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Original Article

Potential Effects of Pomegranate Juice in Attenuating LID in Mice Model of Parkinson Disease

Sarah Rezaee[1], Mahsa Hadipour Jahromy[2*]

ABSTRACT

Purpose: Parkinson's disease (PD) is one of the most important neurodegenerative diseases, known with tremor, rigidity and bradykinesia resulted from chronic degeneration and death of sub thalamic nucleus (STN). According to the treatment benefits of levodopa on Parkinson, long-term levodopa administration causes some complications called levodopa-induced dyskinesia (LID) with poorly understood pathogenesis. Literature shows that polyphenol rich compound like pomegranate protect neurons of animals that are Parkinson induced, with some controversy. **Objectives:** In this study, the potential effects of pomegranate in attenuating LID in parkinsonian mice induced with 4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) were investigated. **Materials:** Mouse model of PD was induced by MPTP. To induce LID, valid PD mice were treated with levodopa (50 mg/kg, i.p) for 21 days. Then the effects of chronic co-administration of pomegranate juice (20 ml/kg) orally, with levodopa and continuing for another 20 days, evaluated. Behavioural tests were performed in all groups, every other day including: Abnormal involuntary movements (AIMs), cylinder and catatonia tests. **Results:** Levodopa in chronic administration induced dyskinesia that observed in AIMs and cylinder tests for 3 weeks when compared to untreated animals (P<0.05 or 0.01 depending the time course). Besides, catatonia was recorded after two weeks and mounted time-dependently compared to control (P<0.01). Chronic pomegranate co-administration improved AIMs scores for next 20 days (P<0.01, in following days, compared to no-pomegranate treated group), attenuated cylinder scores and catatonia rates dramatically and time dependently (P<0.01). **Conclusion:** Chronic pomegranate co-administration improved movements in all test results. It is then, concluded that pomegranate can be a good adjunct for attenuating LID and catatonia in mice.

Key words: Parkinson's disease, Levodopa-induced dyskinesia (LID), Pomegranate, MPTP, mice

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INTRODUCTION

Parkinson's disease (PD) is a degenerative disorder of the central nervous system mainly affecting the motor function. Early in the course of the disease, the most obvious symptoms are movement-related including: shaking, rigidity, slowness of movement and difficulty with walking and gait. Treatments improve the early symptoms of the disease, include; the antiparkinson medications Levodopa and dopamine agonists. As the disease progresses and dopaminergic neurons continue to be lost, these drugs, especially Levodopa, eventually become ineffective whilst at the same time produce a complication characterized by involuntary movements called dyskinesias and fluctuations in the response. Therefore, Levodopa-induced dyskinesia (LID) is a form of dyskinesia often involves hyperkinetic movements, such as chorea, dystonia, and athetosis that most commonly occurs at the time of peak Levodopa plasma concentrations.[1,2] Development of LID is reported to be related with pulsatory stimulation of dopamine.[3] There have been efforts to reduce LID via thalamotomy and some adjunct medications.[4]

The "oxidative stress" hypothesis suggests that the nigrostriatal cell death observed in PD is due to the MPTP-mediated formation of hydroxyl and superoxide radicals that may play a causal role in PD.[5]

The pomegranate (*Punica granatum L.*) is an ancient fruit that has been widely consumed in various cultures for many years. The rich bioactive profile of pomegranate makes it a highly nutritious and desirable fruit crop. Beneficial properties of this fruit have been extensively investigated and candidate it as antioxidant, antidiabetic, hypolipidemic, antibacterial, antiinflammatory, antiviral, and anticarcinogenic activities.[6] The health benefits of pomegranate have been attributed to its wide range of some well-known predominant polyphenols [7,8] Recently some researches focused on different pomegranate extract on neurological, psychiatric and neurodegenerative disorders.[9]

Considering all, there is no study or any investigation regarding the effect of pomegranate on LID. Here we report chronic administration of pomegranate juice

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efficacy, as highly contained polyphenol fruit, on alleviation of LID in MPTP mice model of PD.

MATERIALS AND METHODS

Drugs

4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) 98% purchased from SERVA (FEINBIOCHEMICA, HEIDELBURG/NEWYORK) and Levodopa from Ramopharmin company (Iran). Pomegranate (*Punica Granatum L.*) was collected by one of the colleagues from the agriculture garden (under supervision of Agricultural Research Organization in Fars Province) in Shiraz. Then washed, chilled to 4°C, and stored. The seeds of the fruit containing the intact juice sacs were manually separated from the pericarp, and the whole juice extracted by the aid of electric juicer so that seeds break. Then filtered and stored in clean jars in fridge.

