Original Article

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# Evaluation of the Protective Effect of Olive Leaf Extracts on Anxiety-like Behaviors in an Animal Model of Parkinson's Disease

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## ABSTRACT

**BACKGROUND AND OBJECTIVE:** Oxidative stress is one of the main causes of Parkinson's disease. Mood disorders such as anxiety are commonly reported in these patients. Olive leaf extracts have strong antioxidative and neuroprotective properties due to the presence of various phenolic compounds. The aim of the present study was to investigate the effects of olive leaf extracts on anxiety-like behaviors in an animal model of Parkinson's disease, using elevated plus maze test.

**METHODS:** In this experimental study, 42 rats were divided into six groups (seven rats per group): control, sham, patient and treatment (receiving extracts at doses of 50, 100 and 150 mg/kg) groups. The control group did not receive any injections, whereas the sham and patient groups received saline solutions and the treatment group received 50, 100 and 150 mg/kg of olive leaf extracts via gavage for seven weeks. All groups, except the control and sham groups, were administered unilateral 6-hydroxydopamine in the striatum, using a stereotactic device, and an animal model of Parkinson's disease was established. Three weeks after toxin injections, anxiety-like behaviors were assessed, using the elevated plus maze test.

**FINDINGS:** The injection of 6-hydroxydopamine caused a reduction in the time of animals' entry into the open arm and the number of entries. Administration of different concentrations of the extract caused an increase in the mentioned parameters in all treatment groups, compared to the patient group.

**CONCLUSION:** The results showed that oral administration of olive leaf extracts caused a significant decrease in anxiety-like behaviors, induced by 6-hydroxydopamine in an animal model of Parkinson's disease.

**KEY WORDS:** Parkinson, Elevated Plus Maze Test, Anxiety-like Behavior, Olive Leaf Extract.

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## Introduction

Anxiety, as one of the most common mental disorders, is associated with different physical manifestations (1). Oxidative stress in the central nervous system is one of the underlying causes of anxiety. Due to lipid peroxidation,oxidative stress leads to a decrease in membrane fluidity, damages the proteins in the membrane of neurons and thereby changes the release of neurotransmitters and the overall performance of the brain (2). Oxidative stress is also one of the main causes ofdegenerationin dopaminergic neurons in Parkinson's disease. Parkinson's disease is associated with stress-like behaviors (3, 4), which have unpleasant effects onmobility and quality of life in 40% ofpatients (5). Injection of 6-hydroxydopamine (6-OHDA) (Sigma Aldrich, USA) into the substantia nigraor the striatuminduces an animal model of Parkinson's disease bydegenerating dopamine neurons (6). This toxin after a selective entry through dopamine transmittersleads to the damage, inflammation andultimately deathof neurons by producing reactive oxygen species in the neurons of nigrostriatal pathway (7, 8).

According to many studies, use of vegetable products or polyphenol-enriched supplements maydelay the initiation or progression of conditions such as Alzheimer's disease, Parkinson's disease and the associated neurological disorders (9, 10). Among natural antioxidants, olive tree is commonly known to havestrong antioxidant activities in its oil, fruit and leaf extracts (11). As previous studies have indicated, biophenols in olive possess anti-atherogenic, anitoxidant and anti-inflammatory properties, which can prevent or hinder neuronal destruction. Recently, olive oil has been suggested as a sedative, as well (12). On the other hand, many studies have reported the effects of polyphenols in herbal extracts (e.g., green tea extracts). Based on previous research, these compounds could prevent the degeneration of dopaminergic neurons in substantia nigrain an animal model of Parkinson's disease (13).

Olive leaf extractsare enriched with many phenols such as oleuropein,luteolin-7-glucoside, apigenin-7-o-glucoside, verbascoside and hydroxytyrosol, which neutralizesuperoxides and hydroxyl radicals under laboratory conditions. Under these circumstances, hydroxytyrosolnormally removes peroxyl radicalson the surface of the membrane, and oleuropein functions on the lipid distribution chain of peroxyl radicals (14).

