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The Effects of *Biarum carduchrum* Hydroalcoholic Extract on Oxidative Stress and Catalepsy in 6-hydroxydopamine-induced Rat Model of Parkinson's Disease

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ABSTRACT

Background & Objective: Parkinson is a neurodegenerative disease that leads to incurable and debilitating conditions. Herbal extracts can afford protection against neurodegenerative diseases due to their bioactive compounds. In the present study, we investigated the effect of hydro-alcoholic extract of *Biarum carduchrum* on catalepsy and brain oxidative stress in rat's model of Parkinson's disease.

Materials & Methods: Rats were randomly divided into five groups of eight animals. The control group was left intact. Parkinsonian group received an injection of 6-hydroxydopamine (6-OHDA) in the right anterior mid-brain. Extract treated groups received hydro-alcoholic extract of *B. carduchrum* at doses of 100, 200 and 400 mg/kg by gavage seven days after 6-OHDA injection. 14 days after treatment, bar test was performed and lipid peroxide levels of different brain regions were determined. Data were analyzed by ANOVA followed by Tukey's test using SPSS22 software and $P<0.05$ was considered statistically significant.

Results: In 6-OHDA-lesioned group bar time was increased significantly ($P<0.05$) when compared with the control group (122.50±90.12 versus 0.00±0.00). *B. carduchrum* at doses of 200 and 400 mg/kg significantly reduced 6-OHDA induced catalepsy ($P<0.0.5$). 6-OHDA treatment lead to significant increases in lipid peroxide levels of cerebellum, cortex, hippocampus and striatum ($P<0.05$). Administration of *B. carduchrum*extract at different doses caused significant reduction in the lipid peroxide levels of different brain regions ($P<0.05$).

Conclusion: *B. carduchrum* extract ameliorated 6-OHDA -induced catalepsy and lipid peroxide level of brain in rat's model of Parkinson's disease.

Keywords: *Biarum carduchrum*, Catalepsy, Parkinson's disease, Lipid peroxide

Introduction

Parkinson's disease is a neurodegenerative disease that occurs mainly due to the progressive destruction of dopaminergic neurons in Substantia nigra, pars compacta (SNc) and other regions of the brainstem (1). Dopamine plays a critical role in the movement and motor functions. Acetylcholine is another neurotransmitter that opposes the action of dopamine. In Parkinson's disease, dopaminergic neurons are dying and therefore the balance between the dopaminergic and the cholinergic activity is disturbed, which results in the development of disease symptoms including tremor, bradykinesia, catalepsy, and dystonia (2). Catalepsy is a physical condition characterized by muscular rigidity, fixity of posture, suspension of sensation and loss of contact with environment (3). Other symptoms of the disease include cognitive impairment and speech disorder (4).

Oxidative Stress has been reported to play an important role in the degeneration of dopaminergic neurons in Parkinson's disease (5). Oxidative stress in Parkinson disease arises from elevated iron accumulation, impaired mitochondrial function, increased nitric oxide production and weakened antioxidant defense system. Overproduction of reactive oxygen species can lead to oxidative damage of cellular biomolecules and eventually dopaminergic cell death (6). Oxidative stress can also lead to dopaminergic cell damage by disturbing the process of oxidative phosphorylation and energy depletion (7).

There is currently no cure for the treatment of Parkinson's disease. Some drugs can help alleviate the symptoms of the disease but exert minimal effects on neuropathological changes caused by the disease. In addition, some of these drugs show serious side effects and aren't tolerated by the patient. Therefore, there is a clinical need for new therapeutic agents to stop or slow down the neurodegenerative process in the pathology of disease (8).

Biarum is a genus of about 20 species of flowering plants in the family Araceae that are native to the Middle East, southern Europe, and North Africa **(9)**. *Biarum carduchrum* is a medicinal plant species from this genus and grows wild in Turkey, Syria, Lebanon, Jordan, Iraq and Iran. In Iran, *B. carduchrum* is found on the hillsides of the Zagros Mountains in Fars and Kohgiluyeh and Boyer-Ahmad Provinces **(10)**. There is very limited information about the pharmaceutical effect of this plant. In a study, *B. carduchrum* extract showed potent antioxidant activity in the inhibition of free radicals in vitro. It also showed protective effect against hyperlipidemia induced by high-fat diets in rat model **(11)**. In another study, *B. carduchrum* extract considerably enhanced the antioxidant status of rat brain tissue by improving its thiol level **(10)**. The species of Biarum genus have been reported to contain alkaloids, amines, saponins, cinnamic acid, and flavonoids **(9)**. Due to their potent antioxidant effects, these compounds can protect the body against the harmful effects of free radicals and active oxygen radicals **(12)**. Regarding the antioxidant property of *B. carduchrum* **(10, 11)**, we investigated the effects of hydro-alcoholic extract of this plant on animal catalepsy and lipid peroxidation of different brain regions in rat model of Parkinson's disease.

