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IMPAIRED MOVEMENTS IN 6-OHDA INDUSED PARKINSON'S DISEASE IMPROVES BY HYDROALCOHOLIC EXTRACT OF FERULAGO ANGULATA

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ABSTRACT

Parkinson's disease (PD) is a prevalent neuropathological disorder which is induced due to the degeneration of dopaminergic neurons of the dense part of substantia nigra. Oxidative stress is regarded as a main factor of this disease which causes death of neurons. Considering the protective property of Ferulago angulata, the aim of the present study was to investigate effect of the extract of this plant on motor disorders of animal model of Parkinson's disease. Materials and methods: Animals were divided into 5 groups. To create an animal model, the rats received 6-OHDA neural poison with dose of 8 µg in 2 µl of normal saline solution with 0.01% of ascorbic acid inside medial forebrain bundle **(**MFB**)** on the left side of the brain. The treatment groups received Ferulago angulata with doses of 100, 200, and 400 mg/kg for 14 days as gastric gavage and motor tests were conducted on the rats one day after the last gavage. Results: Ferulago angulata improves motor disorders resulting from Parkinson's disease. Conclusion: Considering the present findings, it can be suggested that extract of Ferulago angulata has a protective effect on 6-OHDA in the experimental model of Parkinson's disease.

Keywords: Ferulago Angulata, Motor Disorders, Parkinson's Disease, Rat

INTRODUCTION

Parkinson's disease (PD) is the second prevalent progressive neurodegenerative disorder after Alzheimer's disease, which is characterized by intensive motor disorders such as vibration at time of rest, hardness or increase of passive motions, posture instability, and slow voluntary motions **[1]**. Among other characteristics of Parkinson's disease are fatigue, depression, and Alzheimer's disease **[2]**. Studies have shown

that the incidence of this disease increases with age **[3]**. Unilateral damage of nigrostreriatal dopaminergic system following 6-OHDA intrastreriatal injection has been recognized as the common animal model of Parkinson's disease, in which gradual reduction of dopamine striatum and regulation of postsynaptic dopaminergic receptors occur. These changes lead to functional-motor dissymmetry which is commonly measured by rotation induction to the same (ipsilateral) and opposite directions (contralateral) with dopaminergic induction with direct (apomorphine) and indirect effects (amphetamine) **[4]**. Performance of therapeutic motions can help prevent debilitation and disability to a great extent **[5]**. In a normal case, there is a balance between production of free radicals and antioxidant defense system which includes special systems for controlling damage resulting from free radicals in the body of a healthy person, while this disrupted balance induces an oxidative stress process which can be effective for the pathogenesis of more than one hundred types of different diseases through different mechanisms such as destruction of metabolic function, etc. **[6-8]**. There are different hypotheses about pathological mechanisms and cause of death of dopaminergic cells of the dense part of substantia nigra such as mitochondrial deficiency relating to electron transport chain, accumulation of iron, dysfunction of some hepatic cytochromes, and increased formation of free radicals **[9, 10]**. Despite the presence of different antioxidants in plasma, defensive system of the body is not able to remove free radicals; thus, it needs to receive antioxidant from external sources, which is supplied through food sources **[11]**. Ferulago angulata belongs to *Apiaceae* family **[12]**. Phenol compounds of anthocyanins and total and edible flavonoid of methanol extract of Ferulago angulata have antioxidant property. Ferulago angulata is also used as a flavor and strong tranquilizer of digestive system **[13, 14]**. In Parkinson's disease, the number of dopaminergic cells is reduced after the increase of oxide nitric radical and destruction of these cells; therefore, removal of free radicals plays an important role in neuron protection and reduced destruction of dopaminergic neural cells in Parkinson's disease **[15]**. The common pharmacotherapy of this disease includes treatment of a symptom by prescribing dopamine precursors, agonists, and other dopamine analogs. The most common drug which has bene applied is L-DOPA that is regarded as the most effective drug. Most patients show a good initial response to this drug; but, they are exposed to harmful effects such as dyskinesia, fluctuating effects of drug,

memory, and lack of effect of drug, as a result of which efficiency of treatment is reduced. Therefore, most Parkinson's patients will experience a disability which will not be controlled by accessible and common treatments. For this reason, extensive efforts have been made to complete a kind of certain treatment for this disease to stop or slow down the neuron destruction trend **[16]**. In this research, attempts were made to study the hydroalcoholic extract of Ferulago angulata on motor activities of animal model of Parkinson's disease in adult male rats and the presented materials aimed to justify the results obtained in this research.

