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Original Article

An Evaluation of the Effect of Naringenin on Perphenazine-Induced Catatonia in Rats

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Abstract

Background and Aim: Parkinson is known as the second most common disease of the nervous system after Alzheimer's disease. Parkinsonism is primarily caused by idiopathic Parkinson's disease. The second most common cause of this disorder is the consumption of drugs. Flavonoid compounds are natural polyphenolic compounds found in many plants. Naringenin (4', 5, 7-trihydroxyflavanone) is a flavonoid found in fruits and vegetables with various protective effects on the nervous system.

Materials and Methods: Rats were divided into five groups of eight rats. The intraperitoneal administration of naringenin was conducted at doses of 100, 200, and 400 mg/kg. The animal received perphenazine thirty minutes following the administration of different doses of naringenin, normal saline and bromocriptine. The rats were analyzed using Morpurgo test for scoring their muscle stiffness 20, 40, 60, 90, 120, 180, and 240 minutes after perphenazine injection. Kruskal-Wallis test was performed to check the differences between the groups (multiple comparisons). We used Mann-Whitney U test in order to compare the distinction between two independent groups.

Results: The reduction of the muscle stiffness of the naringenin-intake group was not significant with the dose of 100 mg/kg compared with the positive control group. ($P < 0.05$). The reductions in stiffness in naringenin intake with the doses of 200 and 400 mg/kg were not remarkable in comparison with the positive control group.

Conclusion: According to the results, naringenin does not have any significant effect on catatonia induced by perphenazine in the dose of 100 mg/kg but its infusion in the doses of 200 and 400 mg/kg showed significant reduction in muscle stiffness.

Keywords: Perphenazine, Catatonia, Naringenin, Parkinson, Drug-induced Parkinsonism

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Introduction

As the second most prevalent progressive neurodegenerative disorder after Alzheimer's disease, Parkinson's disease (PD) is characterized by severe motor disorders such as resting vibration, rigidity or

increased resistance to passive movements, conditional instability and slowness of voluntary movements (1). Parkinsonism is primarily caused by idiopathic Parkinson's disease. The second most common cause of this disorder is the consumption of drugs. It refers to the presence of Parkinsonism without a history of Parkinsonism prior to the use of the offending drug and the beginning of Parkinsonian symptoms during the consumption of the drug (2). Drug induced Parkinsonism (DIP) could occur as a complication of several medications such as antipsychotic agents, antiemetics, cholinomimetics, antidepressants, anti-vertigo medications, calcium channel antagonists, antiarrhythmics, and antiepileptic drugs. The use of these drugs might result in the generation of a Parkinsonian syndrome, worsened PD, or disclose PD ahead of time (3). A differential diagnosis exists between DIP and PD, and these include symmetry of symptoms, the relative absence of rest tremor, coexistence of oromandibular dyskinesias, and a less pronounced if any, response to the levodopa(4). Catatonia is a rare phenomenon with the PD, which is described as a psychomotor disturbance characterized by stupor, catalepsy, waxy flexibility, mutism, negativism, agitation, and stereotypy (5). Morpurgo test is a scoring scale that evaluated the muscle stiffness during catatonia (6).

The progressive loss of dopaminergic neurons in the basal ganglia is the most significant pathologic finding in the brain of patients with Parkinson's disease. The destruction of these neurons leads to a decrease in the dopamine neurotransmitter in this area (1). The exact molecular mechanism for the destruction of dopaminergic neurons and the incidence of complications of Parkinson's disease is unknown, although studies have shown that oxidative stress and increased lipid peroxidation, decreased glutathione levels, inflammation, DNA degradation, iron accumulation and mitochondrial dysfunction are among the most important causes of the degeneration of dopaminergic neurons (7, 8). Oxidative stress results in the destruction of dopaminergic neurons. Moreover, this phenomenon interferes with the process of oxidative phosphorylation, and reduces energy production, leading to cell death (4). Free radicals resulting from the metabolism of dopamine and melanin could be the endogenous sources of oxidative stress. Active oxygen radicals are continuously generated in the midbrain dopaminergic neurons due to the metabolism of dopamine by the enzyme monoamine oxidase B or the dopamine autoxidation (10). Protection against oxidative damage induced by free radicals in the central nervous system, including the dopaminergic neurons, is done by low molecular weight antioxidants such as vitamins E and C and large protein molecules such as superoxide dismutase, glutathione peroxidase, and reduced glutathione (11).