Animals

Male BALB/c mice, weighing 25-30 g were housed under laboratory conditions: temperature 23±1°C, humidity 40-60%, 12h: 12h L/D cycle, lights on at 07:00h. Food and water were available *ad libitum*. All the experiments were carried out between 10:00 and 15:00 in testing rooms adjacent to the animal rooms. Mice were treated in accordance with the current law and the NIH Guide for the Care and Use of Laboratory

To induce PD, 30 mg/kg of MPTP were injected intraperitoneally for five consecutive days to 24 mice.[10] Valid PD mice then were approved by three tests that are defined below, at final day. Sixteen mice then were treated with levodopa (50 mg/kg, i.p) for 21 days [11] and 8 mice received distilled water named control. Dyskinetic movement measured by Abnormal Involuntary Movements (AIMs), catatonia and cylinder test every other day, till the last day of treatment for all 24 mice. To investigate pomegranate effect on dyskinesia, dyskinetic mice then were divided in two groups. A group of 8 mice treated just with levodopa (50 mg/kg, i.p) for 21 days and other group of 8 mice, treated with both levodopa (50 mg/kg, i.p) and pomegranate juice (20 ml/kg, orally, gavage) for 21 days.

All observations were recorded by a camcorder and have been scored and reviewed by the coauthor blind to treatment groups, very carefully.

AIMs test

On test days animals were placed in a cage (30×20×20 cm) on a mirror to observe any abnormal involuntary movements in a total time of 3 hours with 30 minutes intervals for 1 minute each time (totally, seven times in 3 hours). Abnormal involuntary movements included axial, orolingual, limbs and locomotor movements. Severities of 0-4 were assigned for each movement. A score of 0 was assigned for the absence of AIMs; 1 for occasional AIMs (less than 50% of observation time); 2 for frequent AIMs (more than 50% of observation time); 3 for AIMs that were continuous but interrupted by strong sensory stimuli; and 4 for continuous, uninterrupted AIMs.[12]

Catatonia test

Muscular rigidity was assessed by catatonia by giving scores to define activity. Scores included 0-1 based on the severity of each defined activity. A score of 0 assigned for no rigidity, 0.5 in case of movement due to pushing the animal in a flat surface, 0.5 for the ability to keep each forelimb on 1cm height, one for the ability to stay in rigidity and keep each forelimb on 1.5 cm height. Therefore, maximum rigidity score can observe and report 3.5. Each score was recorded in an observation time of 15 seconds.

Cylinder test

On test days animals were placed into a 20 cm height cylinder for 3 minutes and were observed for complete and impaired forelimbs contacts on cylinder wall. The test is used to monitor the antiakinetic drugs.[13] Full contacts and impaired contacts of animals' forelimbs then, were counted and full contacts to impaired contacts ratio were assessed. Higher ratio indicates the instability of mice.

Statistical analysis

Processing of the raw data from recordings and calculations were performed with the OriginLab 6 software. Data were analyzed with one- or two-way analysis of variance (ANOVA). Two-way ANOVA was performed to assess the effects of the different days of treatment between groups. One-way ANOVA was carried out to assess individual differences between groups. All values are presented as mean values ± standard error of mean, and the significance level was set at $p<0.05$.

RESULTS

Effects of pomegranate juice on LID in AIMs test

After 3 days, levodopa decreased scores significantly, when compared to no treated group (***P=0.0001, F=19.698 in One-way ANOVA), indicated its therapeutic effects for attenuating parkinson's symptoms. Continuing treatment, levodopa still had its effects on decreasing AIMs scores (except for the 7th day assessment), till nearly two weeks (the 9th day: **P=0.005, F=9.21; the 11th day: *P=0.044, F=4.44; the 13th day: *P= 0.049, F= 4.235; the 15th day: P=0.0505, F=0.455 in One-way ANOVA). Following treatment for another four days, nearly the same means calculated for two groups, and since day 19, the results getting reverse, in a manner that levodopa scores started to proceed control significantly (the 19th day: **P=0.008, F=8.023; 21st day: ***P=0.0003, F= 16.536 in One-way ANOVA).

