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ORIGINAL ARTICLE

Impact of a 12-week structured exercise program on motor function and exosomal alpha-synuclein levels in Parkinson's disease: A prospective analysis

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ABSTRACT

Objectives: This study aimed to determine whether exercise reduced alpha-synuclein aggregation and ultimately improved symptoms of Parkinson's disease (PD).

Patients and methods: The prospective study was conducted with 26 PD patients (14 males, 12 females; mean age: 58.5±11.3 years; range, 38 to 79 years) between October 2019 and January 2020. A 12-week combined exercise program, including respiratory training, spinal stabilization, and stretching, was performed by the patients. Detailed clinical assessments were conducted, along with alpha-synuclein quantification, before and after the intervention.

Results: The data revealed notable improvements in motor, cognitive, and nonmotor realms ($p<0.05$). However, alpha-synuclein levels remained consistent ($p>0.05$).

Conclusion: While the exercise regimen aids symptom mitigation in PD, it does not alter alpha-synuclein concentrations, emphasizing the need to further investigate the mechanisms behind the exercise-related benefits.

Keywords: Alpha-synuclein, combined exercise training, exosomes, Parkinson's disease.

Idiopathic Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the loss of dopamine-producing neurons within the substantia nigra. This neuronal loss gives rise to the formation of Lewy bodies, aggregates primarily composed of the protein alpha-synuclein.[1-3] These molecular changes precipitate a cascade of motor disturbances, such as tremors, rigidity, and bradykinesia, as well as cognitive deficits that significantly impact the quality of life.[4-6] Although pharmaceutical interventions provide some relief by enhancing dopamine signaling, they often offer only partial and temporary alleviation of symptoms. As a result, there has been a growing interest in exploring alternative therapeutic strategies that target not only the motor symptoms but also the underlying pathophysiological mechanisms of PD. Among these strategies, aerobic exercise has emerged as a promising avenue due to its potential to stimulate neurogenesis, improve balance, enhance gait, and even counter cognitive decline.[7-10]

The benefits of aerobic exercise extend beyond the realm of physical fitness. Accumulating evidence suggests that these exercises possess the capacity to modulate neuroinflammatory processes within the brain, potentially curbing the chronic inflammation that contributes to the progressive degeneration in PD. Furthermore, emerging research hints at exercise's ability to influence protein misfolding, a phenomenon central to the aggregation of alpha-synuclein and the formation of

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Lewy bodies.[11-13] Although the notion of engaging in a 12-week combined exercise training (CET) regimen has gained traction in recent years as a nonpharmacological intervention for PD, the outcomes are inconsistent across various studies.[14,15] Differing methodologies, participant characteristics, and exercise protocols have all contributed to a diverse range of results, leaving a need for further investigation and a clearer understanding of the effects of CET on PD symptoms.[14,16]

Given the paramount role of alpha-synuclein in the pathogenesis of PD,[2,17] this study sought to investigate the effects of CET on the molecular pathways associated with alpha-synuclein. By focusing on these pathways, we aimed to elucidate whether exercise reduced alpha-synuclein aggregation and ultimately improved PD symptoms. In doing so, we hope to contribute to the growing body of knowledge that bridges the gap between physical activity, neurodegeneration, and novel therapeutic strategies for PD.

PATIENTS AND METHODS

The prospective study was conducted with 26 PD patients (14 males, 12 females; mean age: 58.5±11.3 years; range, 38 to 79 years) at the Bezmialem Vakıf University Faculty of Medicine, Department of Neurology between October 2019 and January 2020. In the study, patients with PD were consecutively selected based on the UK Parkinson's Disease Society Brain Bank diagnostic criteria.[18] The patients who presented to the hospital between February 2019 and August 2019 were included in the study. The inclusion criteria were as follows: literacy, diagnosis of PD with Stages 1-3, a Mini-Mental State Examination (MMSE) score ≥24,[19] and stable treatment for at least six months prior to the study. Following the initial selection phase, all eligible cases were subjected to the study activities between October 2019 and January 2020. This comprehensive timeframe was carefully chosen to minimize selection bias and ensure a clear temporal context, thus enhancing the relevance and accuracy of our findings. Patients were rigorously assessed for eligibility to maintain the integrity and validity of outcomes. Exclusion criteria included recent physical activity or any conditions that prevented physical activity to ensure a homogenous participant group.