The effects of polyphenols in cognitive processes and neural destruction are appliedthrough their interactions with neuronal and glial signaling pathways, which lead to the disruption of gene expression and cell death (9). In this study, we aimed to investigate the protective effects of olive leaf extracts on anxiety-like behaviors in an animal model of Parkinson's disease, using elevated plusmaze test.

## Methods

This experimental study was conducted on 42 Wistar rats,weighing200-250 g. The animals were purchased fromAmol Pasteur Institute(Amol, Iran) and kept in separate cages (12 hrsof light and 12 hrsof darkness), with free access to water and food. All the experiments were performed in accordance with the ethical codesof Bioethics Committee of Mazandaran University of Medical Sciences, Mazandaran, Iran. The rats were divided into six groups (seven rats per group): control, sham, patient and treatment (receiving olive leaf extractsat doses of 50, 100 and 150 mg/kg) groups (15, 16). The sham and patient groups received saline solutions via gavage, whereas the treatment groups received hydroalcoholic extracts of olive leaveson a daily basis between 10a.m.and12p.m.

Three weeks after the injections, all rats, except the control group, were anesthetized viaintra peritoneal injection of ketamine (70 mg/kg) and xylazine (4 mg/kg). Afterwards, the rats underwent surgery, using a stereotaxic device. Cannulation was conducted unilaterally in the striatum (right hemisphere), based on Watson and Paxinos rat brain atlas withthe following coordinates: anterior-posterior position (1 mm), lateral position (2.5 mm) and depth of 4.5 mm relative to bregma (17).

After a couple of days, therats in patient and treatment groups were administered 10 mg of 6-OHDA in 2 µlof saline (containing 0.1% ascorbic acid) via a Hamilton syringe. The sham group also received saline solution by Hamilton syringe. Treatment with the extracts continued for three weeks after the surgery intreatmentgroups.

**Behavioraltests**

**Apomorphine-induced rotational behaviors:** Apomorphine (apomorphine hydrochloride

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hemihydrate, Sigma-Aldrich, USA) is an agonist for dopamine, which causes a rotation towards the opposite side of the area damaged by 6-OHDA (18). The rotational behavior induced by apomorphine wasinvestigated 21 days after the surgery in all groups. The animals were stored in acylindrical chamber (28 cm in diameter and height of 38 cm) in order to familiarize them with the environment.

Afterwards,apomorphine with a concentration of 0.5mg/kg, along withsaline (containing 0.1% ascorbic acid), wasintraperitoneally injected in rats (19). One minute after the injection, the rats were placed insidethe chamber and the number of rotations towards the damaged area and the opposite sidewas measured within anhour. The number of pure rotations was calculated as the difference between rotations in two directions.

**Elevated plusmaze test:** In this study, elevated plusmaze test was used to investigate anxiety-like behaviors. The used device was a wooden,cross-shapedmaze. This maze wasequipped with two open arms (without walls) and two closed arms(with a 30 cm wall). The length and width of the open arm were50 and 10 cm,respectively. Also, the open arms were attached to closed arms (10 cm in diameter) in the center area. Theapparatus wasplacedon a foundation ata height of 50 cm abovethe ground. A low-light lamp was used as the source of light in the room during the experiments (15). Before the onsetof experiments, the rats werekeptin a room in which the devicewaslocated (for five minutes)in order tofamiliarize them with the environment. The animals were placedin the center of the device on the opposite side of the open arm.They were allowed to move in the open and closed armsfor five minutes. The percentage of time spent in open arms(OAT) and the percentage of open-arm entries (OAE) were regardedas standard parameters for theevaluation of anxiety (20). These parameters were calculated as follows:

OAE=(Open arm entries/open+closed entries)×100

OAT=(Time of entry to the open arm/time of all entries)×100

In this study, the total number of entries into the arms was regarded as a factor indicatingrats' mobility. The low number of entries to the open arms and the little time spent in these arms were indicative of stress-like behaviors. For statistical analysis and intergroup comparisons, one-way ANOVA and Tukey's test were performed. All calculations were performed, using SPSS version 16. P-value less than 0.05 was considered statistically significant. Moreover, in order to illustrate the figures, SigmaPlot version 12.5 was used.