As shown in figure1-B, administration of pomegranate juice along with levodopa for the rest of treatment, attenuated abnormal involuntary movements' scores compare to mice continuing to be treated only with levodopa, nearly in time-dependent manner. Although not significant changes observed in AIMs scores after ten days of pomegranate juice administration compare to levodopa only treatment, (e.g. the 31st day: P= 0.075, F=3.685 in One-way ANOVA), some significant decrease in scores calculated for the two consequent recordings (at the 33rd day: **P=0.003, F= 12.779; at the 35th day:* P= 0.017, F= 7.218 in One-way ANOVA).

Comparing different days of treatment in pomegranate co treated group, no significant changes in AIMs responses have been occurred at any days (in best condition: day 33 versus day 23: P=0.118, F=2.773 in Two-way ANOVA).

Effects of pomegranate juice on LID in Cylinder test

The cylinder test results were not different significantly till the 9th day of levodopa administration (day 9: **P= 0.002, F=11.182 in One-way ANOVA). Then, the ratio increased gradually comparing control group that shows diskinesia happening in levodopa injected mice (the most increasing reports at day 19: **P= 0.0078, F=8.216, in One-way ANOVA).

Comparing different days of treatment in levodopa treated group, it was also observed that significant increment in cylinder test responses have been occurred at days 19 when compared to the first day assessment (#P=0.030, F=5.188 in Two-way ANOVA).

Figure 2-B shows impaired to full contacts ratio in cylinder test after pomegranate administration in LID mice. We observed that impaired to full contacts ratio decreased dramatically in LID mice in all days of treatment by co-administration of levodopa and pomegranate started

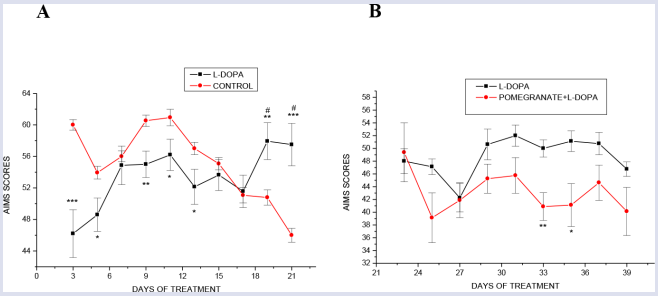

Figure 1: Mean AIMS scores with standard errors versus time (day). A: for mice receiving L-dopa (50mg/kg, i.p) compared to control group (Distilled water) for 21 days after induction of Parkinson using MPTP (n=8). B: for mice receiving L-dopa (50mg/kg, i.p) plus pomegranate juice (20ml/kg, orally by gavage) compared to L-dopa treated group (50mg/kg, i.p) for 20 days after induction of LID (n=8).
*p <0.05, ** p<0.01, and *** p <0.001, compared to no L-DOPA administration(A)/ L-dopa treated group (B) in the same group of animals in One-way ANOVA. #p<0.05, ## p< 0.01, and ###p<0.001 for comparisons between groups at different days with two-way ANOVAs.

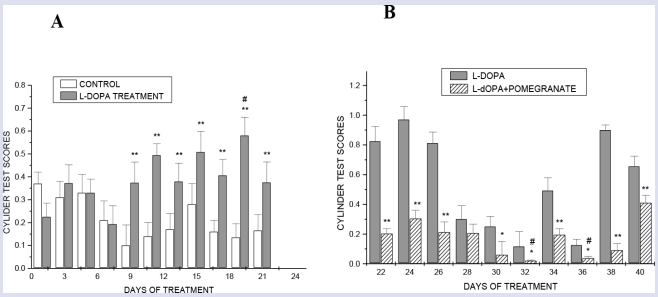

Figure 2: Mean cylinder test scores with standard errors versus time (day). A: for mice receiving L-dopa (50 mg/kg, i.p) compared to control group (Distilled water) for 21 days after induction of Parkinson using MPTP (n=8). B: for mice receiving L-dopa (50 mg/kg, i.p) plus pomegranate juice (20 ml/kg, orally by gavage) compared to L-dopa treated group (50mg/kg , i.p) for 20 days after induction of LID (n=8).
*p<0.05, ** p<0.01, and *** p<0.001, compared to no L-DOPA administration(A)/ L-dopa treated group (B) in the same group of animals in One-wayANOVA. #p<0.05, ## p< 0.01, and ###p<0.001 for comparisons between groups at different days with two-way ANOVAs.

with day one of pomegranate administration (the 22nd day ***P=7.48×10-12, F=421.96 in One-way ANOVA) . The effect was the most in days 30, 32 and 36 of treatment in LID mice. The interesting phenomenon was the pattern of variation in responses of levodopa treated group during all days of experiments (off-on). The results show less variation by days when administering pomegranate juice.