Patients undertook a 12-week CET with weekly supervised sessions and home exercises.[20,21] Clinic sessions lasted 60 min and covered various exercises, and the intensity was monitored for some exercises. Home routines, done thrice weekly for 45 min, included diverse activities.[14,16] Adherence was tracked via an exercise diary. Levodopa equivalent daily dose was also calculated.

Before and after CET, patients were evaluated using the Unified Parkinson's Disease Rating Scale (UPDRS), modified Hoehn and Yahr Stage (mHYS),[22] and cognitive tests, such as the Hospital Anxiety and Depression Scale (HADS) and MMSE. The HADS comprises 14 items, each rated from 0 to 3, with higher scores indicating greater anxiety/depression. The anxiety and depression subscales each have seven items and a maximum score of 21.[23] Additionally, the Parkinson's Disease Questionnaire-39 (PDQ-39) was used to assess the quality of life. The PDQ-39 contains 39 items, each rated from 0 to 4, covering eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort.Mobility metrics included the Tinetti assessment tool and the timed-up-and-go test.[14,18] The Tinetti assessment tool measures an older adult's gait and balance abilities. A low-performance score is associated with a high fall risk in an individual. The Tinetti assessment tool has been validated as a robust fall risk instrument and predictor of falls in the elderly.[24] The timed-up-and-go test assesses dynamic balance and functional mobility. Subjects were instructed to sit back in a standard armchair and to stand up, walk a marked path of 3 m, turn around, and sit back down in the chair. The cutoff value was set at 12 sec based on the reference value for geriatric adults.[25] All results were documented on a dedicated worksheet. The scoring of all scales were double checked by two clinical researchers.

Quantification of exosomal alpha-synuclein

Blood sampling was synchronized with the CET schedule. On the day designated for the initiation of CET, a preintervention blood specimen was collected. At the conclusion of the three-month CET period, a postintervention blood specimen was procured. These collections were strategically timed to facilitate the comparative analysis of biomarkers before and after the exercise intervention. Venous blood was drawn into tubes containing EDTA and promptly centrifuged at 3500 rpm for 10 min at +4°C for plasma separation. Afterward, the samples were preserved at −80°C until analysis. Exosomal isolation from the plasma was performed employing the Norgen

Biotek (NB) Plasma/Serum Exosome Purification Mini Kit (Norgen Biotek Corp., cat.no. 57400, Thorold, ON, Canada) methodology. Following isolation, the plasma was mixed with the specific reagents supplied in the kit and subjected to another centrifugation cycle. The isolated exosomes were then stored at –20°C. Quantitative assessment of alpha-synuclein was conducted using an enzyme-linked immunosorbent assay (ELISA) kit supplied by Elabscience (Elabscience Biotechnology Co., Ltd., cat.no. E-EL-H0983, Wuhan, Hubei, China), with absorbance measured at 450 nm using a MultiSkan Go spectrophotometer (Thermo Scientific, MultiSkan Go Microplate Spectrophotometer, Tokyo, Japan). The assay demonstrated a sensitivity of 9.83 pg/mL across a dynamic range of 15.63 to 1000 pg/mL.

Statistical analysis

Data were analyzed using IBM SPSS version 25.0 software (IBM Corp., Armonk, NY, USA). The statistical approach comprised paired t-tests for comparing mHYS scores before and after CET, alongside the Shapiro-Wilk test for evaluating the normality of data distribution. Nonparametric tests were employed to evaluate nonnormally distributed data. A p-value <0.05 was considered statistically significant. The analysis was designed to elucidate the symptomatic changes related to CET and explore their association with alpha-synuclein level variations. Continuous variables were expressed as mean ± standard deviation (SD) or median values, and categorical variables were expressed as frequencies and percentages. The interplay between clinical traits and alpha-synuclein concentrations were examined by Spearman's rank correlation coefficient, while the pre- and post-CET alpha-synuclein levels were assessed using the Wilcoxon signed-rank test.

Leveraging insights from Chang et al.,[26] who noted a medium effect size (Cohen's d) of 0.61 in mHYS score variations, we performed a priori power analysis. This analysis, with an alpha level of 0.05 and a desired power of 0.80, indicated a minimum requisite of 22 participants to confidently detect significant changes in mHYS scores after CET, affirming the adequacy of our sample size for capturing consequential shifts in PD severity due to the intervention.

