



Investigating effect of chamomile hydroalcoholic extract on movement disorders in the animal model of Parkinson's disease

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ABSTRACT

Background & Aim: Parkinson's disease (PD) is a kind of disorder in the nervous system, which is characterized with multiple movement disorders. Factors such as oxidative stress are the most important causes for the degeneration of dopaminergic neurons in the substantia nigra and occurrence of Parkinson's disease. Thus, medications that have antioxidant functions could be an interesting target for treating the movement disorders caused by Parkinson's disease. Chamomile is the natural source of antioxidants.

Experimental: In this study, 50 adult male Wistar rats were randomly divided into control and Parkinson's groups with 10 rats along with 3 Parkinson's groups, which received chamomile extract by gastric gavage method and doses of 5, 10, and 50 mg/kg once per day for 14 days. Also, 8 µg of 6-hydroxydopamine (6-OHDA) neurotoxin in 2 µl saline containing 1% ascorbic acid was injected into medial forebrain bundle (MFB) of the left hemisphere of the brain of the rats to induce Parkinson's disease. Results were presented as mean ± SD, one-way analysis of variance, and Tukey's post-hoc test.

Results: Following subcutaneous injection 2.5 mg/kg apomorphine 14 days after injury with 6-OHDA in MFB of left brain, animals were rotated 360 degrees to the right by 10 <rpm. Moreover, these rats showed a significant difference in movement tests (balancing, immobility, and step length) compared with the control group. Treatment of the Parkinson's animals using different doses of chamomile extract compared with the untreated group resulted in significant improvement in motor activities and the doses of 10 and 50 mg/kg had maximum therapeutic effects.

Recommended applications/industries: Probably because of its strong antioxidant effect and interference with the activity of movement pathway receptors, chamomile extract can be used to improve and reduce the movement disorders of Parkinson's disease in addition to pharmacotherapy.

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disease which is caused by the gradual loss of dopamine nerve cells in the substantia nigra nucleus of the midbrain (Rosenthal, 1998). The loss of these cells causes a

spectrum of movement disorders such as clinical disorders, resting tremor, muscle rigidity, and slow motion (Philipens *et al.*, 2010). The cause of dopamine cell death in the substantia nigra nucleus has not been fully understood (Shrivastava *et al.*, 2013). Axon of dopaminergic neurons in the pars compacta of the substantia nigra moves along the middle frontal brain

(MFB) and ends in the striatum (Da Cunha *et al.*, 2002). In fact, inputs to the striatum's GABAergic neurons are destroyed in PD (Kleppner and Tobin, 2001). Unilateral injection of 6-OHDA into the MFB in rats is conventionally used to develop an animal model for PD (Sun *et al.*, 2010). The formation of free radicals and oxidative stress may play an important role in the pathogenesis of PD and the central nervous system shows a very high degree of vulnerability to reactive oxygen species (ROS) (Ebadi *et al.*, 1996). Unbalanced and excessive production of ROSs may lead to increased oxidative stress, which can induce many neurological injuries and, eventually, lead to the death of neurons by apoptosis and necrosis (Abou-Sleiman *et al.*, 2006). Healthy cells have a number of mechanisms to resist damage caused by free radicals (Yeh *et al.*, 2009). Antioxidants are considered one of the most important mechanisms for protecting the brain and rapidly prevent the generation of induced ROS (Tanaka *et al.*, 2006). Chamomile with the scientific name of *Matricaria chamomilla* belongs to *Asteraceae* family (Singh *et al.*, 2011). Today, chamomile is used worldwide to treat many diseases, including skin inflammation and tumors (Singh *et al.*, 2011). In the traditional medicine, chamomile is commonly used for relieving pain, acting as antispasmodic and anti-inflammatory agents, treating skin diseases (psoriasis and eczema), curing bronchitis, cold, cough, and fever, healing wounds, and treating gastrointestinal problems (Golparvar *et al.*, 2011; Singh *et al.*, 2011). Chamomile extract is composed of 120 kinds of chemical compounds, which include chamazulenes, flavonoids, and coumarins. Its most active constituent is chamazulene, apigenin, and bisabolol (McKay and Blumberg, 2006). According to the previous scientific research, the compounds contained in chamomile extract have anti-inflammatory, antibacterial, and antioxidant effects (Golparvar *et al.*, 2011). Chamomile is rich in flavonoids, which are effective antioxidants for neutralizing oxygenated radicals (Srivastava *et al.*, 2010). Considering the antioxidant properties of chamomile, in this study, the effect of its different doses on movement disorders was investigated in a PD animal model.