Comparing different days of treatment in pomegranate co treated group, significant changes in cylinder responses have been occurred at any days (in best condition: day 32 versus day 22: #P=0.035, F=5.443 in Two-way ANOVA).

Effects of pomegranate juice on LID in Catatonia test

As shown in figure 3-A, in catatonia test, no scores recorded for the first 14 days of treatment with levodopa. However, for the last seven days, it is observed that in levodopa-treated groups, catatonia scores were increasing compared to control group that was statistically significant

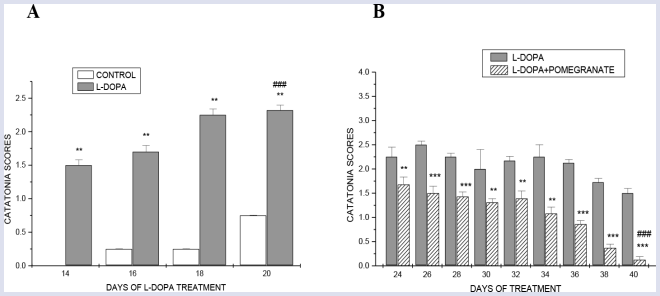

Figure 3: Mean Catatonia test scores with standard errors versus time (day). A: for mice receiving L-dopa (50mg/kg, i.p) compared to control group (Distilled water) for 21 days after induction of Parkinson using MPTP (n=8). B: for mice receiving L-dopa (50mg/kg, i.p) plus pomegranate juice (20ml/kg, orally by gavage) compared to L-dopa treated group (50mg/kg, i.p) for 20 days after induction of LID (n=8).
*p <0.05, ** p<0.01, and *** p <0.001, compared to no L-DOPA administration(A)/ L-dopa treated group (B) in the same group of animals One-wayANOVA. #p<0.05, ## p< 0.01, and ###p<0.001 for comparisons between groups at different days with two-way ANOVAs.

(***P<0.001 in One-way ANOVA, not reported in detail due to very negligible amount). Comparing the day 20th with the day 14th (which was the first sign of catatonia in levodopa treated group), significant increasing was observed (###P=3.5×10-5. F=119.11 in Two-way ANOVA).

Based on results in figure 3-B, animals receiving pomegranate were less rigid than group treated only with levodopa, that was statistically significant (P<0.01). This is more remarkable on last days of treatment with pomegranate plus levodopa compared to levodopa only treated group (***P=5.10×10^{-4}, F=31.34 in One-way ANOVA) and showed time dependent efficacy for pomegranate in co-administration. Comparing last day of pomegranate treatment with day 22nd (which was the first day of its use), significant reduction is reported in muscle rigidity (###P=1.57×10^{-4}. F=44.526 in Two-way ANOVA).

DISCUSSION

Using AIMs test for dyskinetic measurements in this study, we observed that in initial treatment, levodopa at 50 mg/kg could reduce all axial, limb, oroligulal and locomotion scores, however, after chronic Levodopa treatment, scores increased time-dependently. By adding pomegranate juice at this phase, all scores were reduced and stayed low till the last session of treatment.

The cylinder test that was chosen here to assess physiological motor function is very simple, objective, fast in performance and does not require animal pre-training. This test is sensitive to both dopaminergic loss and to the motor improvement produced by antiparkinson drug [13]. In our study, we noticed that just in untreated control group, animals' performance in cylinder were weak and seemed disrupted in sessions that high scores in AIMs test had been observed. A potential drawback of this test is also reported in one studywhich mentioned exploratory action in rats resulting in a reduced sensitivity of the test over long-term studies.[13]

Besides, Levodopa treatment increased cylinder scores quite markedly after a week, implicating that dyskinesia is appearing. The Levodopa results, correlate well with its animal performance in AIMs test (i.e Levodopa increased scores in both test).

Interestingly, in continuing Levodopa treatment, we could observe the drawback in cylinder test with latency compared to AIMs scores, in a

period of ten days (from day 26 till 36). Pomegranate administration markedly reduced all scores in all measured sessions. It seemed that pomegranate could produce a decrease in motor function with smooth slop in chronic treatment.

Catatonia or Rigidity is stiffness and resistance to limb movement caused by increased muscle tone and an excessive and continuous contraction of muscles. In Parkinsonism, the rigidity can be uniform or ratchet.[14] The combination of tremor and increased tone is at the origin of cogwheel rigidity. Rigidity may be associated with joint pain; such pain being a frequent initial manifestation of the disease. In early stages of Parkinson's disease, rigidity is often asymmetrical, and it tends to affect the neck and shoulder muscles prior to the muscles of the face and extremities. With the progression of the disease, rigidity typically affects the whole body and reduces the ability to move.