Materials and Methods

Preparation of Hydroalcholic Extract of *B. carduchrum*

B. carduchrum samples were collected from the Izeh vicinity, Khuzestan Province, South-West Iran during spring 2018. After identification by a botanist, the plant specimens were stored in the herbarium of Islamic Azad University of Izhe (Number: 45679). Then, the leaves were separated and dried in the open air under shadow. The dried leaves were finely pulverized into particles less than 0.4 mm in diameter. The resulting powder was macerated with 70% v/v ethanol for 72h at room temperature. Then, the resulting extract was filtered and the filtrate underwent vacuum evaporation to remove alcohol (the extract yield was calculated 28%) **(13)**.

Grouping of Animals:

Male Wistar rats weighing 200-250g were housed under standard conditions [(21±2)°C temperature and 12-h light-dark cycle] with free access to the same water and food. The rats were assigned into five groups with eight rats in each. The Control group was left intact. Parkinsonian group received injection of 6-OHDA in the right anterior mid-brain **(14)**. Extract treated groups received *B. carduchrum* extract at doses of 100, 200 and 400 mg/kg by gavage for 14 days, seven days after Parkinson induction **(15, 16)**. The rats were given 7 days to heal their wound, and then the treatment began. Doses of the extract was selected based on previous studies **(10, 11)**. After treatment period, behavioral test was performed. The study was approved by the Ethics Committee of Islamic Azad University (Cod: IR. IAU. Ahwaz. REC. 1395.53) and all animal procedure was based on Guidelines for the Care and Use of Laboratory Animals **(17).**

Inducing of Parkinson's Disease

The rats were anesthetized using an IP injection of ketamine hydrochloride at 90 mg/kg plus xylazine at 10 mg/kg. Then, the rats were placed in a stereotaxic apparatus and stabilized by a mouthpiece and the rods inside the headphone and the hairs in the back of its cranium was shaved. The rat head skin was fumigated with alcohol cotton and a linear section was made from the back of the head between the two eyes to the midpoint of the back of the middle ears. The connective tissues on the cranium surface were removed and the bregma was displayed. The bregma and lambda were placed on an equal surface and the apparatus marker was set on it. Correspondent to Atlas of Neurosurgical Techniques, the MFB was defined at peculiarities AP:-3.8, ML±1.8, and DV:-3.8mm. Parkinson's disease was enforced by unilaterally injecting neurotoxin-6-OHDA (8µg) (dissolved in 2 µg of normal saline containing 1% ascorbic acid) in the MFB (Figure 1) **(14)**.

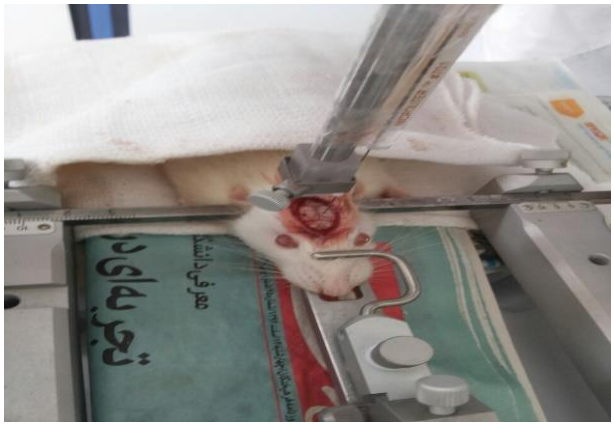

Figure 1. Finding the positions of Substantia Nigra

Bar Test (Catalepsy)

In the present study, bar test was used to evaluate the 6-OHDA induced catalepsy. The device used in this test was a wooden bar with a platform. The height of the floor from the platform was 9 cm and the diameter of the horizontal bar was 0.9 cm. To perform the experiment, the animal was placed on the platform and its two front paws were placed lightly on the horizontal bar. The duration of time animal remained in this inflicted condition was discussed as the bar time. The end point of catalepsy was defined to occur when both front paws were lifted from the bar or if the animal moved its head in a probative method. The cut off time of the test was 720 sec and the test was done in four continuous times with 1h interval **(18).**

Measuring Lipid Peroxide Levels in the Brain Tissues

The rats' brains were placed in a plate containing normal saline which was cooled on ice and then the brain regions including cerebellum, hippocampus, striatum and cortex were separated by scalpel and immediately weighed. One gram of each section was homogenized in 10 mL of cold 1.5% KCl solution. Then, 0.5 mL of homogenized sample, 3 mL of 1% phosphoric acid and 1 mL and 1 mL

of 6% thiobarbituric acid were added to a test tube and heated in a boiling water bath for 45 min. After cooling, 4 mL of n-butanol was added and mixed vigorously. After centrifugation at 2000 rpm for 15 minutes, the absorbance read at 535 nm wavelength **(19)**.