MATERIAL AND METHODS

Animals: In this research, 50 Wistar rats with the weight range of 200-250 g (obtained from Ahvaz Jundishapur University of Medical Sciences) were used. The animals were kept in a bright place for 12 h and dark place for 12 h at 21±2˚C with free access to sufficient water and food inside the individual cages and divided randomly into the following groups.

1- Control group: Animals of this group were not injured.
2- Parkinson's group: Animals of this group received 8 µg 6-OHDA neurotoxin in 2 µl of normal saline solution with 0.01% of ascorbic acid in MFB area.
3- Three treated Parkinson's groups: They were like Parkinson's group and received 400, 200, and 100 mg/kg FAE for 14 days as gavage after 7 days of convalescence period and behavioral tests were performed on the 15th day **[17]**.

Ferulago Angulata Extract (FAE) Preparation

In early April, Ferulago angulata was collected from Zagros mountain ranges in Khuzestan province. Top branches of the plant were kept in a dark place for 2 weeks to dry. After powdering and damaging the plant, 450 g of the plant was weighted and its volume was increased with 100 ml of alcohol 96%. After three days of maintenance in the laboratory environment and stirring (for isolating all plant constituents in water and alcohol) and finally filtering, it was spread in a tray to dry. Purity of this extract was calculated as 27%. After drying, powder of the plant was collected and kept for producing different doses of the extract **[17, 18]**.

Animal Model of PD

The rats were first weighted and then anaesthetized by the intraperitoneal injection of 90 mg/kg hydrochloride ketamin per kg of body weight and 10 mg/kg of xylazine per kg of body weight (both were produced by Dutch Alosphane Company). Then, the rats were placed in

stereotaxy and fixed with mouthpart and ear bars on the device. Then, hair of the frontal area of the skull was shaved. Head skin of the rats was disinfected with alcoholic cotton and a longitudinal cut was made in the middle of the posterior part of the head between two eyes to middle posterior part of the ears. The connective tissues on the surface of skull were removed and Bregma point was manifested. Bregma and Lambda points were put on an equal surface and the indicator of the device was adjusted on it. Then, coordinates (MFB) (with coordinates of -4.8; a relative to Bregma point ±1.6, ML, -8.2; DV) were specified considering coordinates extracted from the brain surgery atlas. In this study, unilateral injection of 6-OHDA was used in medial forebrain bundle **(**MFB) to create the animal model of Parkinson's disease **[19]**.

6-OHDA: 6-OHDA (American Sigma Company) with concentration of 8 µg was prepared in 2 µl of normal saline with 0.01% of ascorbic acid. Preparation of apomorphine solution (American Sigma Company): This drug was dissolved in normal saline 0.02% of ascorbic acid.

Apomorphine-induced Circling Behavor

Rotational behavior of the rats was tested by injecting hydrochloride apomorphine, 2.5 mg/kg. Full rotations were measured in a cylindrical case for 60 min in 10-min intervals **[20]**.

Catalepsy test (horizontal bar): Two hands of the animal were put on the bar with height of 9 cm, while its feet were put on the floor of the wooden box and the time required by the animal for lifting its hands was noted **[21, 22]**.