During the last decades, potential effects of folk medicinal plants on muscle rigidity have been elicited. In our experiments, it seems that pomegranate had significant beneficial effects on muscle rigidity.

The role of dopamine oxidation in mitochondrial dysfunction has been implicated in Parkinson's disease.[15] Clinical trialsl have shown that administration of L-DOPA in PD patients could develop severe motor fluctuations and dyskines.[16]

On the other hands evidences suggest that mitochondrial dysfunction and oxidative stress have important roles in the dopaminergic neurodegeneration.[17] Some studies have reported the efficacy of polyphenols to reduce neuronal death in different animal models of neurodegeneration due to antioxidant and anti-inflammatory actions.[18] Pomegranate is rich in polyphenols and has antioxidant and anti-inflammatory activity.[19]

In the present work, pomegranate juice efficacy has been observed in chronic administration on reducing LID in co-administration with levodopa in treating MPTP mouse model of PD.

Antioxidants, pro-oxidants and their controversy have been widely studied for many years for their potential benefits and adverse effects.[20] For example, the antioxidant and pro-oxidant activities of green tea polyphenols and their role in cancer prevention have been described by Lambert and Elias. They proposed that the pro-oxidant effects might be attributed to the induction of endogenous antioxidant system in normal tissues.[21]

It is believed that LID has consistently been related to excessive dopamine (DA) although not strictly paralleled by a raise in striatum DA tone. It seems that although dopamine provision is the main and most important therapy for parkinson' disease, its excessive amounts after many years of therapy, could impose bradykinesia via unknown mechanism probably due to its oxidation. That might be the reason why antioxidants may postpone LID when co-administered with levodopa in clinic.

In current study, co-administration of pomegranate juice with levodopa in treating LID as the statics driven from AIMs, cylinder test show, subside the dyskinetic features including bradykinesia.

Pomegranates mainly known as a powerful antioxidant in traditional and herbal medicine can exert pro-oxidant activity reported by Ardakani *et al.* According to their experiments, it is shown that pomegranate at lower concentrations have pro-oxidant activity via stimulation OH. formation while at higher concentrations, act as a free radical scavenger.[22]

In our experiments, pomegranate also attenuated muscle rigidity in catatonia test during LID in mice. Although catatonia is one of the fast features of Parkinson's that especially can be induced by perphenazin or some anti-psychotic drugs in animals as a model, we encountered this sign along with LID. Many reports have revealed role of antioxidants in improvement of catatonia in animal models.[23]

CONCLUSION

It can be concluded that pomegranate either via its antioxidant or pro-oxidant properties, can have some beneficial effects on catatonia and LID. Prevention of dopamine oxidation might be one of the important processes to postpone LID, as their metabolites are harmful to dopaminergic neurons. However, more researches are needed to evaluate different doses and velocity of pomegranate juice as an adjuvant to levodopa in hope of see more effective results.

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CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

ABBREVIATIONS

LID: Levodopa Induced Dyskinesia; **MPTP:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **AIMS:** Abnormal Involuntary Movement Scale.

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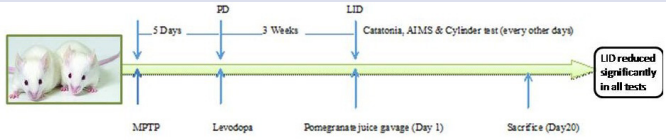
GRAPHICAL ABSTRACT



SUMMARY

- Parkinson's disease (PD) is one of the most important neurodegenerative diseases. The treatment benefits of levodopa on Parkinson, long-term levodopa administration causes some complications called levodopa-induced dyskinesia (LID) with poorly understood pathogenesis. In this study, the potential effects of pomegranate in attenuating LID in parkinsonian mice induced with 4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) were investigated. Mouse model of PD was induced by MPTP. Then the effects of chronic co-administration of pomegranate juice (20 ml/kg) orally, with levodopa and continuing for another 20 days, evaluated. Behavioural tests including abnormal involuntary movements (AIMs), cylinder and catatonia tests were performed in all groups, every other days. Results showed that chronic pomegranate co-administration improved movements in all test. It is then, concluded that pomegranate can be a good adjunct for attenuating LID and catatonia in mice.

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