2. Materials and Methods

In this study, 50 Wistar rats with the weight range of 200-250 g (prepared from Ahvaz Jundishapur

University of Medical Sciences) were used. The animals were kept in individual cages in 12 h light and 12 h dark conditions, temperature of $21\pm 2^{\circ}\text{C}$, and access to enough food and water ad libitum. Then, they were randomly divided into the following groups:

- 1- Control group to which no lesion was induced.
- 2- Rats with PD which received 2 μl of 8 μg 6-hydroxydopamine neurotoxin in the MFB.
- 3- Three treated Parkinson's groups: which were similar to the Parkinson's group and received intragastric gavage of chamomile extract 7 days after the recovery (5, 10, and 50 mg/kg) for 14 days. On the 15th day, the behavioral tests were performed (Gholami Z and M, 2014).

2.1. Stereotaxic surgery method

First, the rats were weighed and anesthetized by intraperitoneal (IP) injection of 90 mg/kg of ketamine hydrochloride and 10 mg/kg of xylazine per kg of body weight (both drugs were produced by Alosfan Company in the Netherlands). Afterwards, the animals were placed in the stereotaxic device, on which they were fixed using a mouthpiece and intramedullary rods. The hair at the dorsal skull was also shaved. The head skin was disinfected using a piece of soft cotton and a longitudinal incision was made through the back of the head between the two eyes up to the middle dorsal point of the ears. Connective tissues on the skull surface were removed and the bregma point was made visible. Bregma and lambda points were placed at an equal level, on which the device indicator was set. Then, according to the coordinates extracted from Atlas of Neurosurgical Techniques: Brain, the MFB coordinate (with coordinates of -4.8; a relative to Bregma point ± 1.6 , ML, -8.2; DV) was determined (Sarkaki *et al.*, 2013). In this study, to make a PD animal model, the unilateral injection of 6-OHDA into the MFB was used.

2.2. Preparing 6-hydroxy-dopamine dissolution

6-hydroxy-dopamine (Sigma Company) was prepared with the concentration of 8 μg in 2 ml of normal saline containing 0.01% ascorbic acid (Sarkaki *et al.*, 2013).

2.3. Preparing apomorphine dissolution

(Sigma Corporation of America): This drug was dissolved in the normal saline containing 0.02% ascorbic acid.

2.4. Preparing chamomile extract

Chamomile flowers were collected from around Ize, Khuzestan Province, early in May. The flowering branches were maintained for two weeks in a dark and dry environment in order to dry. After powdering and grinding the plant, 250 g was weighed and reached the volume using 1,000 ml of 70% alcohol. After keeping the plant for 3 days in the laboratory environment and mixing (to isolate all the plant constituents in water and alcohol), they were scattered on the tray to dry. Purity degree of the extract was 25%. After drying, the powdered plant was collected and kept for making different doses of the extract (Seifi Zangeneh *et al.*, 2015).

2.5. Apomorphine-induced rotation test

The rotational behavior of the rats was tested by injecting 2.5 mg/kg of apomorphine hydrochloride. Complete rotations (in a cylindrical chamber) were measured for 60 min in 10 min intervals (Sarkaki *et al.*, 2013).

2.6. Catalepsy test (horizontal bar)

Both hands of the animals were placed on a bar with the height of 9 cm; while their legs were on the bottom of a wooden box, the period of time it takes for the animal to remove the hands was recorded (Dekundy *et al.*, 2006).

2.7. Rotarod test (motor coordination test)

This test is performed to measure motor performance and coordination. For this purpose, the animals were placed on the Rota rod with variable speed. The initial rotation speed of the rod was 5 rpm, which was later gradually increased to 25 rpm within 300 sec (5 min). The main criterion for the balance in all the groups was 25 rpm. The animals were formerly familiarized with this test. Then, each rat was tested 3 times per day with 45 min interval between the sessions. Also, the mean time was calculated (Sarkaki *et al.*, 2012).

2.8. Stride length test

This device consisted of a dark wooden box with a sliding door and dimensions of 10×17×20 cm, to which a narrow tunnel with the dimensions of 4.5×10×45 was connected. The end of the tunnel was open. The boundary between the square part and the tunnel was separated by a guillotine blade. There was a plastic square box with the ink-stained floor at the open end of the tunnel, the floor of which was coated with a white

paper tape with the width of 4.3 cm. 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 (Sarkaki *et al.*, 2012).

3. Results and discussion

3.1. Apomorphine rotation test

Apomorphine was injected subcutaneously into the control group and, 2 weeks after the surgery, into the rats with PD after the MFB lesion. It caused a significant contralateral rotation in the lesioned rats ($P < 0.001$). Intra-gastric administration of chamomile extract to the rats suffering from PD at the doses of 10 and 50 mg/kg significantly reduced the rotations ($P < 0.001$) compared with the Parkinson's group (Figure 1).