RESULTS

This program was designed to improve motor, nonmotor, and cognitive functions, the specifics of which are detailed in Table 1. Significant

TABLE 1
Demographic and clinical data of the patients (n=26)

	n	%	Mean±SD
Age (year)			58.5±11.3
Sex			
Male	14	53.8	
Female	12	46.2	
Height (cm)			167.9±12.7
Weight (kg)			76.2±11.1
BMI (kg/m^2)			27.1±3.37
Educational status			
Primary	18	69.2	
Secondary/college	7	26.9	
University	1	3.9	
Smoking	5	19.2	
Alcohol consumption	1	3.9	
Symptom duration (month)			76.9±53.2
Exercise history per week	10	38.5	
Phenotypes			
Tremor dominant	19	73.07	
Rigidity dominant	7	26.93	
LEDD (mg)			571.5±227.2

SD: Standard deviation; BMI: Body mass index; LEDD: L-Dopa equivalent daily dose.

TABLE 2
Evaluation of motor, nonmotor, and cognitive functions of the patients before (pretest) and after (posttest) CET

	Pretest		Posttest		
	Median	Min-Max	Median	Min-Max	*p*
Modified Hohn and Yahr Scale					
UPDRS grades					
1 (cognitive)	13	4-22	7	0-22	<0.001
2 (daily life action)	4	1-27	3.5	0-27	0.656
3 (motor)	27	16-38	20	4-37	<0.001
4 (treatment complication)	0	0-11	0	0-9	0.943
NMSQ					
Brief pain inventory					
Normal work	0	0-10	0	0-8	0.027
Interpersonal relationship	0	0-10	0	0-8	0.397
Sleep	0	0-10	0	0-8	0.140
Epworth Sleepiness Scale	7.5	0-18	5.5	0-18	0.170
RLS severity rating scale	0	0-32	0	0-29	0.058
PDQ-39					
Social support	29.16	0-66.67	8.33	0-66.67	0.006
Cognition	25	0-87.5	9.37	0-62.5	0.008
Communication	0	0-75	8.33	0-75	0.147
Bodily discomfort	25	0-91.67	16.66	0-75	0.208
Total	17.34	1.56-54.43	12.73	0.63-44.69	<0.001
HADS					
Anxiety	5	0-17	2	0-13	0.039
Depression	5.5	0-17	3	0-38	0.008
Total	11	0-32	6	0-40	0.005
MMSE	30	27-30	30	26-30	0.157
FAB	15	11-18	16	11-18	0.037
WMS-R					
Digit span-forward	6	5-8	6	3-8	0.276
Digit span-backward	3	1-6	3	1-6	0.219
Abstract thinking					
Interpretation	2	0-3	2	0-3	0.011
Similarity	5	3-10	7	4-11	<0.001
Selective reminding					
Short-term storage	4	0-8	5.5	1-10	<0.001
Long-term storage	6	0-12	7	2-27	0.049
Clock Drawing test	4	1-4	4	1-4	0.157
Verbal fluency phonemic	18	6-43	21.5	4-43	0.006

CET: Combined exercise training; UPDRS: Unified Parkinson's Disease Rating Scale; NMSQ: Non-Motor Symptoms Questionnaire; RLS: Restless leg syndrome; PDQ: Parkinson's Disease Questionnaire; HADS: Hospital Anxiety and Depression Scale; MMSE: Mini Mental State Examination; FAB: Frontal assessment battery; WMS: Wechler Memory Scale.

improvements were observed in cognitive functions, with UPDRS Part I scores decreasing from 13 to 7 ($p<0.001$). Motor symptoms, evaluated by UPDRS Part III, showed notable improvement, with scores reduced from 27 to 20 ($p<0.001$). Positive changes were also observed in nonmotor symptoms, with Non-Motor Symptoms Questionnaire scores dropping from 10 to 8 ($p=0.005$). Noteworthy improvements in anxiety and depression levels were measured by the HADS, with scores significantly decreasing ($p=0.039$ and $p=0.008$, respectively).

TABLE 3
Evaluation of mobility and balance of the patients before (pretest) and after (posttest) CET

	Pretest		Posttest		
	Median	Min-Max	Median	Min-Max	*p*
Tinetti Gait and Balance	32	9-35	34	15-35	0.009
Gait	9	2-9	9	4-9	0.056
Balance	23.5	6-26	25	10-26	0.008
Tinetti Falls Efficiency Scale	13	10-69	10	10-55	0.021
Timed Up & Go test	10.5	5-18	9.5	7-20	0.094

CET: Combined exercise training.

