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# EFFECT OF MORIN ON PERPHENAZINE INDUCED PSEUDO-PARKINSONISM IN RAT

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## ABSTRACT
Parkinson's disease (PD) is a common neurodegenerative disease characterized by progressive loss of midbrain dopaminergic neurons. Morin has been shown to exert neuroprotective and anti-oxidant effects in different models of neurodegenerative diseases. In this pilot study 40 male rats (weight range: 160-200 g) were randomly divided into 5 equal groups (n= 8). In group 1 (300 mg/kg morin), group 2 (400 mg/kg morin), group 3 (500 mg/kg morin), group 4 (10 mg/kg L-Dopa) and group 5 (5 ml/kg normal-saline) intraperitoneal injection was performed. In all groups, after 30 minutes of the first injection, 5 mg/kg perphenazine was intraperitoneally injected. The muscle stiffness, using Morpurgo method, rate of catalepsy using BAR test, and the amount of Malondialdehyde (MDA) and Glutathione (GSH) levels were evaluated at different time points after injection in all groups. According to Morpurgo test results**,** mean rate of muscle stiffness was significantly lower in the morin 400 and 500 mg/kg groups compared to the 300 mg/kg morin group at all time points. Muscle stiffness values in the 400 mg/kg morin group were significantly greater than the 500 mg/kg group only at 60 and 90 minutes after perphenazine injection, whereas for the other periods the two groups showed no significant differences. According to BAR test results, the mean length of muscle stiffness period was not significantly different between the 400 and 500 mg/kg morin and L-Dopa groups, whereas this period in the 300 mg/kg morin group was significantly lower than these three groups. The mean of MDA in the L-Dopa group was significantly lower than the other groups, followed by the morin 500 and 400 mg/kg groups, respectively. The L-Dopa group showed the greatest mean GSH value that was statistically significant compared with other groups. The second and third rank of GSH values was respectively for the morin 500 and 400 mg/kg groups. The results of study reported the effectiveness of morin on improving muscle stiffness and muscle weakness, which it was dose dependent and were more effective at higher doses.

**KEYWORDS:** Parkinson, Morin, Muscle Stiffness, Malondialdehyde, Glutathione.

## INTRODUCTION
Parkinson's disease (PD) is a common neurodegenerative disease, characterized by the main clinical features include tremor, muscle stiffness, slowness and instability.[1-3] Although the exact etiology of PD is not known, its pathology is characterized by gradual and selective loss of midbrain dopaminergic neurons. The origin or root cause of this nerve degradation is unknown and may result from such damages as oxidative stress, inflammation, accumulation of damaged proteins, or mitochondrion disturbance.[4,5]

Oxidative stress, a condition that occurs due to imbalance in oxidant and antioxidant status, has been known to play a vital role in the pathophysiology of different neurodegenerative diseases including PD. The excess production of reactive oxygen species (ROS) results in progressive loss of membrane lipid domains and lipid peroxidation of the cell in the substantia nigra and consequently the cell death.[6] Previous studies have shown that the lack of antioxidants and, consequently, disorders of the antioxidant system are highly contributing to the disease.[7] Antioxidant compounds have a high biological activity spectrum.[8-11] Therefore, imbalance in dopamine metabolism due to oxidative stress has been recognized as a contributor to PD. Antioxidants protect the human body against free radicals[12-15] and delay the progression of many chronic diseases by improving lipid peroxidation.[16-21]

Natural antioxidants are found in all herbs, microorganisms, fungi and even animal tissue.[22-25] Phenols are secondary plant metabolites that naturally exist in all herbal substances, including plant foods with

specified identifiers.[26-29] Most natural antioxidants are phenol compounds and flavonoids are the most important group of antioxidants.[30-34]

Morin is a natural polyphenolic compound that has been shown to exert antioxidant, anti-inflammatory, anti-diabetes, and anti-cancer properties (in vivo and in vitro).[35-41] Moreover, different studies have reported that morin could exert neuroprotective effects in different models of neurodegenerative diseases. The neuroprotective mechanism of morin may be attributed to its antioxidant activity. Due to its antioxidant and anti-apoptosis properties, morin causes neuroprotection effect in brain against ischemic injury.[42]

The current treatments of PD only help reduce the disease's symptoms but not stop the disease progression. Therefore, developing new medications that could effectively prevent or impede the disease progression is necessary. The present study aims to investigate the effects of morin on pseudo-parkinsonism induced by perphenazine in rats.

