylene blue dye was injected in 10 animals as pilot (fig 1). Thereafter, the brains were perfused and after cutting by Atlas, the injection site was examined under a microscope. Finally, the animals' brain was studied by Neisser staining to evaluated the density of neurons in the SNc.

Evaluation of learning and memory: In this study, to investigate the process of learning and consolidation of spatial of memory, Morris water maze was used (23) two weeks after 6-OHDA injection. This maze consists

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of a metal tank, with a diameter of 150 cm and depth of 70 cm, which is filled with water up to 50 cm. The maze is supposedly divided into equal quadrants as North, South, East, and West, and a platform with diameter of 10 cm is submerged in the middle of one of the hypothetical quadrants. A digital camera was placed on top of the maze and all the animals' behaviors were recorded in a computer memory to be used for subsequent analysis. At the end, the videos were analyzed by a software (Radiab, Ver. 2.1, Iran) and the time spent by the animals to find the platform and the speed of animals' movement were provided for the researcher. Considering that the speed of animals is deemed as a confounding factor, after calculation of the speed, it was entered into COANOVA to remove its effect.

The test process

The learning stage: During this stage, the animal was released in one of the four quadrants of the water maze. The maximum testing time was considered 60 seconds at each stage. If the animal found the platform within this period, the animal was allowed to remain on the platform for 15 more seconds. On the other hand, if the animal was not able to find the platform within the specified time, the mouse was slowly guided toward the platform by the experimenter. Then, the animal was moved away, and after 10 minutes, the experiment was repeated, but this time the animal was released from a different quadrant. Each rat experienced four training sessions in a day, with an interval of 10 minutes. Overall, this stage lasted for four days (24).

Probe trial: On the fifth day, the platform was removed from the maze and the assessment was carried out. In this stage, we determined in which of the four quadrants the mice spent most of the time in 30-second sessions. Each rat was assessed only once, and the time spent in the target quadrant (in which the platform was placeed in the learning stage) was considered the criterion for the rate of recall (25).

Histological studies: After behavioral assessment, perfusion was performed with 500 ml of 10% neutral-buffered formalin (NBF) for 2 h (26). Immediately after the perfusion, the brain was carefully removed from the skull and was placed in a fixative solution for 24 h at room temperature to complete the fixation of the brain tissue. After 24 h, the tissue samples were placed in a tissue processor. The tissues were molded, and by using a microtome, five slices were obtained. Then, to assess tissue damage in the SNc, Neisser staining was used (27)

Quantitative assessment: To count neurons in the SNc, a microscope camera (Nikon Eclipse Ti-SR) was used with a magnification of 200×, and neurons in the target area were counted.

Statistical analysis: Data are expressed as mean±standard deviation. Findings of the Morris water maze test were compared using Repeated measures ANOVA. The findings of neural count were compared by performing three-way ANOVA, and if there was a significant difference, Fisher's LSD post-hoc test was carried out. P-value less than 0.05 was considered statistically significant.

Result

Morris water maze test

Learning stage: A: Elapsed time to find the submerged platform: data obtained from Morris water maze on the four training days showed statistically significant differences between all the groups on different days ($p<0.0001$, $F_{5,182}=16.854$). There was a significant difference between the control group and the Parkinsonism ($p=0.0001$) and Parkinsonism-ovariectomized ($p=0.0001$) groups, that is, the time spent to find the platform increased in these two groups compared to the control group. Ovariectomy increased acquisition duration in the Parkinsonism-ovariectomy group ($p=0.002$). The results showed that genistein compared with combination of genistein and tamoxifen ($p=0.008$) improved learning, such that no significant difference was observed between the control and genistein groups (fig 2-a).

