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Original Article

Therapeutic effects of quercetin-loaded phytosome nanoparticles in a preclinical model of Parkinson's disease: The modulation by antioxidant pathways and BDNF expression

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ABSTRACT

Quercetin, one of the most abundant polyphenolic flavonoids, displays many health-promoting biological effects in many diseases. Quercetin-loaded phytosome nanoparticles (QLP) may improve antioxidant properties and decrease behavioral signs of Parkinson's due to its antioxidant properties. This study was conducted to assess the therapeutic effects of QLP for the treatment of Parkinson's in a rat model. A group of rats (n=10) did not receive Rotenone and was considered a healthy control (Cont). Another group was administered with Rotenone and did not receive any treatment and was considered to control the disease (Rotn). Other groups were administrated with Rotenone and treated with 50 mg/kg of and 100 mg/kg of body weight of QLP (QLP50 and QLP100). Behavioral responses of immobility time, retention latency and climbing and the activities of superoxide dismutase (SOD) and glutathione peroxidase (GPx) and also the expression of brain-derived neurotrophic factor (BDNF) were investigated 21 days after induction of disease. The results showed that induction of Parkinson increased immobility time (P=0.0001) and decreased retention latency (P=0.0001), climbing (P=0.0001), SOD (P=0.0001), GPx (P=0.0001) and BDNF (P=0.0001) compared with healthy controls. The results also showed the treatment with QLP, especially at a higher dose of 100 mg/kg, decreased immobility time (P=0.0001) and increased retention latency (P<0.05), climbing (P<0.05), SOD (P<0.05), GPx (P<0.05), and BDNF (P<0.05), compared with those in Rotn group. In conclusion, QLP decreased the negative effects of Parkinson's by modulation antioxidant enzymes and the concentration of BDNF.

KEYWORDS: Antioxidant, BDNF, Parkinson, Phytosome, Preclinical model, Quercetin

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1. Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder characterized by the progressive death of dopaminergic neurons in the substantia nigra pars compacta (SNc). PD is a multifactorial disorder, with several different factors being suggested to play a synergistic pathophysiological role, including oxidative stress, autophagy, underlying pro-inflammatory events and neurotransmitters abnormalities [1]. Parkinson's disease is the second most common neurodegenerative disease with a global prevalence of more than 6 million individuals. This number corresponds to a 2.5-fold increase in prevalence over the past generation, making Parkinson's disease one of the leading causes of neurological disability [2]. The clinical hallmark of Parkinson's disease is a motor syndrome characterized by bradykinesia, rest tremor, and rigidity as well as changes in posture and gait. The motor disturbances cause progressive disability with impairment in activities of daily living and reduced quality of life. [3]. Although Parkinson's disease is defined as a movement disorder, it is associated with a variety of non-motor symptoms (NMS) in virtually all patients, including hyposmia, constipation, urinary dysfunction, orthostatic hypotension, memory loss, depression, pain, autoimmune, cognitive, tremor, behavioral and sleep disturbances [4]. Numerous factors can have effects on the pathogenesis of Parkinson's. It is commonly known with signs such as the progressive degeneration of dopaminergic neurons [5]. Dopaminergic neurons are prone to oxidative damage owing to their dopamine's inherent metabolism, that are oxidized and produce reactive oxygen species that result in cellular oxidative stress [6]. The role of oxidative stress in the pathogenesis of disorder has been known [7]. A growing body of evidence suggests that BDNF is involved in the pathophysiology not only of mood disorders but also of other neuropsychiatric and neurodegenerative disorders. Brain-derived neurotrophic factor (BDNF) belongs to neurotrophins (NTs) a family of proteins that support the function of the central nervous system (CNS). Brain-derived neurotrophic factor (BDNF) has a major role in the progression of the nervous system via influencing cell differentiation, neuronal development, growth and survival, neurogenesis, synaptogenesis, and synaptic plasticity [8]. Previously reported that Brain-derived neurotrophic factor (BDNF) promotes neuroprotection and neurodegeneration. In animal models of Parkinson's disease (PD), BDNF enhances the survival of dopaminergic neurons, improves dopaminergic neurotransmission and motor performance [9]. Current research focuses on the evidence that increasing BDNF level due to gene modulation or physical exercise has a neuroprotective effect and could be considered as adjunctive therapy in PD. Antioxidant response element impact on Parkinson's disease, there are required to supplement and the treatment with antioxidants. One of the important component Quercetin is a polyphenolic flavonoid that is significantly present in some plant sources such as onions, cherries, tea and red wine [10]. Studies have also shown that Quercetin prevents from some diseases such as osteoporosis, cancer, tumors, lung and cardiovascular diseases due to its antioxidant properties [11]. It exhibits a strong antioxidant activity due to its high solubility and bioavailability that forms a complex or a combination for forming some novel preparations used for human health care [12, 13]. However, it has limitations for bioavailability. For improving bioavailability, Quercetin is commonly loaded into phytosome nanoparticles with the help of the thin film hydration method [14]. Our hypothesis was quercetin-loaded phytosome nanoparticles (QLP) may improve antioxidant properties and decrease behavioral signs of Parkinson's due to its antioxidant properties. This study was conducted to assess the therapeutic effects of QLP for the treatment of Parkinson's in a rat model by assessing antioxidant responses, antioxidant properties and the expression of BDNF.