TABLE 4
Exosomal and total plasma alpha-synuclein levels of patients before (pretest) and after (posttest) CET

	Pretest		Posttest		
	Median	Min-Max	Median	Min-Max	*p*
Exosomal alpha-synuclein (pg/mL)	227	80.2-517	213	66.3-813	0.159
Total plasma alpha-synuclein (pg/mL)	4350	1115- 21000	5350	1515-16200	0.230

CET: Combined exercise training.

Quality of life, as quantified by the Parkinson's Disease Questionnaire-39, showed marked progress in social support, cognition, and bodily discomfort (all $p<0.01$). Furthermore, the Brief Pain Inventory reflected significant improvements in the ability to work and maintain interpersonal relationships ($p=0.027$). Other cognitive assessments indicated slight enhancements in overall function, with substantial progress in specific cognitive tasks noted ($p<0.01$); these results are comprehensively summarized in Table 2.

Assessments of mobility and balance also showed notable improvements. The Tinetti Gait and Balance Scale scores increased from 32 to 34 ($p=0.009$), and balance scores improved from 23.5 to 25 ($p=0.008$). The Tinetti Falls Efficacy Scale scores decreased from 13 to 10 ($p=0.021$), suggesting increased fall efficiency. However, changes in the timed-up-and-go test did not achieve statistical significance ($p=0.094$), as outlined in Table 3.

Regarding biological markers, alpha-synuclein levels measured before and after the exercise program did not change significantly. Exosomal alpha-synuclein showed a slight decrease from 227 pg/mL to 213 pg/mL ($p=0.159$), and total plasma alpha-synuclein levels exhibited a minor increase from 4,350 pg/mL to 5,350 pg/mL ($p=0.230$). These findings are displayed in Table 4.

DISCUSSION

This study highlights the profound effects of a 12-week CET on PD symptoms. Despite marked improvements in motor, nonmotor, cognitive, and movement areas, alpha-synuclein levels remained unchanged, indicating other mechanisms may drive these benefits.

Parkinson's disease is a multifaceted neurodegenerative disorder with both motor and nonmotor manifestations. Recent focus on exercise as a therapeutic avenue stems from its neuroprotective characteristics. Various modalities, from aerobic exercises to dance therapies, have been investigated for PD management. Dance interventions have shown to enhance movement coordination and cognitive function, likely due to improved sensorimotor coordination and social aspects.[27]

However, the range of CET approaches emphasizes the need for standardized protocols. Different research outcomes could arise from exercise modality variations, differing intensities, or patient demographics. For instance, contrasting findings by Vitório et al.[16] and Hubble et al.[28] might be attributed to methodological differences or patient specifics. Maintaining CET adherence over time is challenging. Innovative strategies, such as app-based reminders, could boost participation. Furthermore, technology-augmented remote CET delivery may increase patient engagement.

Although some debate the extent of exercise's influence on PD severity, our research found notable improvements after CET. This could indicate symptom relief rather than genuine disease regression. Additionally, the depressive aspect of PD, overshadowed by prominent motor symptoms, needs consideration. Group activities, such as dancing, might offer therapeutic effects due to their social and neurochemical components.[27] Sage and Almeida reported that sensory attention focused exercise had a beneficial effect on motor symptoms in PD patients.[29] From a molecular perspective, some hypothesize that exercise benefits in PD are related to decreased alpha-synuclein accumulation and reduced inflammation.[5,30] Preliminary research suggests exercise might deter abnormal protein build-up.[2,3,17,31,32] However, consistent alpha-synuclein levels in our findings necessitate further investigations.

This study is limited by its participant pool and lack of a control group, potentially affecting generalizability.

In conclusion, this study emphasizes the significant role of exercise in PD symptom management. Comprehensive research is essential to validate these findings and understand CET's comprehensive effect on PD.