Moreover, some drugs could block dopamine D2 receptors or reduce dopamine release that may result in Parkinsonism (12). The occurrence of DIP with neuroleptics (also known as antipsychotics) was first described by Thiebaux *et a1*. (1954)(13). Soon, it was discovered that all typical antipsychotics had the potency to cause the extrapyramidal syndrome, including Parkinsonism, acute dystonia, akathisia, and tardive dyskinesia (14). The relative mechanism indicates that neuroleptic-induced Parkinsonism is primarily caused by the functional blockage of extrapyramidal dopaminergic receptors. Hence, this dopamine hypothesis indicates that neuroleptic-induced Parkinsonism could be caused by the blockade of D2 dopamine receptors (15). There is a central dopaminergic pathway containing the mesolimbic, mesocortical, tuberoinfundibular, and nigrostriatal pathways. The therapeutic effects of antipsychotic drugs is due to their blocking of dopamine receptors in the limbic system. The D2 receptor blockage leads to GABA and encephalin-containing striatal neurons disinhibition at the origin of indirect pathway , followed by disinhibition of the subthalamic nucleus through using neuroleptics. This mechanism results in the increased GABAergic inhibition of the thalamocortical projection via the facilitation of the inhibitory projection from the globus pallidus/substantia nigra pars reticulate (12).

One of these typical neuroleptic drugs is phenothiazines .Tremor is not common in drug-induced Parkinson's disease, but movement slowness is the most significant sign. Symptoms of drug-induced Parkinsonism usually develop within three months after the onset of the consumption of a drug depending on the dose and age of the patient, and

disappear within weeks to months after discontinuation of the drug. Depending on the severity of the symptoms and the necessity of taking the medication, discontinuing the drug, replacing the drug with drugs that lessen the blockage of dopaminergic receptors, and taking anticholinergic drugs such as trihexyphenidyl and biperiden could be effective in the prevention of the emergence of side effects. The use of L-DOPA with the continued use of dopaminergic receptor antagonist drugs is not beneficial. However, L-DOPA could be effective provided that these drug are discontinued. It should be noted that the use of L-DOPA to inhibit Parkinsonism caused by neuroleptics will exacerbate the patient's mental illness (16).

The basic treatment of Parkinson's disease is based on the replacement of dopamine deficiency. Since dopamine does not cross through the blood-brain barrier, L-DOPA, its metabolic precursor, should be used. It should be noted that in relation to this disease, other drugs such as dopamine agonists, dopamine-releasing compounds, catechol o methyltransferase, monoamine oxidase, anticholinergics, etc. are also used. The protracted consumption of these drugs leads to the emergence of side effects for patients, which is a major problem (1) Hence, the need for compounds that can reduce the symptoms of Parkinson's motor disorders and decrease the need for medication is undeniable. Natural chemical compounds with high antioxidant activity are found in high concentrations in certain plants. They might account for the preventive effects of plants in neurodegenerative diseases. Studies have indicated that at the molecular level, plant phenols such as flavonoids and flavonoligans along with phenolic acids can act as antioxidants (17, 18). In recent years, it has been shown that the use of medicinal plants plays a pivotal role in human health (19). Flavonoid compounds naturally belong to polyphenolic compounds found in many plants, and many of these plants are consumed by humans. It has been shown that flavonoids have a wide range of biological impacts, including various neuroprotective activities (20). Naringenin (4',5,7-trihydroxyflavone) flavonoids that are found in fruits and vegetables such as grapefruit, tomatoes and oranges, have various biological effects, such as neuroprotective effects (21). They are inhibitors of the monoamine oxidase enzyme (22), have anti-inflammatory and antioxidant activities (23), and improve memory activity (24). Considering the studies conducted on naringenin and the reports on the various protective effects of naringenin in neural systems, we decided to investigate the possible effects of naringenin on the reduction and improvement of muscle tone symptoms.