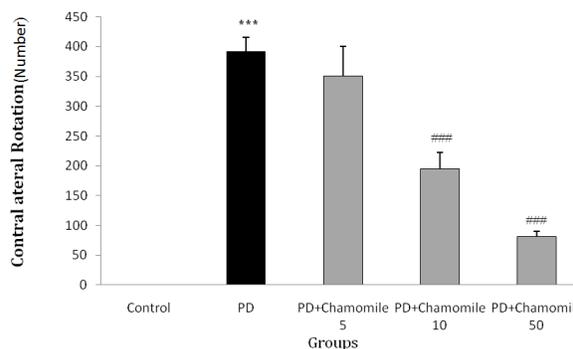


Fig. 1. Effect of 14-day intragastric gavage of 5, 10, and 50 mg/kg of chamomile extract on rotation in the PD animal model. Results were presented as mean \pm SD, one-way analysis of variance, and Tukey's post-hoc test ($n=10$ per group). * and # on the columns show the significant difference from the control and PD groups, respectively. ***= ($P < 0.001$) and ###= ($P < 0.001$)

3.2. Immobility test (catalepsy)

In this test, immobility disorder rate in the PD group was significantly increased compared with the control group ($P < 0.001$) and treatment with chamomile extract (10 and 50 mg/kg) significantly reduced the catalepsy level ($P < 0.01$) and ($P < 0.001$) compared with the Parkinson's group. However, 5 mg/kg of the chamomile

extract had no therapeutic effect on immobility (catalepsy) caused in the PD rats (Figure 2).

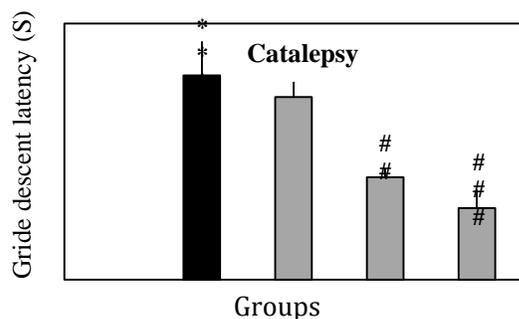


Fig. 2. Effect of 14-day intragastric gavage of 5, 10, and 50 mg/kg of chamomile extract on the immobility (catalepsy) in the PD animal model. Results were presented as mean \pm SD, one-way analysis of variance, and Tukey's post-hoc test (n=10 per group). * and # on the columns show the significant difference from the control and PD groups, respectively.***= (P <0.001) and ###=(P <0.001),## =(P <0.01).

3.3. Motor coordination

The motor coordination level in the PD group showed a significant decrease (P <0.001) compared with the control group and the treatment with chamomile extract (50 mg/kg) could significantly increase the motor coordination compared with the PD group (P <0.001) (Figure 3).

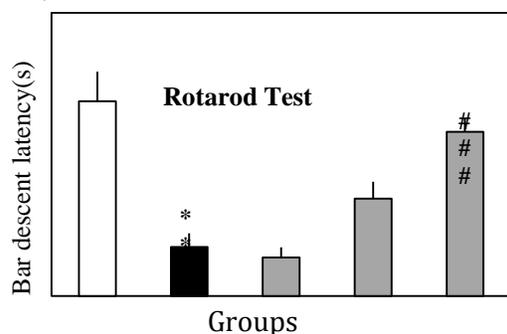


Fig. 3. Effect of 14-day intragastric gavage of 5, 10, and 50 mg/kg of chamomile extract on the motor coordination (rotarod) in the PD animal model. Results were presented as mean \pm SD, one-way analysis of variance, and Tukey's post-hoc test (n=10 per group). * and # on the columns show the significant difference from the control and PD groups, respectively.***= (P <0.001) and ###=(P <0.001).

3.4. Stride length test

In measuring the step length, a significant decrease was observed in the PD group compared with the control one (P <0.001). Treatment with chamomile extract (10 and 50 mg/kg) compared with the PD group could significantly increase the step length (P <0.01 and P <0.001, respectively) (Figure 4).

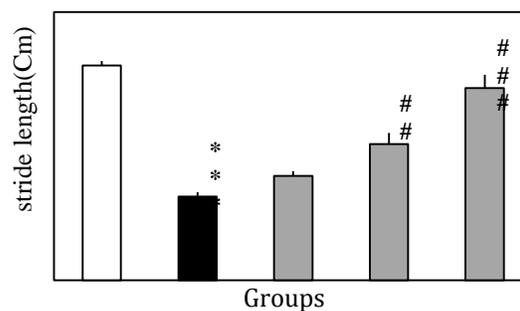


Fig.4. Effect of 14-day intragastric gavage of 5, 10, and 50 mg/kg of chamomile extract on the step length in the PD animal model; Results were presented as mean \pm SEM, one-way analysis of variance, and Tukey's post-hoc test (n=10 per group). *and # on the columns show the significant difference from the control and PD groups, respectively.***= (P <0.001) and ###=(P <0.001),## =(P <0.01).