## MATERIALS AND METHODS

### Materials

Morin was purchased from Sigma Chemical Co. (St.Louis, MO, USA). L-Dopa was purchased from Sigma Chemical Co. (St.Louis, MO, USA). Malondialdehyde (MDA) Detection Kit and GSH Colorimetric Detection Kit were obtained from ZellBio (ZellBio GmbH, Germany). All other chemicals and reagents used in the study were analytical grade.

### Animals

In this study, 40 male Wistar rats weighing 160-200 g obtained from the Laboratory of Animal Breeding Center of Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran were used. After weighing, the rats were randomly divided into 5 groups (each group of 8 Rat) and were kept at the animal room of the Pharmaceutical Faculty, AJUMS at 23 ± 2 °C, 50% humidity, and a light: dark cycle of 12:12 hours. The Rat used compressed animal food and urban refined water. The Rat arrived at the lab one hour before the experiment to be acclimated with the laboratory environment.

### Experimental Design

In this pilot study animals were randomly divided into five groups (n=8) and were pre-treated with a single dose of morin (300, 400 and 500 mg/kg), most effective dose of L-Dopa (10 mg/ kg) and normal saline (5ml/kg) via intrapritoneal. Morin was solved by physioligal saline before injection. After 30 minutes, all animals received an IP injection of 5mg/kg perphenazine hydrochloride. After the injection of morin and perphenazine into the experimental groups, behavioral and biochemical parameters were assessed and recorded. In this study, muscle stiffness was measured by Morpurgo method, the rate of catalepsy was measured using Bar Test, and Malondialdehyde (MDA) and Glutathione (GSH) was measured and assessed.

### Morpurgo test

Relative muscular rigidity was determined for given minutes after injection as follows; 20, 40, 60, 90, 120, 180 and 240. The method of Morpurgo was used to determine muscular rigidity. We closely observed the development of catatonia and the following scores were achieved: Stage 1, free movement of rat on the table, score allocated = 0; Stage 2, rat moves only by touch or push, score allocated = 0.5; Stage 3, the rat's front paws are alternately placed on a high block of 3cm height. Failure to correct the posture in 10 seconds, score allocated = 0.5 for each paw with a total Score of 1 for this stage. Stage 4, the rat front paws are alternately placed on a 9cm high block. Failure to correct the posture in 10 seconds, score allocated = 1 for each paw with total score of 2 for this stage. Therefore, the maximum possible score for a single rat, would be 3.5 displaying total catatonia. Lower score suggests a lower degree of catatonia.[43]

### Bar test

To test catalepsy standard bar test was used. In this method, two front legs of the animal were placed on a wooden and horizontal rod with a diameter of 1.25 cm and a height of 10 cm from the floor, and the length of time that lasts until the animal took one or two hands from the rod was recorded. The study period was 180 seconds. If the animal refuses to get the rod up to three times, 1 second would be recorded for it.[44]

### MDA and GSH

After performing behavioral tests, the animals were anesthetized with an intraperitoneal injection of ketamine 10% (50 mg/kg) and Xylazine 2% (10 mg/kg) and then euthanized. The brain tissue of the animal was then removed; the transparent liquid was removed and stored at 80 °C. According to the German specific Zellbio kit, optical absorption at 535 nm was read and, by obtaining the standard curve line equation, its MDA was measured. According to the German Zellbio manufacturer's specific kit instruction, optical absorption was read at a wavelength of 412 nm and, by obtaining the standard curve line equation, its GSH was measured.