There are several empirical models that cause the destruction of dopaminergic neurons in the substantia nigra of the striatum, one of which is the perphenazine model. The intraperitoneal injection of perphenazine (5 mg/kg) in this model induces muscle tightness in mice. The severity of this kind of muscle tightness could be evaluated using the Murpurgo test (25, 26).

Extrapyramidal adverse effects of typical antipsychotics could produce a pseudoparkinsonism condition. The role of flavonoids in reversing catatonia through DIP has been evaluated previously. As far as we know, the effect of naringenin on perphenazine-induced catatonia in rats has not been examined yet. In this study, we evaluated the impact of naringenin on muscle stiffness induced by perphenazine.

Materials and Methods

Animals

In this study, young male rats weighing 200-220 g were used. The rats were kept in the animal room at 23 ± 23 ° C, 50% humidity and 12 hours of darkness and 12 hours of light. Rats consumed compact foods for animal and purified water. Adult male Wistar rats were divided into five groups, each group containing eight rats. This research was conducted under ethical interventions. Moreover, we meticulously tried to minimize animal suffering. This study was approved by the local Ethics Committee of Mazandaran University of Medical Sciences. Ethical Inspection No. IR.MAZUMS.REC.1397.282.

Drug Preparation and Intervention

Naringenin powder (purity: ≥90% from citrus fruit), was purchased from Sigma-Aldrich Co., Germany, and perphenazine was purchased from Iran Daro Pakhsh Company. All the chemicals were dissolved in 0.9% saline except naringenin, which was dissolved in 0.1% Carboxy Methyl Cellulose (CMC). Drug solutions were prepared freshly, and the room

temperature was controlled to prevent drug metabolization.

The positive control group was injected 5 ml/kg of normal saline, and half an hour later, 5 mg/kg of perphenazine was administered via intraperitoneal (IP) injection. The standard group received bromocriptine at the dose of 30 mg/kg via IP injection, and half an hour later, the IP injection of perphenazine at the dose of 5 mg/kg was carried out. In treatment groups, the rats first received the IP administration of naringenin at the doses of 100, 200 and 400 mg/kg, and half an hour later they received the IP injection of perphenazine with the dose of 5 mg/kg. Finally, the range of animals muscle stiffness from each group was measured by the Murpurgo test 20, 40, 60, 90, 120, 180, and 240 minutes after the injection of perphenazine (16). To reduce errors, injections were administered intraperitoneal by the presenter, and the results were evaluated and recorded by the student to use blind materials.

Behavioral Test

The assessment of muscle stiffness during catatonia as a clear sign of DIP was performed using the Morpurgo method (6) as follows:

1- The animal was placed on the table. If the animal was standing and walking, it would not receive a score (zero scores) but if the animal was placed on the table and underwent the stiffness of the muscles, it remained or began to move effortlessly by moving the arms and legs, the animal would be given 0.5 points (Figure 1a).

2- The animal's right hand should be placed on a wooden platform at a height of 3 cm. If the animal did not leave his hand for at least 10 seconds, he would receive 0.5 points. This test was also performed on the left hand if the hand was not removed from the platform for at least 10 seconds, 0.5 points would be given to the animal. This stage had a total of 1 score (Figure 1b).

3- The right hand of the animal should be placed on a wooden platform with 9 cm high. If the animal did not leave its own hand from the platform for at least 10 seconds, it would have scored 1. The same experiment was repeated for the left hand, and if the left hand was not removed from the platform for at least 10 seconds, it would have scored 1 and received a total score of 2 points. The Parkinsonian animal should have a total score of 3.5 (complete Parkinson's), or in relation to the severity of the disease caused by a total of 3.5 score points Healthy animals were scored zero (Figure 1c).