Our findings suggested that dose-dependent chamomile extract could reduce apomorphine- induced rotation and, thereby, reduce the destructive effects of 6-OHDA toxin, which could be probably due to the protective effect on dopamine neurons. Further, treatment with different doses of chamomile extract significantly improved 6-OHDA-induced movement disorders, including catalepsy, step length, and motor coordination, compared with the untreated group. However, this effect was not the same at all doses, among which 10 and 50 mg/kg had a greater effect on the treatment of movement disorders. Many studies have shown that 6-OHDA can lead to dysfunctions in the performance of those parts of the brain responsible for the motor coordination via generating free radicals. It seems that chamomile extract could reverse the above movement disorders and push them toward normal conditions through the elimination of free radicals. In physiological conditions, 6-OHDA toxin is quickly oxidized and converted into hydrogen peroxide, and into hydroxyl radicals during a reaction, which are the most destructive free radicals for living cells (Orallo *et al.*, 2002; Berghauzen-Maciejewska *et al.*, 2016).

Immobility or akinesia that occurs in Parkinson's disease is often because, following a decrease in dopamine secretion in the basal ganglia, its limbic system secretion may be decreased, which may drastically reduce the neural stimulation for physical activity, as a result of which akinesia occurs (Jankovic, 2008). On the other hand, since motor plans need to be continuously changed between excitation and inhibition modes, lack of the inhibitory effect of dopamine prevents the initiation and progression of successive plans requiring inhibitory steps in addition to stimulatory steps, which is exactly what happens in akinesia (Braak *et al.*, 2006). The imbalance process between the free radical production and antioxidant defense system is toward the antioxidants which cause more damage and plays a central role in the pathogenesis of neurological and neurodegenerative diseases such as Parkinson's, trauma, Alzheimer's, and stroke (Tarawneh and Galvin, 2010). Results of Garcia *et al.*'s (2006) study suggested that short-term consumption of juices rich in phenolic compounds improved the body's antioxidant status (Javier *et al.*, 2006). Chamomile essence and extract are considered the natural sources of antioxidant. The active and main chemical elements in chamomile flowers mainly include flavonoids and their oxides (Zick *et al.*, 2011). Further, in Bob *et al.*'s (2003) study, the consumption of fruit juices containing phenolic compounds was shown to reduce oxidative damage to DNA and improve the immune system function (Bub *et al.*, 2003). Polyphenols have protective effects against neurodegenerative diseases (Ebrahimi and Schluesener, 2012). Flavonoids are easily absorbed through the gastrointestinal tract (Ahmad, 2012). The protective effect of flavonoids depends on their hydrogenation ability or scavaging of free radicals (Rice-Evans *et al.*, 1996). Polyphenols have protective effects on dopaminergic neurons in the substantia nigra (Blanchet *et al.*, 2008), which is associated with the activity inhibition of microglia (Li *et al.*, 2006). It has been well proven that the shortage of GABA neurotransmitters is accompanied by several neural disorders such as Huntington's sphere, Parkinson's, Alzheimer's, and other mental disorders such as anxiety, depression, pain, panic, or mania. In recent years, increasing interest has been seen in the synthesis of new drugs derived from GABA derivatives or the drugs with similar effects, which can be used as strong medications for treating neurological disorders (Gajcy *et al.*, 2010).

Any drug that can increase the production and release GABA binding to its receptors is effective for the treatment of degenerative brain diseases such as seizures, Parkinson's, epilepsy. Polyphenols are mainly the ligands for receptors in the central nervous system (Marder, 2002). Among these receptors, some specific reference has been made to GABA receptors, to which polyphenols act as benzodiazepine-like molecules (Kahnberg *et al.*, 2002). Chamomile's action mechanism is not exactly known. This mechanism may take place by binding to GABA receptors (Sarris *et al.*, 2011). Chamomile is also effective for the activity of monoamine neurotransmitter system (noradrenaline, dopamine, and serotonin) (Amsterdam *et al.*, 2009). Considering the foregoing discussion and the results of this research, it can be concluded that chamomile extract not only removes free radicals by its antioxidant activity and prevents more neuronal injury and its development, but also improves movements in the PD animal model via affecting GABA receptors, which requires more biochemical and molecular research.

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