### Statistical Analysis

All analyses were performed using SPSS statistical software version 22.

## RESULTS

The results showed that the mean muscle stiffness values in the 500 and 400 mg/kg morin groups at all measurement times were significantly lower ($P < 0.05$) than that the 300 mg/kg morin group. On the other hand, muscle stiffness values in the 400 mg/kg morin group were significantly greater than the 500 mg/kg group only at 60 and 90 minutes after perphenazine injection (p

<0.05), whereas for the other periods the two groups showed no significant differences.

Mean length of muscle stiffness at all times and in all doses of morin groups was significantly (P <0.05) less than the control group (physiological serum) (Fig.1).

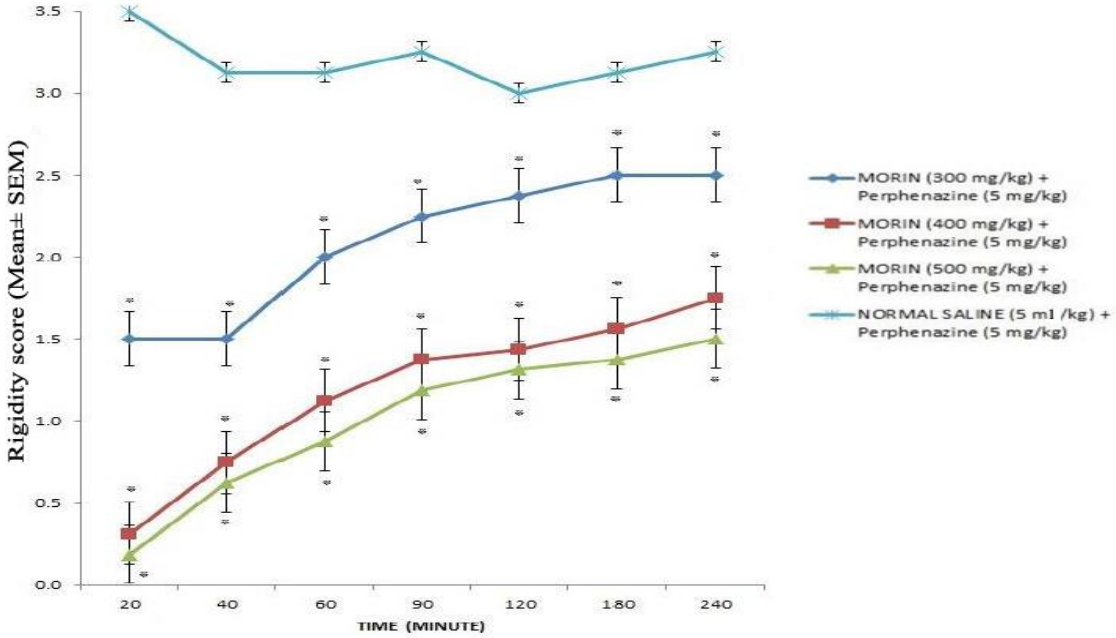


**Figure 1: Comparison of the mean rate of muscle stiffness in the groups receiving doses of 300, 400, and 500 mg/kg morin with the negative control (physiological serum) groups; *shows the significant difference with the negative control group (physiological serum) (P <0.05); Data are presented as mean ± standard error (SEM). (n = 8).**

Mean muscle stiffness was significantly higher in the morin group of 300 mg/kg (P <0.05) than that in the positive control group (L-Dopa). Mean muscle stiffness in the 400 and 500 mg/kg morin groups only at 60 minutes after the injection of perphenazine was significantly higher (P <0.05) than that in the L-Dopa group, and at other times of measurement there was no significant difference between mean muscle stiffness in the two groups (Fig.2).