Results and Discussion

A- Effect of Bromocriptine on Muscle Strength of Perphenazine in Rats

Kruskal-Wallis test was performed to check the differences between the groups (multiple comparisons). Mann-Whitney U test was used to compare the differences between two independent groups.

To display information in graphs, for each group, the average rankings were compared to the corresponding times. The results of the evaluation of muscle stiffness in healthy animals showed that all the animals were scored zero in all stages of evaluation and their muscular stiffness was normal. Moreover, the results of the evaluation of muscle stiffness in the negative control group (normal saline recipient and half an hour later, perphenazine) showed that the total score obtained in these animals was 3.5 after 240 minutes from the injection of perphenazine, that would mean the complete parkinsonization of this group of animals due to the administration of this drug (Figure 2a). The results of Murpurgo test showed that receiving bromocriptine after perphenazine (the positive control group) could significantly reduce the muscle stiffness scores (a significant decrease in muscle stiffness) compared to the negative control group (normal saline recipient and the next half hour was perphenazine ($p<0.05$) at all times (Figure 2a) that represents a good therapeutic effect of bromocriptine on perphenazine muscle stiffness.

B- A Comparison of the Effect of Naringenin at the Dose of 100 mg/kg with the Negative Control Group (normal saline) and the Positive Control Group (bromocriptine) on Perphenazine Muscle Stiffness in Rats.

The results of the present study indicated that receiving naringenin at the dose of 100 mg/kg could reduce muscle tone due to perphenazine injection. This decrease was statistically significant in comparison to the negative control group at the 40^{th}, 90^{th} and 120^{th} minutes ($p<0.05$). However, there was a remarkable difference between the positive control