B: Animal swimming speed to find the submerged platform: the difference between the groups in terms of speed of animals in the maze was statistically significant ($p<0.0001$, $F_{5,182}=16.459$). There was a significant difference between the control group and the Parkinsonism and Parkinsonism-ovariectomized groups ($p=0.0001$), that is, the speed to find the hidden platform in these two groups was reduced compared to the control group. Furthermore, ovariectomy reduced the speed of animals in finding the target quadrant in the Parkinsonism group ($p=0.0001$). Genistein compared with combination of genistein and tamoxifen increased the swimming speed ($p=0.0001$). There was no significant difference between the control and genistein groups (fig 2-b)

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Figure 1. Histological image of coronal sections of substantia nigra pars compacta based on verification of injection site

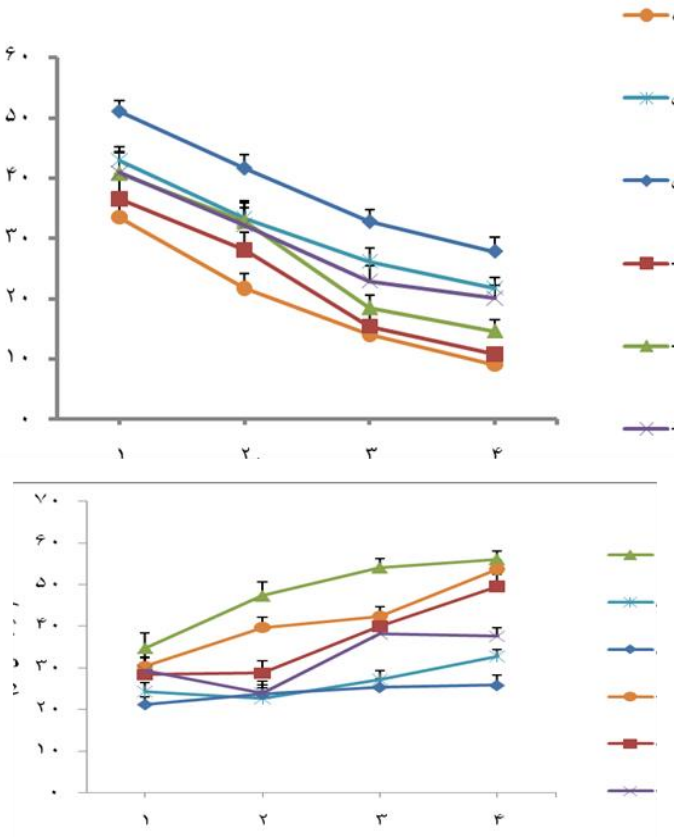

Figure 2. (a) elapsed time and (b) swimming speed of the animals to find the submerged platform in the Morris water maze

Probe trial

The time spent in the target quadrant: the results showed that the mean time the Parkinsonism-ovariectomized and Parkinsonism groups spent in the target quadrant was significantly more than the control group (4.21±0.26 s and 5.94±0.61 s vs. 0.33±12.15 s; p=0.0001; fig 3). The Parkinsonism-ovariectomized animals spent less time in the target quadrant compared to the Parkinsonism group. In addition, the genistein group compared with the group receiving genistein and tamoxifen spent more time in the target quadrant (11.85±0.46 s vs. 6.37±0.86 s; p=0.0001). No significant difference was observed between the control and genistein groups.

Histological studies: the histological findings indicated that the number of neurons in the SNc decreased in the Parkinsonism-ovariectomized and Parkinsonism groups compared to the controls (295.86±23.74 and 449.68±45.12 vs. 746.14±20.54; p=0.0001; fig 4, fig 5). Ovariectomy reduced the number of neurons in the animals with Parkinson's disease (p=0.004). Genistein was more effective in preventing neuronal loss in the SNc compared to the group receiving genistein and tamoxifen (p=0.010), such that there was no significant difference between the control and genistein groups (p=0.081). Genistein prevented neural loss in the substantia nigra.