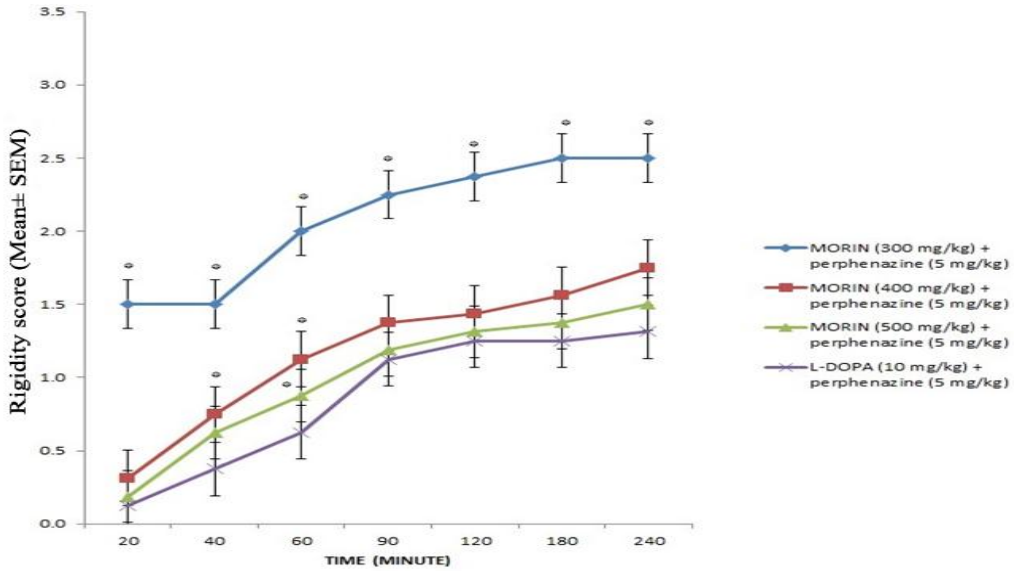


**Figure 2: Comparison of the mean rate of muscle stiffness in the groups receiving doses of 300, 400, and 500 mg/kg morin with the positive control (L-dopa) groups; *shows the significant difference with the positive control (L-dopa) (P <0.05); Data are presented as mean ± standard error (SEM). (n = 8).**

The mean of muscle weakness in the 300, 400, and 500 mg/kg morin and L-dopa groups was significantly lower than the physiologic serum group (P <0.05). The mean muscle weakness in the 300 mg/kg morin group of (P <0.05) was significantly higher than the L-Dopa group, while the difference between the 400 and 500 mg/kg morin groups and the L-dopa group was not significant. Mean muscle weakness in the 500 and 400 mg/kg morin groups (P <0.05) was significantly lower than that 300 mg/kg morin group, while muscle weakness between the 500 and 400 mg/kg groups was not significant (Fig.3).

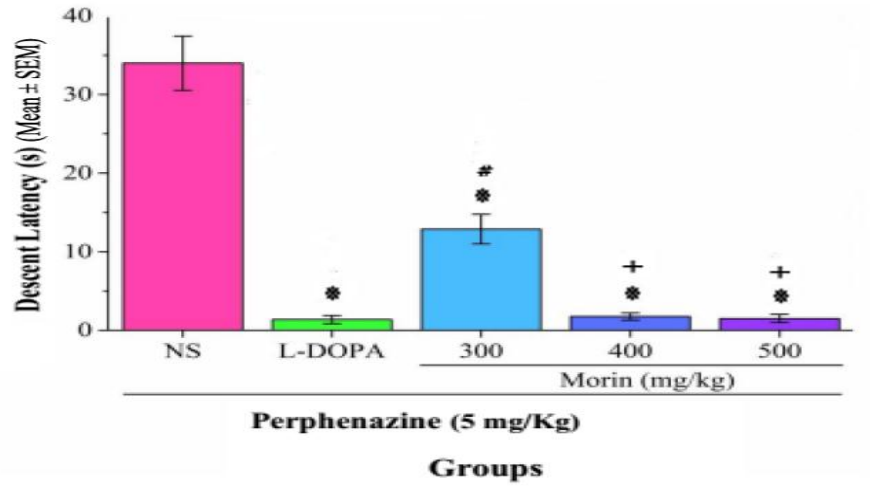


**Figure 3: Comparison of the mean muscle weakness in the groups receiving doses of 300, 400, and 500 mg/kg morin with the positive control (L-dopa) and negative control (physiological serum) groups; * shows the significant difference with the negative control group (physiological serum) (P <0.05); # shows significant difference with the positive control group (L-Dopa) (P <0.05); + shows significant difference with 300 mg/kg morin group (P <0.05). Data are presented as mean ± standard error (SEM). (n = 8).**