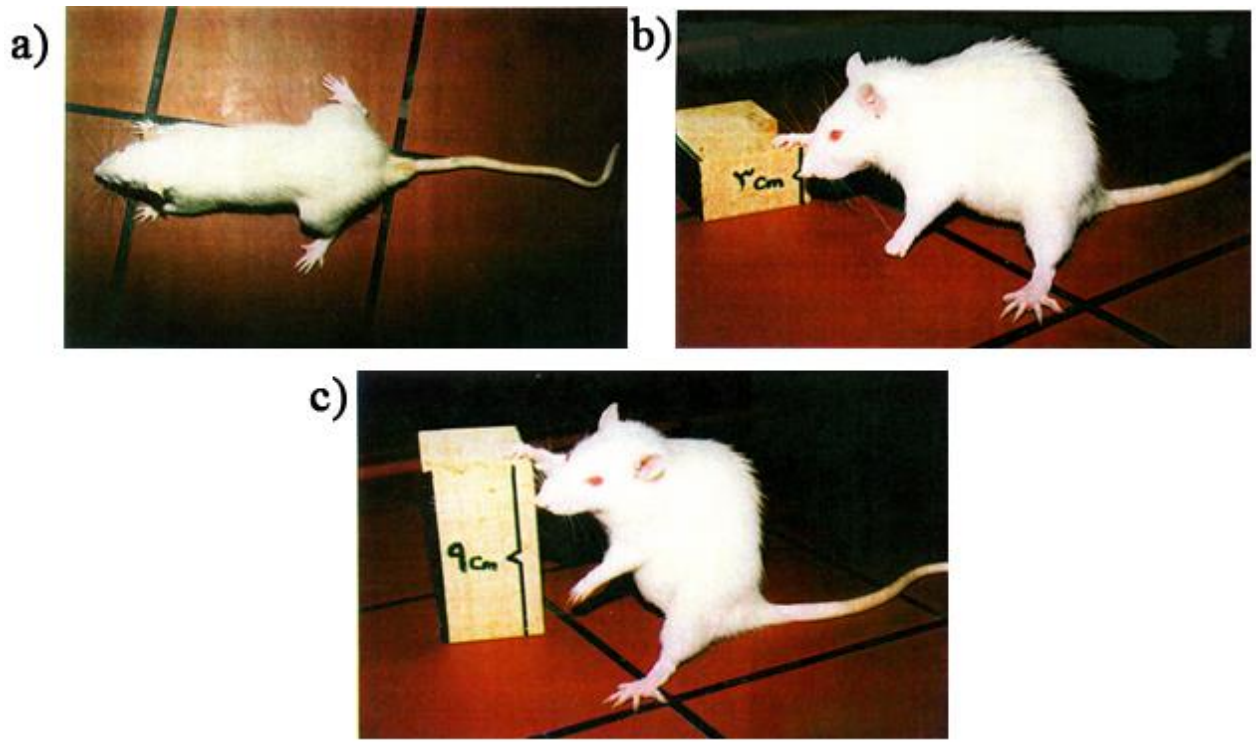

Figure 1. (a) The rat stops without moving on the table and only moves with the touch of a hand.; (b) Measurement of muscle stiffness using a wooden platform up to 3 cm; (c) Measurement of muscle stiffness using a wooden platform up to 9 cm.

group ($p<0.05$). This means that it has not had a desirable effect compared to bromocriptine.

Figure 2b: A Comparison of the Effect of of Naringenin at the Dose of 100 mg/kg with the Negative and Positive Control Groups on Perphenazine Muscle Stiffness in Rats.

C- A Comparison of the Effect of 200mg / kg Naringenin with the Negative Control Group (normal saline) and the Positive Control Group (bromocriptine) on Perphenazine Muscle Stiffness in Rats

The results of the study showed that receiving naringenin at the dose of 200 mg/kg could significantly reduce the muscle stiffness induced by perphenazine. This decrease was statistically significant in comparison to the negative control group at all times ($p<0.05$). However, there was a significant difference between the positive control groups ($p<0.05$). This means that compared to normal saline, it has a good effect. Nonetheless, it has not been able to be more efficient than bromocriptine.

Figure 2c: A Comparison of the Effect of 200 mg/kg Naringenin with the Negative and Positive Control Groups.

D- A Comparison of the Effect of Naringenin at the Dose of 400 mg/kg with the Negative Control Group (normal saline) and the Positive Control Group (bromocriptine) on Perphenazine-Induced Muscle Stiffness in Rats

The results of the study showed that taking naringenin at the doses of 400 and 200 mg / kg could significantly reduce the muscle stiffness of perphenazine. This decrease was statistically significant in comparison with the negative control group at all times ($p<0.05$). However, there was a significant difference between the positive control group ($p<0.05$). This means that compared to normal saline, it has a beneficial. Nevertheless, it has not been able to be more efficient than bromocriptine.

Figure 2d: A Comparison of the Effect of Naringenin at the Dose of 400 mg/kg with the Negative and Positive Control Groups on Perphenazine Muscle Stiffness in Rats.

E- A Comparison of the Effect of Different Doses of Naringenin on Muscle Stiffness Induced by

Perphenazine in Rats

The results revealed that 100 mg/kg dose did not sufficiently reduce muscle tone compared with 200 and 400 doses at all times ($p<0.05$)