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Ethics Committee Approval: The study protocol was approved by the Bezmialem Vakıf University Faculty of Medicine Hospital Ethics Committee (date: 09.01.2019, no: 2019-448). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Takahashi H, Wakabayashi K. The cellular pathology of Parkinson's disease. Neuropathology 2001;21:315-22. doi: 10.1046/j.1440-1789.2001.00403.x.
2. Sokouti H, Mohajeri D, Nourazar MA. 6-hydroxydopamine-induced neurotoxicity in rat model of Parkinson's disease: Is reversed via anti-oxidative activities of curcumin and aerobic exercise therapy. Physiol Res 2022;71:551-60. doi: 10.33549/physiolres.934929.
3. Dutta D, Paidi RK, Raha S, Roy A, Chandra S, Pahan K. Treadmill exercise reduces α-synuclein spreading via PPARα. Cell Rep 2022;40:111058. doi: 10.1016/j.celrep.2022.111058.
4. Crotty GF, Schwarzschild MA. Chasing protection in Parkinson's disease: Does exercise reduce risk and progression? Front Aging Neurosci 2020;12:186. doi: 10.3389/fnagi.2020.00186.
5. Fan B, Jabeen R, Bo B, Guo C, Han M, Zhang H, et al. What and how can physical activity prevention function on Parkinson's disease? Oxid Med Cell Longev 2020;2020:4293071. doi: 10.1155/2020/4293071.
6. Kam TI, Park H, Chou SC, Van Vranken JG, Mittenbühler MJ, Kim H, et al. Amelioration of pathologic α-synuclein-induced Parkinson's disease by irisin. Proc Natl Acad Sci U S A 2022;119:e2204835119. doi: 10.1073/pnas.2204835119.
7. Domingos J, Dean J, Fernandes JB, Ramos C, Grunho M, Proença L, et al. Lisbon Intensive Falls Trampoline Training (LIFTT) Program for people with Parkinson's for balance, gait, and falls: Study protocol for a randomized controlled trial. Trials 2023;24:101. doi: 10.1186/s13063-023-07131-4.
8. Gobbi LT, Oliveira-Ferreira MD, Caetano MJ, Lirani-Silva E, Barbieri FA, Stella F, et al. Exercise programs improve mobility and balance in people with Parkinson's disease. Parkinsonism Relat Disord 2009;15 Suppl 3:S49-52. doi: 10.1016/S1353-8020(09)70780-1.
9. Hackney ME, Earhart GM. Effects of dance on balance and gait in severe Parkinson disease: A case study. Disabil Rehabil 2010;32:679-84. doi: 10.3109/09638280903247905.
10. Sage MD, Almeida QJ. Symptom and gait changes after sensory attention focused exercise vs aerobic training in Parkinson's disease. Mov Disord 2009;24:1132-8. doi: 10.1002/mds.22469.