The mean MDA in the group receiving different morin doses (300, 400, and 500 mg/kg) and the L-Dopa group showed a significant decrease (P <0.05) in comparison with the physiological serum group. The mean of MDA in the L-dopa group was significantly (P <0.05) lower than that in the groups received different morin doses (300, 400, and 500 mg/kg). The mean of MDA in the 400 and 500 mg/kg morin groups (P <0.05) was lower than the 300 mg/kg morin group. The mean of MDA between the 400 and 500 mg/kg morin groups was not significantly different (Fig.4).

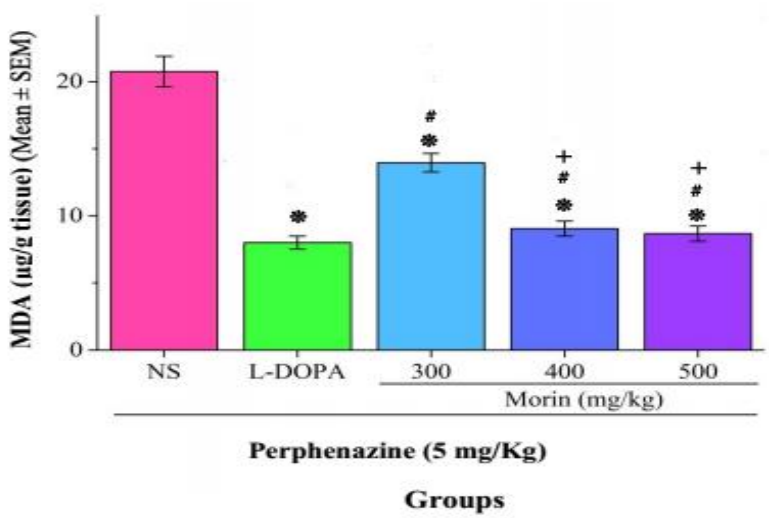


**Figure 4: Comparison of the Malondialdehyde (MDA) values in the 300, 400, and 500 mg/kg morin groups with the positive control (L-dopa) and negative control (physiological serum) groups. *shows significant difference with the control group (normal saline) (P <0.05); #shows significant difference with the control group (L-dopa) (P <0.05); + shows significant difference with the 300 mg/kg morin group (P <0.05). Data are presented as mean ± standard error (SEM) (n = 8).**

The mean of GSH in the groups received different doses of morin (300, 400, and 500 mg/kg) and the L-Dopa group showed a significant increase (P <0.05) compared to the physiological serum group. The mean of GSH in the 400 mg/kg morin group (P <0.05) was significantly lower than that in the 500 mg/kg morin group and L-dopa, but it was significantly higher than the 300 mg/kg morin group and the serum physiologic group (P <0.05). The mean of GSH in the 500 mg/kg morin group was significantly lower than that in the L-dopa group, but it was significantly higher than in the 300 and 400 mg/kg morin groups and the physiologic serum group (P <0.05) (Fig.5).