## Results

**The results of apomorphine-inducedrotational test:** The results of apomorphine-induced rotational test showed that the number of induced rotations in the control and sham groups was lowerthan 30.No significant difference was observed in the number of complete rotations between these groups. In addition, the number of complete rotations in the patient group significantly increased,compared to the control group (P<0.001). Useof olive leaf extracts also significantly reducedthe number of rotations towards the opposite side in treatment groups, receiving extractsat doses of 50, 100 and 150 mg/kg (p<0.001) (table 1).

**Table 1. The mean number of total rotations, induced by the intraperitoneal injection of apomorphine three weeks after the surgery**

| Groups | The meannumber of pure rotations (Mean±SE) |
|---|---|
| Control group | 12.71±3.03 |
| Sham group | 13.71±3.03 |
| Patient group(10 µg per rat) | 137.85±25.75*** |
| Treatment group (50 mg/kg) | 50.14±9.09*** +++ |
| Treatment group (100mg/kg) | 17.85±3.23 +++ |
| Treatment group (150 mg/kg) | 15.71±4.49 +++ |

*** Significant difference with the control group (P<0.001)

+++ Significant difference with the patient group (P<0.001)

The results are expressed as Mean±SE (n=7)

**The effects of 6-OHDA injection on anxiety-like behaviors:** The results of 6-OHDA administrationon anxiety-like behaviors within three consecutive weeks showed that OAT and OAE parameters significantly reducedin treatment groups, compared to the control group (P<0.001). These results indicatedthe occurrence of anxiety-like behaviors in an animal model of Parkinson's disease, which were amplified astime passed.

**The effects of olive leaf extracts on anxiety-like behaviors by the end of the first week:** OAT% and

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OAE% in treatment groups, receiving different doses of olive leaf extracts, and patient group significantly reducedin the first week, comparedto the control group. However, data relatedtorats' mobility did not reveal any significant differences betweenthese groups, compared to the control group (fig 1).

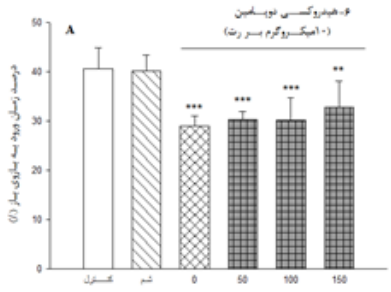


**Figure A:Thepercentage of time spentin the open arm**

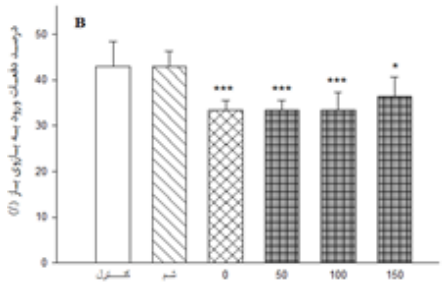


**Figure B:Thepercentage of the number of entries to the open arm**

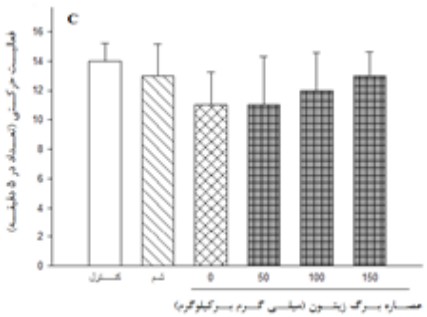


**Figure C: Physical mobility**

**Figure 1. The effects of different doses of olive leaf extracts on anxiety-like behaviors, induced by 6-OHDA in elevated maze plus test in the first week**

Significant difference with the control group ($^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$)

The results are expressed as Mean±SE (n=7)

**The effect of olive leaf extract on anxiety-like behaviors by the end of the second week:** Similar to the first week, a significant decline was reportedin OAT% and OAE% parameters intreatment groups, receiving different doses of olive leaf extracts, compared to the control groupbythe end of the second week. The evaluation of anxiety-like behaviors bythe end of the second week indicated that the oral administration of different doses of olive leaf extracts caused a significant declinein anxiety-like behaviors, induced by the toxin in the animal model of Parkinson's disease (Figure 2).