11. Sage MD, Almeida QJ. A positive influence of vision on motor symptoms during sensory attention focused exercise for Parkinson's disease. Mov Disord 2010;25:64-9. doi: 10.1002/mds.22886
12. Daniele S, Costa B, Pietrobono D, Giacomelli C, Iofrida C, Trincavelli ML, et al. Epigenetic modifications of the α-synuclein gene and relative protein content are affected by ageing and physical exercise in blood from healthy subjects. Oxid Med Cell Longev 2018;2018:3740345. doi: 10.1155/2018/3740345.
13. Hwang DJ, Koo JH, Kwon KC, Choi DH, Shin SD, Jeong JH, et al. Neuroprotective effect of treadmill exercise possibly via regulation of lysosomal degradation molecules in mice with pharmacologically induced Parkinson's disease. J Physiol Sci 2018;68:707-16. doi: 10.1007/s12576-017-0586-0.
14. Jang Y, Koo JH, Kwon I, Kang EB, Um HS, Soya H, et al. Neuroprotective effects of endurance exercise against neuroinflammation in MPTP-induced Parkinson's disease mice. Brain Res 2017;1655:186-93. doi: 10.1016/j.brainres.2016.10.029.
15. Kim A, Yun SJ, Sung KS, Kim Y, Jo JY, Cho H, et al. Exercise management using a mobile app in patients with Parkinsonism: Prospective, open-label, single-arm pilot study. JMIR Mhealth Uhealth 2021;9:e27662. doi: 10.2196/27662.
16. van Wegen EEH, Hirsch MA, van de Berg WDJ, Vriend C, Rietberg MB, Newman MA, et al. High-intensity interval cycle ergometer training in Parkinson's disease: Protocol for identifying individual response patterns using a single-subject research design. Front Neurol 2020;11:569880. doi: 10.3389/fneur.2020.569880.
17. Vitório R, Teixeira-Arroyo C, Lirani-Silva E, Barbieri FA, Caetano MJ, Gobbi S, et al. Effects of 6-month, multimodal exercise program on clinical and gait parameters of patients with idiopathic Parkinson's disease: A pilot study. ISRN Neurol 2011;2011:714947. doi: 10.5402/2011/714947.
18. Zhou W, Barkow JC, Freed CR. Running wheel exercise reduces α-synuclein aggregation and improves motor and cognitive function in a transgenic mouse model of Parkinson's disease. PLoS One 2017;12:e0190160. doi: 10.1371/journal.pone.0190160.
19. Daniel SE, Lees AJ. Parkinson's Disease Society Brain Bank, London: Overview and research. J Neural Transm Suppl 1993;39:165-72.
20. Velayudhan L, Ryu SH, Raczek M, Philpot M, Lindesay J, Critchfield M, et al. Review of brief cognitive tests for patients with suspected dementia. Int Psychogeriatr 2014;26:1247-62. doi: 10.1017/S1041610214000416.
21. Wu PL, Lee M, Wu SL, Ho HH, Chang MH, Lin HS, et al. Effects of home-based exercise on motor, non-motor symptoms and health-related quality of life in Parkinson's disease patients: A randomized controlled trial. Jpn J Nurs Sci 2021:e12418. doi: 10.1111/jjns.12418.
22. King LA, Wilhelm J, Chen Y, Blehm R, Nutt J, Chen Z, et al. Effects of group, individual, and home exercise in persons with Parkinson disease: A randomized clinical trial. J Neurol Phys Ther 2015;39:204-12. doi: 10.1097/NPT.0000000000000101.
23. Hoehn MM, Yahr MD. Parkinsonism: Onset, progression, and mortality. 1967. Neurology 2001;57(10 Suppl 3):S11-26.
24. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361-70. doi: 10.1111/j.1600-0447.1983.tb09716.x.
25. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc 1986;34:119-26. doi: 10.1111/j.1532-5415.1986.tb05480.x.
26. Bischoff HA, Stähelin HB, Monsch AU, Iversen MD, Weyh A, von Dechend M, et al. Identifying a cut-off point for normal mobility: A comparison of the timed 'up and go' test in community-dwelling and institutionalised elderly women. Age Ageing 2003;32:315-20. doi: 10.1093/ageing/32.3.315.
27. Chang HC, Lu CS, Chiou WD, Chen CC, Weng YH, Chang YJ. An 8-week low-intensity progressive cycling training improves motor functions in patients with early-stage Parkinson's disease. J Clin Neurol 2018;14:225-33. doi: 10.3988/jcn.2018.14.2.225.
28. Duarte JDS, Alcantara WA, Brito JS, Barbosa LCS, Machado IPR, Furtado VKT, et al. Physical activity based on dance movements as complementary therapy for Parkinson's disease: Effects on movement, executive functions, depressive symptoms, and quality of life. PLoS One 2023;18:e0281204. doi: 10.1371/journal.pone.0281204.
29. Hubble RP, Naughton G, Silburn PA, Cole MH. Trunk exercises improve gait symmetry in parkinson disease: A blind phase II randomized controlled trial. Am J Phys Med Rehabil 2018;97:151-9. doi: 10.1097/PHM.0000000000000858.
30. de Almeida EJR, Ibrahim HJ, Chitolina Schetinger MR, de Andrade CM, Cardoso AM. Modulation of inflammatory mediators and microglial activation through physical exercise in Alzheimer's and Parkinson's diseases. Neurochem Res 2022;47:3221-40. doi: 10.1007/s11064-022-03713-x.
31. Alarcón TA, Presti-Silva SM, Simões APT, Ribeiro FM, Pires RGW. Molecular mechanisms underlying the neuroprotection of environmental enrichment in Parkinson's disease. Neural Regen Res 2023;18:1450-6. doi: 10.4103/1673-5374.360264.
32. Askar MH, Hussein AM, Al-Basiony SF, Meseha RK, Metias EF, Salama MM, et al. Effects of exercise and ferulic acid on alpha synuclein and neuroprotective heat shock protein 70 in an experimental model of Parkinsonism disease. CNS Neurol Disord Drug Targets 2019;18:156-69. doi: 10.2174/1871527317666180816095707.