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2. Materials and Methods

2.1. The induction of Parkinson and grouping

The used protocols for animals were in agreement with recommendations presented by Ethical Committee of International Center for Neuroscience Research (GE-ICNR-2021-10049). To induce disease, the rats were anaesthetized with the help of administration of ketamine and xylazine and then administrated with Rotenone as recommended by others [15]. A group of rats (n=10) did not receive Rotenone and considered as control (Cont). Another group was administrated with Rotenone and did not receive any treatment and considered as control with disease (Rotn). Other groups were administrated with Rotenone and treated with 50 mg/kg of and 100 mg/kg of body weight of QLP (QLP50 and QLP100). QLP was prepared as reported by others with the help of thin film hydration method using molar ratio of Quercetin, phosphatidyl choline and cholesterol (1:2:0.2) [14]. A recovery period of 5h was considered after the administration. For decreasing damages, the animals were individually kept in cages and treated for 4 days. All the administrations were performed by intragastric route, twice/week and for 3 weeks. Quercetin was prepared from Sigma-Aldrich (GmbH, Germany) Company and Phosphatidyl choline was prepared from Lipoid Company (Ludwigshafen, Germany).

2.2. Behavioral tests

The forced swim test (FST) evaluates active behavior consisting of ascending guided forepaw movements along the side of the swim compartment in rodents, as well as climbing behavior, and is the most common test used to assess a depressive-like phenotype. Rats were put in the cylinder filled with water (water temperature 25 °C) and video was captured for 6 min and then analyzed offline. At the end of the examination, the animals were removed from the container, dried with towels, and kept warm under a lamp in their home cages. The forced swimming test (FST) was conducted as a behavioral test as reported by others [16] with the help of a glass cylinder 20 cm × 90 cm (diameter × height) filled with water to a height of 75 cm. Hippocampal-dependent memory deficit was considered as another test and conducted as reported by others [17] with the help of an apparatus (25 × 25 × 25 cm).

2.3. The assessment of antioxidants and the expression of BDNF in the brain

After 3 weeks, the animals (n=5) in each group were sacrificed with the help of cervical decapitation; the striatum and substantia nigra were separated and placed on ice. The tissue homogenates were centrifuged at 10,000 × g for 15 min. Protein concentration was assessed based on previous protocols [18]. Tissue lipid peroxides was also assessed by others [19]. Superoxide dismutase (SOD) activity was assessed based on previous protocols [20]. Glutathione peroxidase (GPx) activity was investigated based on other reports [21]. An aliquot of samples was used for the investigation of the expression of genes of brain-derived neurotrophic factor (BDNF). RNA was extracted, and cDNA was amplified. The amplification of amplified PCR product was performed on 1.5% agarose gel and the ladder marker of 100 bp (100-1000 bp) as the standard. Primers were as follows; BDNF; forward (5′-TTTGATGAGACCGGGTTCC-3′) and reverse (5′-AGGATGGTCATCACTCTTCTCA-3′), and β-actin forward (5′- TCCGTAAAGACCTCTATGCCA-3′) and reverse (5′- CAGCTCAGTAACAGTCCGCC-3′).