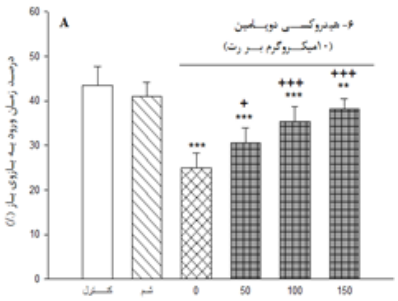


**Figure A:The percentage of time spent in the open arm**

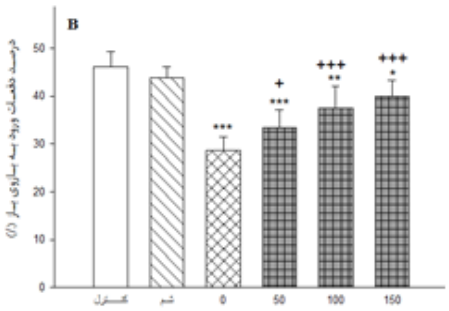


**Figure B:The percentage of the number of entries to the open arm**

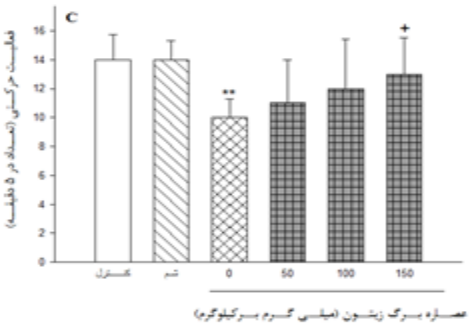


**Figure C:Physical mobility**

**Figure 2. The effects of different doses of olive leaf extract on anxiety-like behaviors, induced by 6-OHDA in elevated plus maze test during the second week**

Significant difference with the control group ($^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$)

Significant difference with the patient group ($^{+}p<0.05$, $^{++}p<0.01$, $^{+++}p<0.001$)

The results are expressed as Mean±SE (n=7)

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**The effects of olive leaf extracts on anxiety-like behaviors by the end of the third week:** Similar to the second week, a significant increase was reported in OAT% and OAE% parametersin treatment groups, comparedto the patient group. This indicated the effect of the extracts on decreasing anxiety-like behaviors, induced by 6-OHDA. The evaluation ofanxiety-like behaviors by the end of the third week showed that the oral administration of different doses of leaf extracts not only significantly reduced anxiety-like behaviors, but also normalized these behaviors (Figure 3).

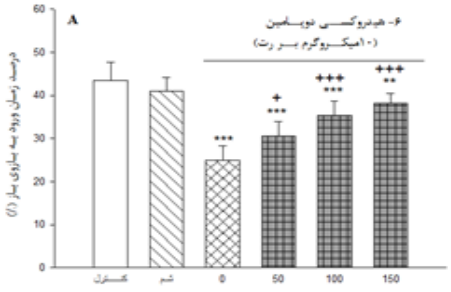



**Figure A: The percentage of timespent in the open arm**

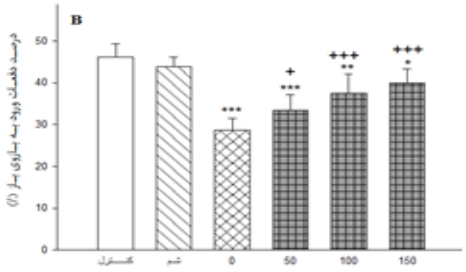



**Figure B: The percentageof the number of entries to the open arm**

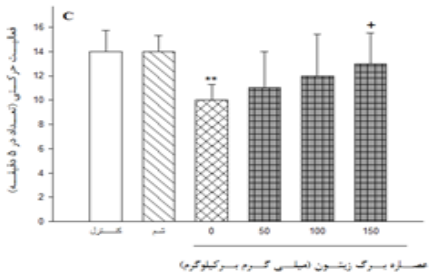



**Figure C. Physical activity**

**Figure 3: The effects of different doses of olive leaf extract on anxiety-like behaviors, induced by 6-OHDA in elevated plus maze test in the third week of the experiment**