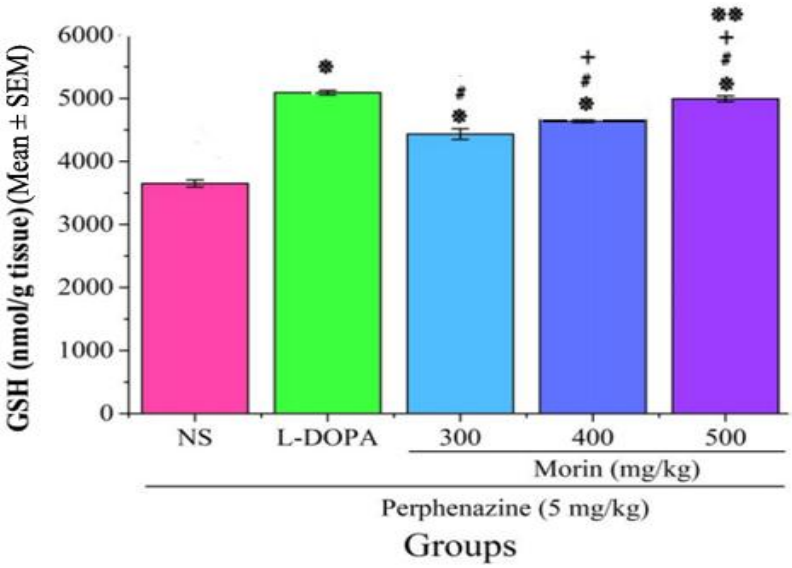


**Figure 5: Comparison of the mean GSH values in the 300, 400, and 500 mg/kg morin groups with the positive control (L-dopa) and negative control (physiological serum) groups. *shows significant difference with the control group (normal saline) (P <0.05); # shows significant difference with the control group (L-dopa) (P <0.05); + shows significant difference with the 300 mg/kg morin group (P <0.05). **shows significant difference with the 400 mg/kg morin group (P <0.05). Data are presented as mean ± standard error (SEM) (n = 8).**

## DISCUSSION

Despite new advances for treatment of PD symptoms, most patients will ultimately become disabled and unable to work. Until now, definitive treatment and appropriate medication for this disease have not been established. Therefore, finding a more effective drug with undesirable effects to deal with the symptoms of this disease is very important.[45] Chen et al. (2017) investigated the therapeutic effects of morin (30 mg/kg) in focal cerebral ischemia and reported positive therapeutic effects including MDA reduction, which support our findings.[46] Our findings showed a positive dose-dependent effect of morin on the GSH levels so that increasing the mean dose increases the GSH level. Comparing the effects of different doses of morin with L-Dopa showed that the L-Dopa resulted in greater levels of GSH compared with the other morin groups. It is consistence with our findings. Chen et al. (2017) reported that morin (30 mg/kg) increased the levels of antioxidants (SOD, GSH, and $GP_x$) that have therapeutic effects in focal cerebral ischemia. Similarly, the findings of the Subash et al.'s study (2009) showed that morin (30 mg/kg) increased the levels of different antioxidants (SOD, GSH, and $GP_x$) in chronic hyperammonemia induced by ammonium chloride in rat models.[47] Zhang et al. (2010) showed that morin has a neuroprotective effect in both in vitro and in vivo environments and may be used as a new treatment for PD and other neurodegenerative diseases.[39] Moreover, Chen et al. (2017) demonstrated the beneficial effect of morin on cerebral ischemia through reducing oxidative stress, inhibiting apoptosis and inflammation, and suggesting that neuroprotective morin effects may be useful as a strong supplement to improve the ischemic stroke symptoms.[46] Lee et al. (2016) reported the multiple neuroprotective mechanisms of morin for PD, suggesting that Morin could be used as a potential and prophylactic treatment for PD.[48] The findings of these studies support our findings. The findings of our study showed that morin could have an antioxidant and protective effect on the dopaminergic neurons of substantia nigra against the oxidative stress induced by perphenazine. This effect was dose-dependent and higher doses were more effective. PD is a chronic neurodegenerative disease in humans; thus, using morin in PD, particularly during the first stages of the disease, can reduce or slow down the death of dopaminergic neurons and may be effective in reducing the progression of disease symptoms. Pharmacological data of the present study reinforce the hypothesis of using morin as a new drug in the treatment of PD. In conclusion, it is suggested that future studies focus on antioxidant capacity and neuroprotective effects of morin.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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