Rotarod test (motor balance test)

This test was performed to measure motor performance and coordination. For this purpose, the animals were placed on the Rotarod, in which motion speed was variable and initial rotation speed was 5 rpm and then rotation speed of rod gradually increased within 300s (5 min) to 25 rpm. The main criterion for balance in all groups was 25 rpm. The animals got familiar with the test performance and then each rat was tested three times a day in 45-min sessions and mean time was calculated **[4]**.

Stride Length Test

This device was composed of a dark wooden box with a slide door with the dimensions of 10*17*20 cm, to which a narrow tunnel with the dimensions of 4.5*10*45 cm was connected, and end of the tunnel was open. The border between square part and tunnel was also separated by a guillotine blade. At the open end of the tunnel, there was a plastic square box, the floor of which was inky, and floor of the tunnel was a white tape paper which was carpeted in 4.3 cm width. Then, motor organs of the rats with its tail were placed in

the inky box and directed toward the tunnel; once the rats entered the dark box, guillotine blade was released and they were confined inside the dark box to prevent returning and walk on the paper inside floor of the tunnel. Then, the paper tape was removed from the tunnel floor to dry the fingerprints. In this manner, paces were recorded on the paper. It is necessary to note that the animal got familiar with the box before the test **[4]**.

Testing 3 and 9 cm Platforms

Right hand of the animal was put on a platform with the height of 3 cm; when the animal did not lift its hand on the platform at least for 10 s, it was scored 0.5. Left hand of the animal was put on a platform with the height of 3 cm; when the animal did not lift its hand on the platform at least for 10 s, it was scored 0.5 again. Right hand of the animal was put on a platform with the height of 9 cm so that other parts of the body did not contact the platform; when animal did not lift its hand on the platform at least for 10 s, it was scored 1. Left hand of the animal was put on a platform with the height of 9 cm so that other parts of the body did not have contact with the platform; when animal did not lift its hand on the platform at least for 10 s, it was scored 1 again **[22]**.

Walking Test

The animal was placed on a flat surface on a desk or mosaic floor of the laboratory; when it started walking, it was scored 0. In case it did not move or started moving with hand contact, it was scored 0.5 and rigidity was calculated along with platform tests **[23]**.

RESULTS AND DISCUSSION

All the animals tolerated stereotaxic surgery well and no mortality was observed during the study. According to the statistical analysis, results of studying motor behaviors and motor balance inducted by apomorphine for 1 h showed that the difference was found two weeks after the surgery in the damaged group before surgery and apomorphine caused a rotational behavior to the damaged area ($P<0.001$). Prescription of hydroalcoholic extract of Ferulago angulata to the damaged groups reduced rotation with apomorphine ($P<0.05$). Effect of different values of Ferulago angulata on rotation due to induction of 6-OHDA in Parkinson's groups:

The present results showed that rotation of the Parkinson's groups significantly increased compared with the control group after the creation of MFB lesion due to injection of 6-OHDA in the rats ($P<0.001$). In the treatment Parkinson's groups which received extract of Ferulago angulata, 100, 200, and 400 mg/kg for 14 days as gavage, it was specified that rotation in the groups receiving Ferulago angulata significantly decreased (100, 200 mg/kg ($P<0.001$) and

400(P<0. 01) mg/kg) compared with the Parkinson's group **(Figure 1)**.

Effect of treatment with different doses of Ferulago angulata on catalepsy test in the rats with Parkinson's disease: The results demonstrated that catalepsy in the Parkinson's groups significantly increased compared with the control group after the induction of MFB lesion due to injection of 6-OHDA in the rats (P<0.001). In the treatment Parkinson's, catalepsy was significantly reduced in the groups receiving Ferulago angulata (100 and 200 mg/kg) compared with the Parkinson'ss group (P<0.01) and a significant reduction was found in the group receiving 400 mg/kg of the extract of Ferulago angulata (P<0.05) compared with the Parkinson's group too **(Figure 2)**.