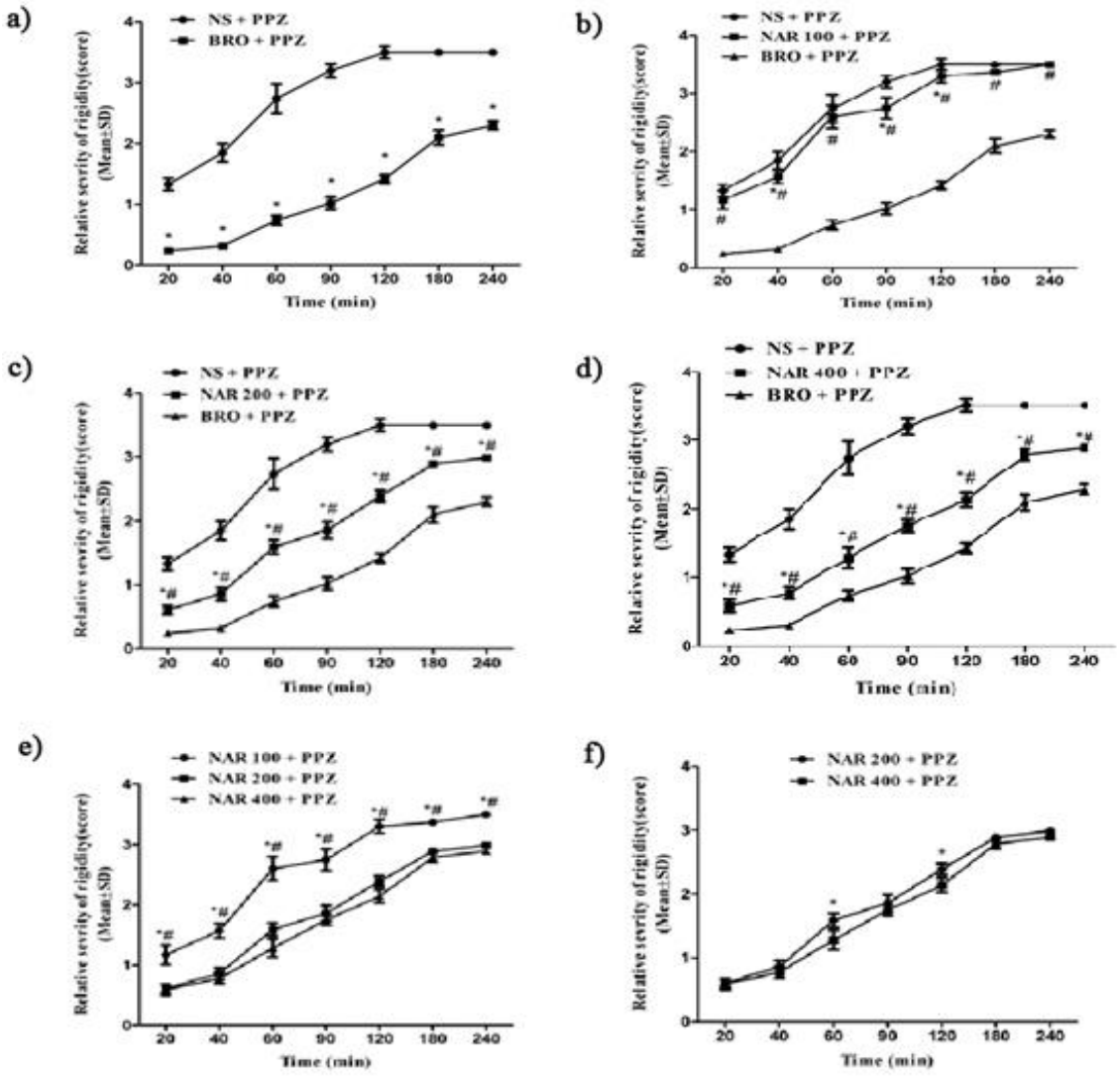

Figure 2. (a) Effects of normal saline (NS) and bromocriptine (BRO) on perphenazine (PPZ) induced muscle stiffness in rats; ***** Significant difference with the negative control group at the relevant time ($p<0.05$).
(b) Comparison of the effect of 100 mg/kg naringenin (NAR) with negative and positive control groups on perphenazine induced muscle stiffness in rats; * Significant difference with the negative control group (normal saline) at the relevant time ($p<0.05$)
Significant difference with the positive control group (bromocriptine) at the relevant time ($p<0.05$).
(c) Comparison of the effect of 200 mg/kg naringenin with negative and positive control groups on perphenazine induced muscle stiffness in rats; ***** Significant difference with the negative control group (normal saline) at the relevant time ($p<0.05$)
Significant difference with the positive control group (bromocriptine) at the relevant time ($p<0.05$).
(d) Comparison of the effect of 400 mg/kg naringenin with negative and positive control groups on perphenazine induced muscle stiffness in rats; ***** Significant difference with the negative control group (normal saline) at the relevant time ($p<0.05$)
Significant difference with the positive control group (bromocriptine) at the relevant time ($p<0.05$)
(e) Comparison of the effect of different doses of naringenin on perphenazine induced muscle stiffness in rats; (f) Comparison of 400 and 200 mg/kg naringenin doses on perphenazine induced muscle stiffness in rats;
* Significant difference in dose of 200 mg/kg at the relevant time ($p<0.05$)
# Significant difference in dose of 400 mg/kg dose at the relevant time ($p<0.05$).