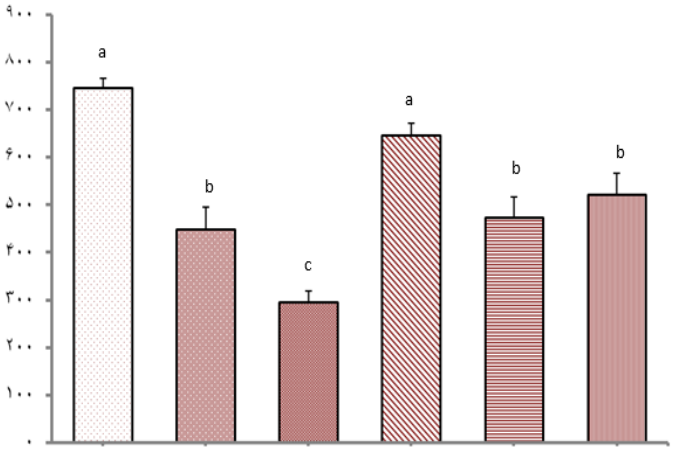

Figure 3. The time spent in the target quadrant in the probe trial; similar letters: lack of significant difference, dissimilar letters: significant difference

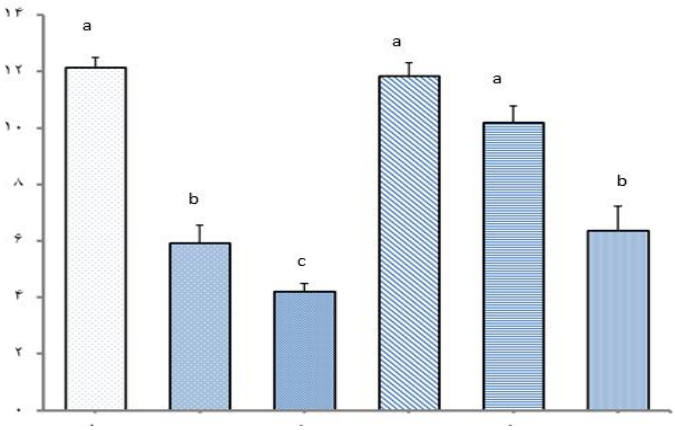

Figure 4. The number of neurons in 1 mm^2 of substantia nigra pars compacta in the studied groups; similar letters: lack of significant difference, dissimilar letters: significant difference

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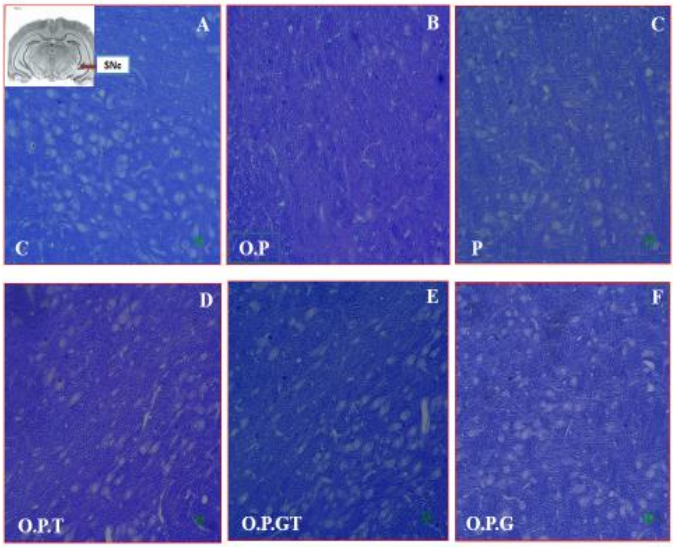

Figure 5. Scanning photomicrographs (magnification 200×) coronal section (5 micrometers) of substantia nigra pars compacta representing neurons stained through Neisser staining method

Discussion

Our findings indicate that bilateral drug-induced Parkinsonism (DIP) impaired memory and that ovariectomy enhanced memory disorders. In addition, genistein administration improved learning and memory in ovariectomized rats with Parkinsonism. 6-OHD is used to create a similar model of Parkinsonism in rodents. This neurotoxin enters the dopaminergic terminals of the corpus striatum and causes DNA fragmentation, and thus, leads to apoptosis by producing hydroxyl (28). Our findings showed that DIP model impaired spatial learning and memory consolidation in rats, which is consistent with the results of other studies showing cognitive deficit after injection of 6-OHDA (29).