Treatment effect of different doses of Ferulago angulata on motor balance test (Rota rod) of the rats with Parkinson's disease: As observed above, motor balance in the Parkinson's group was significantly reduced compared with the control group (P<0.01). Comparison between Parkinson's groups with and without the extract of Ferulago angulata represented that 14-day prescription of this extract (200 and 400 mg/kg) significantly increased motor balance of the animals with Parkinson's disease (P<0.05), while treatment with dose 100 of Ferulago angulata did not show any significant increase **(Figure 3)**.

Studying different doses of Ferulago angulata extract on stride length test in rats with Parkinson's disease: stride length in the Parkinson's groups significantly decreased compared with the control group (P<0.001). In the treatment Parkinson's group with extract of Ferulago angulata stride length in the groups receiving 100 and 200 mg/kg of the extract significantly increased compared with the Parkinson's group (P<0.05). It had no effect in the group receiving 400 mg/kg of Ferulago angulata and was not significantly different from Parkinson's group **(Figure 4)**.

Effect of different quantities of Ferulago angulata extract on muscular spasm (rigidity) in Parkinson's group: In another part of this research, rigidity significantly increased in the Parkinson's group (P<0.001) compared with the control group and it was also specified that treatment with doses of 100, 200, and 400 mg/kg the extract significantly decreased rigidity (P<0.05). Therefore, prescription of all three doses of Ferulago angulata extract improved muscular rigidity in the rats with Parkinson's disease **(Figure 5)**.

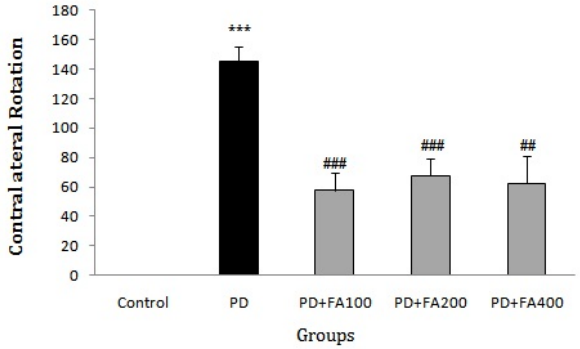

Figure 1: Effect of 14-day oral administration (gastric gavage) of 400, 200, and 100 mg/kg of hydroalcoholic extract of Ferulago angulata on rotation in the animal model of Parkinson's disease. Results were presented as mean ± SEM. One-way ANOVA and Tukey's test (in each group, n=8) were used. * on the columns shows significant difference from the control group and # on the columns shows significant difference from the Parkinson's group.

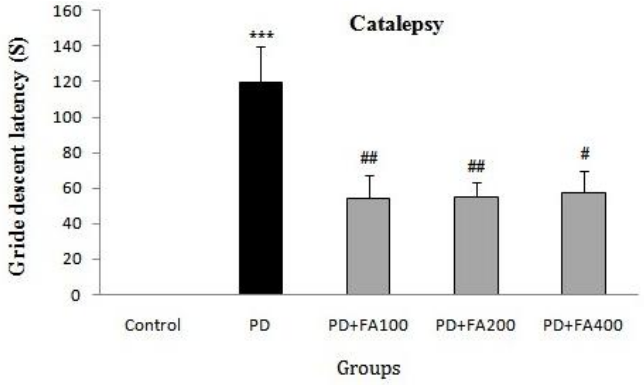

Figure 2: Effect of 14-day oral administration (gastric gavage) of 400, 200, and 100 mg/kg of hydroalcoholic extract of Ferulago angulata on catalepsy in the animal model of Parkinson's disease. Results were presented as mean ± SEM. One-way ANOVA and Tukey's test (in each group, n=8) were used. * on the columns shows significant difference from the control group and # on the columns shows significant difference from the Parkinson's group.