Significant difference with the control group ($^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$)

Significant difference with the patient group ($^{+}p<0.05$, $^{++}p<0.01$, $^{+++}p<0.001$)

The results are expressed as Mean±SE (n=7)

## Discussion

The results of the present study showed that one month of treatment by different doses of olive leaf extracts did not have any significant effects on anxiety-like behaviors in an animal model of Parkinson's disease during the first week of evaluation. Overall, injection of 6-OHDA into the brain of rats is being widely applied for establishing an animal model of Parkinson's disease. The main mechanism of 6-OHDA toxicity is related to the production of oxygen radical species through autoxidation. Also, 6-OHDA injection into the striatum can gradually degenerate dopaminergic neurons (22).

Asmany studies have indicated, oxidative stress is an effective factor for decreased cognitive function imaging (23). Deumens et al. also showed that the injection of 6-OHDA could be used as a suitable model for investigating the symptoms of Parkinson's disease. Use of this injection could also add to the current information about the pathological mechanisms of such neurological disorders (24). In this regard, Tadaiesky and colleagues reported that the damage caused by 6-OHDA in the striatum of rats could increase anxious responses in elevated plus maze test (25).

Polyphenols in herbal extracts have various antioxidant and anti-anxiety properties (26, 27).In this regard, Shrivastava et al. reported that piperine, due to its antioxidant properties, has protective effects against Parkinson's disease (induced by 6-OHDA) through an anti-apoptotic mechanism (17). In addition, some studies have revealed the positive effects of herbal extracts on anxiety disorders. Shah Gagan et al. investigated the anti-stress properties of the methanolic extract of Cymbopogon citratusleaf and suggested that the existence of flavonoid compounds leads to an increase in OAE and OAT parameters in elevated plus maze test (28). In another study, the relaxing effects of Passiflora actinialeaf extracts were reported (29). According to previous studies, olive leaf extracts are also enriched with polyphenol compounds (26, 30) and have strong protective neuronal activities, which improve oxidative stress and nerve damage in animals (31).

In the present study, the evaluation of behavioral parameters by the end of the second and third weeks showed that over time, use of different doses of olive leaf extracts significantly reduced stress-like behaviors in treatment groups. By the end of the

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sixth week of extract use at higher doses, anxiety-like behaviors returned to the normal level, which is probably related to the protective effects of this compound on the induced damage in Parkinson's model.

Many studies have shown that pre-treatment with polyphenols in olive leaf significantly prevents the production of super oxides and nitric oxides after ischemia and prohibits lipid peroxidation (32). In fact, these flavonoids can probably protect nerve cells via different mechanisms such as stimulating the regeneration of damaged neurons and increasing the performance of remaining neurons. On the other hand, flavonoids may affect protein modulation and lipid kinase signaling pathways by inhibiting MAP kinase signaling cascades such as p38 or ERK1/2 (9). The results of the present study showed that the use of olive leaf extract in the long run can significantly protect the neurons against damages caused by 6-OHDA,due to it antioxidant properties. Thereby, these extract sreduce the induced behaviors by 6-OHDA. Researchers have suggested the protective effect of this extract against neurological disorders such as Parkinson's disease.

According to the findings of this study, oral administration of olive leaf extracts at higher doses may increase the time and number of entriesto the open arm in elevated plus maze test. This indicates rats' recovery from the damage, induced by 6-OHDA, in an animal model of Parkinson's disease.

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