Figure 2e shows the effect of the doses of 100, 200 and 400 mg/kg of naringenin on perphenazine-induced muscle stiffness in rats.

F- A Comparison of the Effect of 400 mg/kg and 200 mg/kg Doses of Naringenin on the Muscle Strength of Perphenazine in Rats

The results of the present study showed that the effects of the 400 mg/kg and 200 mg/kg doses of naringenin on muscle stiffness caused by perphenazine were approximately the same. Moreover, there was a significant difference between them at the 60^{th} and 120^{th} minutes (Figure 2f).

Effective treatment with basic Parkinson drugs often improves the patients' motor function, but it could be the cause of other problems in patients. L-dopa, which is the basic drug for the treatment of PD symptoms, itself causes dyskinesia, motor dysfunctions and other symptoms. Furthermore, its efficacy decreases in the long period (27).

In this study, the effect of naringenin on the prevention of catatonia caused by the use of perphenazine in rats was demonstrated. Certain studies have indicated that flavonoids are capable of protecting mesencephalic dopamine (DA) neurons from injury and reduce apoptosis produced by oxidative stressors. Furthermore, as a dietary flavonoid, naringenin was found to be a neuroprotective agent in Parkinson disease (28).

Flavonoids are popular for promoting neuronal survival and synaptic plasticity. The interaction of flavonoids with critical protein and lipid kinase signaling cascades in the brain accounts for their protecting mechanism. Furthermore, their positive effects on the vascular system could change the cerebrovascular blood flow, possibly leading to angiogenesis, neurogenesis and alterations in neuronal morphology. By this mechanism, the neurodegeneration and age-dependent loses in cognitive performance could be slower through the use of flavonoid-rich foods throughout life (19, 29, 30)

Several studies have been carried out on the effects of natural antioxidant compounds on various types of Parkinson's and catatonic models in rats. One of these studies is the research on the protective effect of the hydroalcoholic extract of red lentils on perphenazine-induced catatonia in rats. In this study, Houshmand *et al.* state that the hydroalcoholic extract of red lentils could have a protective effect on perphenazine-induced catatonia in rats(25). Red lentils contain various flavonoids and polyphenols (31).

Tardive dyskinesia (TD) is a neuroleptic extrapyramidal complication. The pathophysiology of this adverse effect remains unclear, but some studies stated that it could be due to free radicals (32). Bishnoi *et al*. conducted a research in which they confirmed the involvement of oxidative stress in the development of haloperidol-induced orofacial TD (33). Several studies have revealed that flavonoid quercetin (3,5,7,3′,4′-pentahydroxyflavone) is able to reverse the side effects of haloperidol-induced extrapyramidal catalepsy. Catalepsy could be defined as a physical condition characterized by the suspension of sensation, muscular rigidity, stability of posture, and often loss of contact with surroundings(34). Apart from this effect, quercetin could decrease lipid peroxidation in human plasma caused by a first-generation antipsychotics, haloperidol in ex vivo experiments (35).