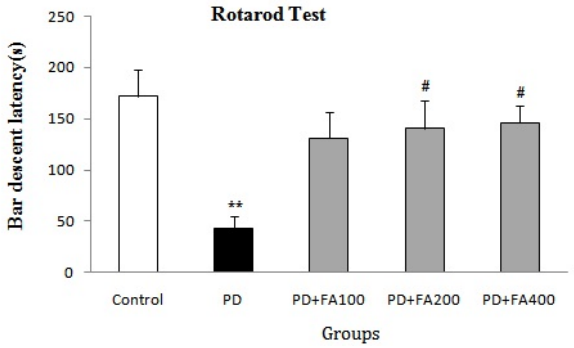

Figure 3: Effect of 14-day oral administration (gastric gavage) of 400, 200, and 100 mg/kg of hydroalcoholic extract of Ferulago angulata on motor balance (rotarod) in the animal model of Parkinson's disease. Results were presented as mean ± SEM. One-way ANOVA and Tukey's test (in each group, n=8) were used. * on the columns shows significant difference from the control group and # on the columns shows significant difference from the Parkinson's group.

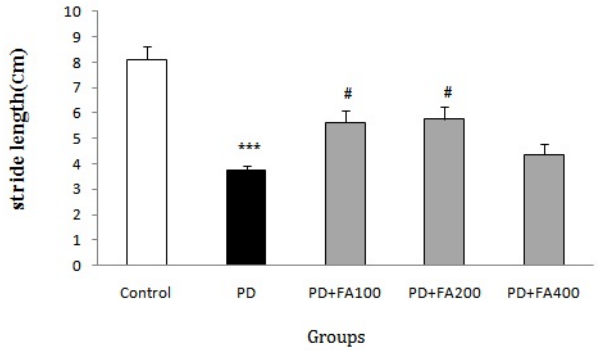

Figure 4: Effect of 14-day oral administration (gastric gavage) of 400, 200, and 100 mg/kg of hydroalcoholic extract of Ferulago angulata on stride length in the animal model of Parkinson's disease. Results were presented as mean ± SEM. One-way ANOVA and Tukey's test (in each group, n=8) were used. * on the columns shows significant difference from the control group and # on the **columns shows significant difference from the Parkinson's group**

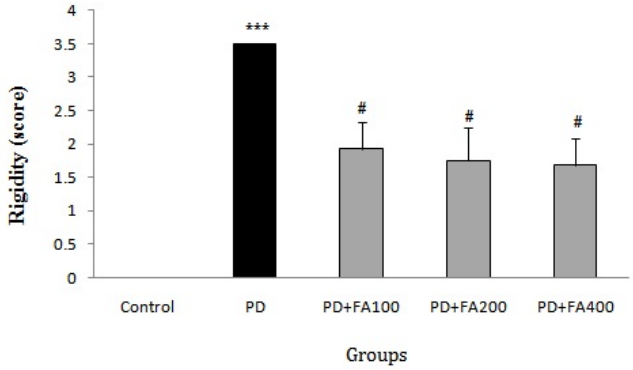

Figure 5: Effect of 14-day oral administration (gastric gavage) of 400, 200, and 100 mg/kg of hydroalcoholic extract of Ferulago angulata on rigidity in the animal model of Parkinson's disease. Results were presented as mean ± SEM. One-way ANOVA and Tukey's test (in each group, n=8) were used. * on the columns shows significant difference from the control group and # on the **columns shows significant difference from the Parkinson's group**

DISCUSSION

Many studies have proved the role of free radicals as a pathogenic chemical substrate in Parkinson's disease. For example, lipid peroxidation is high in the brain of these patients. 6-OHDA causes Parkinson's disease by inducing oxidative stress. Rotation of the destruction groups in all 10-min intervals and total rotation in 1 h compared with the control group indicated lesion and destruction of dopaminergic neurons, while rotation in the treatment group was much lower than that in the destruction group in all 10-min intervals, which can represent prevention from the destruction of dopaminergic neurons and reduction of motor dissymmetry following this destruction with the prescription of Ferulago angulata extract. Treatment with different doses of Ferulago angulata (100, 200, and 400 mg/kg) could significantly improve motor disorders resulting from prescription of 6-OHDA including stride