The results revealed that ovariectomy increased the memory impairment associated with Parkinson's disease. Azizi et al. demonstrated that reduced levels of estrogen during menopausal period leads to cognitive deficit and that ovariectomy impaired spatial learning process (30). It was shown that ovariectomy, through increased oxidative stress, plays an important role in memory degradation (31-33). In this study, pre-treatment with genistein improved memory disorders, which indicates the relationship between phytoestrogens and memory (10, 21, 36, 37). Phytoestrogens, as estrogen agonists (34), play a major role in reducing nerve damage through countering oxidative stress (35). Phytoestrogens are effective in cholinergic deficit caused by Parkinson's disease, and they diminish neural loss and cognitive deficit in rats (36). Treatment with phytoestrogens in ovariectomized rats enhances visual-spatial memory, which may be due to increased acetylcholine transferase mRNA in the frontal cortex of the brain (37). Isoflavonoids in *Glycine hispida* have neuroprotective function against diseases associated with estrogen deficiency after menopause (38). Quercitin, as a flavonoid compound, improves the induced pathological damage caused by 6-OHDA injection (39). Hosseini et al. indicated that long term consumption of olive leaf extract, as a combination of flavonoids, causes neuroprotection and decreased memory impairment caused by 6-OHDA (40). The neuroprotective role of genistein in addition to its antioxidant activities was reported among Parkinson's disease patients (41, 42).

Our results disclosed that tamoxifen reduces the time spent and increases the distance travelled to find the platform; in addition, it increases the time spent in the target quadrant. Tamoxifen, as a selective regulator of estrogen, has semi-agonist-antagonist effects on estrogen receptors in different areas of the brain (43). Tamoxifen just as estrogen leads to increased choline acetyltransferase mRNA expression in the frontal lobe of the brain (44) and has neuroprotective effects on nigrostriatal dopaminergic neurons (45, 46). Moreover, it has estrogen agonist activity on N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (47).

As a result, tamoxifen may act as genistein through its agonist-antagonist effects; such that in the absence of estrogen receptors it acts as agonist of estrogen receptors (43) and may play an important role in neuroprotection and enhanced learning and memory (46). In addition, the results showed that combination of genistein and tamoxifen reduces the time and increases the rate of finding the target quadrant, but compared to the genistein group, its effect is weaker and is significantly different from this group. Selective estrogen receptor modulators such as raloxifene and tamoxifen have both agonist and antagonist effects on estrogen depending on their chemical properties in the target tissue (43, 48). Some reports have demonstrated that tamoxifen blocks the function of genistein (17). Since tamoxifen is a partial agonist of estrogen receptors, it competes with genistein and inhibits the binding of genistein to estrogen receptors and blocks the effects of genistein to some extent, but does not completely prevent the effects of genistein in binding to the receptor. Another possibility is that genistein

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applies its effects from a pathway other than estrogen receptors. The histological findings exhibited that the number of neurons decreased in the substantia nigra in the Parkinsonism and Parkinsonism-ovariectomized groups and genistein had neuroprotective effect on neurons of the substantia nigra. These results are consistent with findings of Bagheri showing a reduction in the number of neurons in substantia nigra of mice with Parkinson's disease and lack of reduction among rats receiving genistein (49). Other studies suggest no variation in the number of neurons in the SNc of mice with Parkinson's disease treated with Milk thistle extract (50). Pre-treatment with genistein (10 mg per kilogram of body weight) can improve the learning process and consolidation of spatial memory in the ovariectomized rat model of Parkinson's disease, and it can prevent the reduction and damage to dopaminergic neurons of SNc.

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