In a similar study by Sonia Angeline *et al*. on rotenone-induced PD, a model that induces neuronal damage in substantia nigra and striatum and motor skill impairment, the neuroprotective of naringenin was evaluated. They reported via using naringenin (10mg/kg), that the level of Tyrosine hydroxylase (TH), and DJ1 (a neuroprotective protein which has a role in the antioxidative stress reaction and the mutations of DJ1 lead to cell death (36)), which was down-regulated in the rotenone treated brain regions, was reversed following the treatment with naringenin. Moreover, TH positive neurons were observed in striatal nigra regions treated with naringenin (10mg/kg). Another mechanism involved in PD is misfolded or aggregated proteins and inclusion bodies that disrupt the protective function of several influential proteins. Parkin (Skeletal muscle is a major site of normal parkin expression (37)) and DJ1 are two important proteins that become down-regulated during PD. They are related to muscle tissues increasing susceptibility to mitochondrial toxins, which results in the dysfunction of muscle cells and eventually leads to myodegeneration. However, it has been stated that naringenin (10mg/kg) could reverse the level of these important proteins during DIP. Increasing levels of these two proteins protect muscles from mitochondrial

damage. Also, it has been reported that flavonoids have the potency to inhibit caspase activation and reduce cell death in brain and muscle regions with their anti-apoptotic property (38).

Zhang *et al*. conducted a study on the use of quercetin as a flavonoid in which they demonstrated that quercetin could prevent 6-OHDA-stimulated dopaminergic neuron damage and could have a neuroprotective effect (39).

The neuroprotective effects of chrysin (5, 7-dihydroxyflavone) as a flavonoid was evaluated in a study. It was indicated in this research that it could have anti-oxidative effects on dopaminergic neurons primarily by increasing the expression of Nuclear Factor Erythroid 2 -related factor 2 (NRF2) which decreases the levels of intracellular nitric oxide (NO). Also, by activating Myocyte Enhancer Factor 2D (MEF2D), the motor activity is improved. Chrysin anti-apoptotic activities suppress the MPP-induced upregulation of c-caspase and Bax as well as the downregulation of anti-apoptotic protein Bcl2. Chrysin could increase the level of dopamine in the striatum by the inhibition of mono amine-oxidase B (MAO-B) (40).

Naringenin is one of the most significant natural sources and flavonoid families for the management of Parkinson's disease. Its potency has been reported in certain studies. It has been reported that as an antioxidant, naringenin stabilizes and prevents cell membrane damage, and by this protective effect on cell membrane attenuates lipid peroxidation (41). The antioxidant potency of naringenin is due to its ability to increase Glutathione (GSH) and Superoxide dismutase (SOD) by reducing free radicals. Moreover, it might improve the integrity of plasma and mitochondrial inner membranes and prevent their enzymes from leakage via this mechanism (42, 43).

Maximal Electroshock (MES) model is a seizure-inducing method in mice which is accompanied by severing Hind-Limb Extension. Khodayar *et al*. showed that naringenin (200mg/kg) could remarkably decrease the duration of hind limb tonic extension in comparison with the untreated group(44). This impact on seizure comes from the anticonvulsant effects of flavonoids by binding to the benzodiazepine binding site on GABA receptors in the central nervous system (45). Also, oxidative damage is one of the leading causes of seizures. Flavonoids such as naringenin are capable of increasing the antioxidant activity in the body and intensifying the activity of antioxidant enzymes that decrease the production of oxygen free radicals and tissue damage (21).

El Madani *et al*. and Li *et al*. reported that naringenin could reduce the learning and memory deficits, improve locomotor activity as well as mitochondrial complex I-IV enzymes activities, and promote neuronal differentiation and survival (41). As an important member of flavonoids, naringenin has a significant role in the protection against Parkinson's disease and it can be a good alternative for L- dopa because of better efficacy and lower incidence of side effects.

Conclusion

The administration of a 100 mg/kg dose of naringenin indicated that it could have a slight effect on the prevention of catatonia. Increasing the dose of naringenin to 200 mg/kg resulted in an increase in the effect of naringenin on the prevention of catatonia. In this stage, the catatonisity of the use of perphenazine in the test group was less severe than the negative control group. Though the effects of naringenin at 200 and 400 mg/kg doses are nearly identical, the best dose is 200 mg/kg. Accordingly, it could be stated that naringenin is effective in preventing pseudoparkinsonism disease caused by the use of perphenazine in rats.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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