length, motor balance, catalepsy, and rigidity compared with the untreated group. Free radicals cause cellular reaction and many diseases **[24]**. Cellular organism produces many endogenesis antioxidants such as catalase, superoxide dismutase; but, exogenesis antioxidants have been recently introduced which are supplied through food and plants **[25]**. Epidemiological studies have proved useful effects of the food rich with plants and fruits on the reduction of affliction with diseases **[26]**. Akinesia which is made in Parkinson's disease is due to the fact that its secretion in the limbic system is also reduced following the reduction of dopamine secretion in Basal ganglia, which may reduce mental stimulation for the performance of motor activity leading to akinesia **[27]**. On the other hand, since motion designs require successive changes between stimulation and suppression, therefore, lack of suppressive effect of dopamine prevents the start and progress of consecutive designs which need stimulation in addition to suppressive stages and this exactly occurs in akinesia **[15, 28]**. Lack of the balance between production of free radical and defensive antioxidant system is due to oxidants, which leads to more lesions and also plays a central pathogenic role of the neurodegenerative and neurological diseases such as Parkinson's, trauma, and Alzheimer's diseases and stroke **[29, 30]**. Natural phenolic acids are the compounds which affect free radicals **[15]**. Free radicals play an important role in chronic diseases such as brain disorders and cancer **[31]**. Phenol compounds are able to inhibit free radicals due to antioxidant activity. Hence, they can be effective for the prevention of many diseases such as cancer, cardiovascular diseases, and neural diseases **[32, 33]**. Based on the abundant studies which have been conducted to identify and extract all antioxidant materials of Ferulago angulata (Schlecht) Boiss, it can be said that extract of the aerial part of this plant contains components with different therapeutic effects. The extract with phenolic and antioxidant properties is one of the herbs, which is able to be used as a natural antioxidant in food, pharmaceutical, and cosmetic industries owing to its antihelmentic, antimicrobial, and antidiabetic property **[34, 35]**. Extract of Ferulago angulata has analgesic and inhibiting effects of the pre-Inflammatory factors of cytokines could reduce sensitivity to environmental stimuli, decrease neuropathic pain, strengthen memory, protect neurons, and improve memory disorders and pain in the ischemia model of hipoperfusion **[36, 37]**. Khan Ahmadi in 2010 reported antioxidant activity of Ferulago angulata using two iron measurement tests (Thiocyanate and

Thiobarbituric acid) and mentioned that extract of Ferulago angulata had an antioxidant activity. He also reported that extract of FA reduced lipid peroxide **[38]**. Rafiei Rad et al. (2014) showed that Ferulago angulata was able to remove oxidant materials from special areas of the brain and was also effective for the reduction of oxidative stress in ischemic hypoperfusion. Moreover, they observed that different doses of Ferulago angulata was able to reduce malondialdehyde as a lipid peroxidation index in ischemic hypoperfusion model **[17]**. Administration of some other plant extracts has had a positive effect on Parkinson's disease. For example, oral administration of ginseng plant extract caused stoppage of cellular destruction of substantia nigra and reduction of functional disorders in Parkinson's rats **[39]**. In the conducted photochemical studies, extract of barberry had an antioxidant activity and effectively reduced peroxidation products of lipids and also inhibited MAO-A; therefore, level of monoamines and dopamine increased in the brain of rats. MAO inhibitors increased value of norepinephrine and dopamine in neural synapses and caused an antidepressant effect **[40, 41]**. Baluch Nejad et al. (2011) reported that intraperitoneal prescription of the extract of Ferulago angulata had a protective effect on 6-OHDA in the experimental model of Parkinson's disease **[42]**.

CONCLUSION

Developing an animal model of Parkinson's disease in rats by prescribing 6-OHDA MFB in the brain led to the induction of motor disorders. Considering results of this research and findings of others, it can be recommended that treatment with different doses of Ferulago angulata (100, 200, and 400 mg/kg) could remove free radicals in special and sensitive areas from the brain and reduce motor disorders resulting from Parkinson's disease.

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