Statistical analysis

Data analysis was conducted by SPSS version 22. First, normal distribution of the data was investigated by Kolmogorov-Smirnov test and variance homogeneity was studied by Levene's test. Then, to investigate the significance of difference between the treatments, one-way ANOVA was used, and to compare the mean values, Tukey's test. The data were expressed as mean (standard. deviation) and $p<0.05$ was considered statistically significant.

Results

The effect of hydro-alcoholic extract of *B. carduchrum* on 6-OHDA induced catalepsy in the bar test was shown in Table 1. Injection of 6-OHDA into the rat brain caused a significant increase in the bar time compared to the control group ($P<0.05$). Treatment of 6-OHDA-lesioned rats with *B. carduchrum* extract at doses of 200 and 400 mg/kg significantly reduced the bar time compared to the 6-OHDA group ($P<0.05$). Mean bar time in 6-OHDA-lesioned group receiving extract at a doses of 100 mg/kg was significantly higher than group receiving extract at doses of 200 and 400 mg/kg ($P<0.05$). Mean bar time in 6-OHDA-lesioned groups receiving extract at doses of 200 and 400 mg/kg had no significant difference (Table 1).

The effect of *B. carduchrum* extract at doses of 100, 200, and 400 mg/kg on lipid peroxide levels in different brain regions of rats was shown in Figure 2. There was a statistically significant difference in the lipid peroxide levels of cerebellum, cortex, hippocampus and striatum tissues between the control and 6-OHDA-lesioned groups ($P<0.05$). Treatment of 6-OHDA-lesioned group with *B. carduchrum* extract (at all doses) caused significant decreases in lipid peroxide levels of the all brain regions ($P<0.05$, Figure 1). *B. carduchrum* extract at 100 mg/kg showed better activity in lowering brain lipid peroxide compared to doses of 200 and 400 mg/kg.

Table 1. The effect of *B. carduchrum* hydroalcoholic extract on 6-OHDA induced catalepsy in the bar test

Experimental group	Bar time (seconds) Mean+SD	P values
6-OHDA-lesioned group	122.50±9.02	
Control	00.00±00.00*	
Extract (100mg/kg)	93.66±5.45	0.05
Extract (200mg/kg)	22.00±1.35#&	
Extract (400mg/kg)	29.33±2.8#&	

Data were analyzed by one-way ANOVA followed by Tukey's test. *Shows significant difference between 6-OHDA-lesioned and control groups at $P<0.05$. #Shows significant difference between 6-OHDA-lesioned and extract treated groups at $P<0.05$. & show significant different between 6-OHDA-lesioned group receiving extract at a dose of 100 mg/kg with 6-OHDA-lesioned groups receiving extract at doses of 200 and 400 mg/kg.

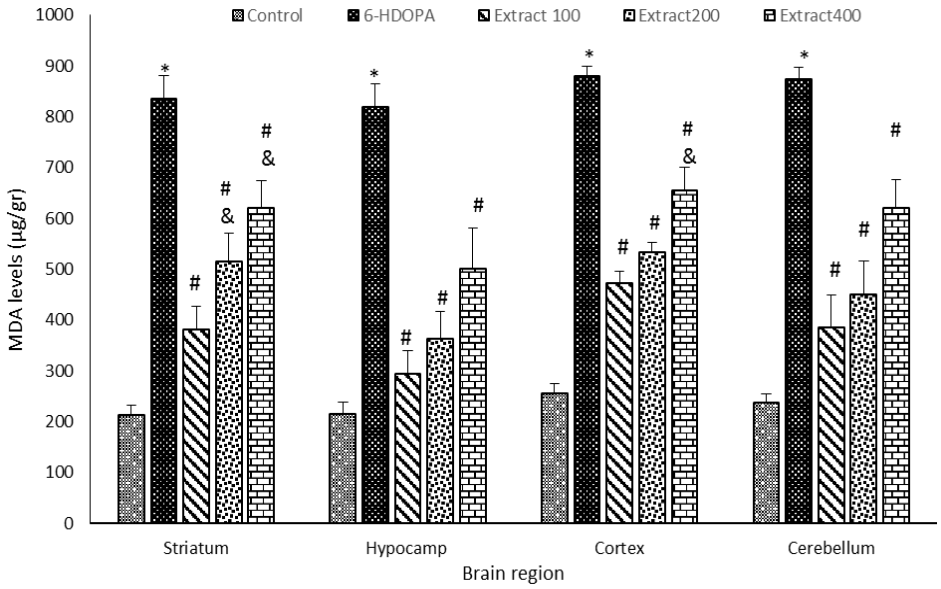

Figure 2. The effect of *Biarum carduchrum* extract at doses of 100, 200, and 400mg/kg on lipid peroxide levels of different brain region; *Shows significant difference between 6-OHDA-lesioned and control groups at $P<0.05$. # shows significant difference between 6-OHDA-lesioned and extract treated groups, & show significant different between 6-OHDA-lesioned group receiving extract at a dose of 100 mg/kg with 6-OHDA-lesioned groups receiving extract at doses of 200 and 400 mg/kg.

Discussion

Our results showed that 6-OHDA injection was able to cause catalepsy, this result is consistent with previous studies reporting catalepsy inducing activity for 6-OHDA **(15, 20)**. Generally, 6-OHDA is a neurotoxic agent used to induce nigrostriatal damage and establish an animal model of Parkinson's disease. It cannot pass the blood brain barrier, so it must be directly injected in the SNc **(20)**. It was shown that progressive degeneration of dopaminergic neurons of SNc and other brain regions due to 6-OHDA toxicity results in motor disabilities such as muscle rigidity (catalepsy), akinesia, tremor and postural abnormalities **(15)**.

In our study, intra-striatal injection of 6-OHDA caused significant increases in lipid peroxides levels of different brain regions. Previous studies have also reported different degrees of oxidative stress following intrastriatal administration of 6-OHDA. Haddadi *et al.* and Hosseini *et al.* reported rise of brain lipid peroxidation in 6-OHDA-lesioned rats **(21)**. Khan et al reported elevated levels of thiobarbituric acid reactive substances (TBARS) and protein carbonyl and reduced activities of antioxidant enzyme in different brain regions of parkinsonian rats **(22).**

It has been well established that neurotoxin-6-OHDA causes degeneration of the brain areas involved in motor function by producing free radicals and reactive oxygen species. Under physiological conditions, this toxin is readily oxidized and converted to hydrogen peroxide and, through a specific reaction, hydroxyl radicals, which are one of the most harmful free radicals for living cells **(23, 24)**. Hydroxyl radical and other reactive oxygen species can cause oxidative damage to biologically vital molecules such as lipids, proteins and DNA which ultimately leads to neuronal cell injury and death **(25)**. Brain tissues contain a high amount of unsaturated fatty acids that are particularly vulnerable to free radicals' attack. It is argued that lipid peroxidation is a predominant and specific type of neuronal oxidative stress that damages the cell membrane and produces secondary metabolites which show neurotoxic effects **(26).**

Our results showed that the treatment of 6-OHDA-lesioned rats with *B. carduchrum* extract at different doses significantly suppressed the rise in lipid peroxidation of brain areas. There is limited information about *B. carduchrum* and very few studies have been conducted to determine the phytochemical composition and biological activities of this plant. The study of Hosseini *et al.* indicated that *B. carduchrum* extract acts similarly with or even more potently than certain nature-derived or synthetic antioxidants in vitro. They also investigated the activity of hydromethanolic extract of *B. carduchrum* on the serum lipids in rats and reported that this extract could improve fat-rich diet-induced increase in serum lipids due to potent antioxidant property **(11)**. In another study conducted by Zanganehnejad *et al.*, it was found that treatment with *B. carduchrum* extract significantly increases antioxidant potential in the different brain regions of parkinsonian rats **(10)**.

Potent products derived from plants, fruits, and vegetables exert considerable antioxidant effects against neuronal oxidative stress due to certain compounds such as flavonoids, steroidal lactones, alkaloids, caffeine, saponins, anthocyanins, and curcuminoid **(27)**. The plants of *Biarum* genus can synthesize many compounds such as flavonoids, phenols, alkaloids, amines and saponins **(9)**. Regarding the protective effects of these compounds on oxidative stress-induced neuronal injuries **(28-31)**, it can be argued that the antioxidant compounds of *B. carduchrum*, including phenolic and flavonoids, may prevent the progression of nervous system neurodegeneration through reducing oxidative stress parameters.

In this study, *B. carduchrum* extract at 100 mg/kg showed better activity in lowering brain lipid peroxidation than 200 and 400 mg/kg doses. It has also been observed that some herbal extracts that contain high levels of polyphenols may exacerbate oxidative stress by interfering with oxidative-antioxidant balance **(22)**. So, it seems that lower effects of 200 and 400 mg/kg doses of *B. carduchrum* are related to the imbalance of oxidative-antioxidant status.

Conclusion

In the present study, for the first time, the supporter effects of *B. carduchrum* on catalepsy and lipid peroxidation in 6-OHDA-lesioned rats were displayed, which may be due to the antioxidant effects of the plant. The supporter effects of this plant may also be ingeminated to the other mechanisms involved in Parkinson pathophysiology which need further study.

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Conflict of Interest

Authors declared no conflict of interests.

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