2.4. Statistical analysis

The data were analyzed for normality and because the data were normal, a one-way ANOVA in SPSS software (Version 23) was used and $P< 0.05$ was considered as significant. Graphs were illustrated by Graph Pad Prism Software (version 6.07). The data were reported as mean ± SD.

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3. Results

Figure 1 depicts the effects of QLP on behavioral responses in rats with Parkinson's. The results showed that induction of Parkinson's increased immobility time (P=0.0001) and decreased retention latency (P=0.0001) and climbing (P=0.0001) compared with healthy controls (Cont). It means that Parkinson's could have effects on behavioral responses. The results also showed the treatment with QLP, especially in a higher dose of 100 mg/kg, decreased immobility time (P<0.05) and, increased retention latency (P<0.05) and climbing (P<0.05). It means the protective effects of QLP, especially in higher concentrations.

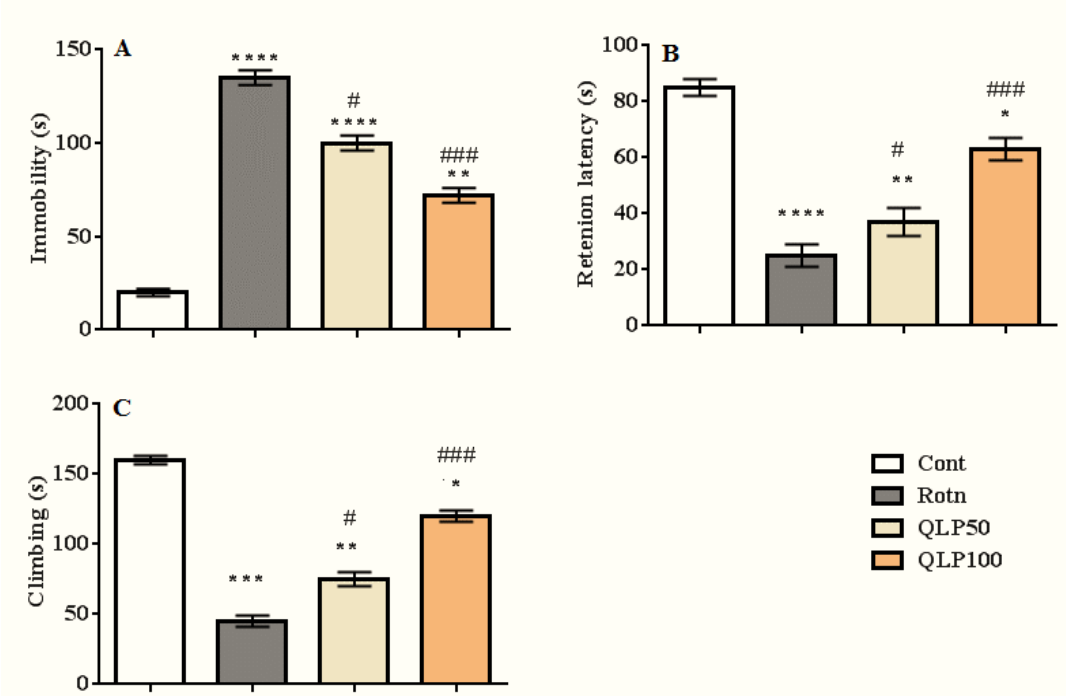

Figure 1. The effects of QLP on behavioral responses in rats with Parkinson's. Control healthy (Cont), Control Parkinson (Rotn) and the patient rats treated with 50 mg/kg of and 100 mg/kg of body weight of QLP (QLP50 and QLP100). (A) Immobility is significantly higher in Rotn QlP treatment prevented (B) Retention latency lower in Rotn (C) Climbing significantly increased in QlP as compared to other groups. Data are represented as mean ± SEM; *p < 0.05; **p < 0.01, ***p < 0.001; two-way ANOVA analysis.

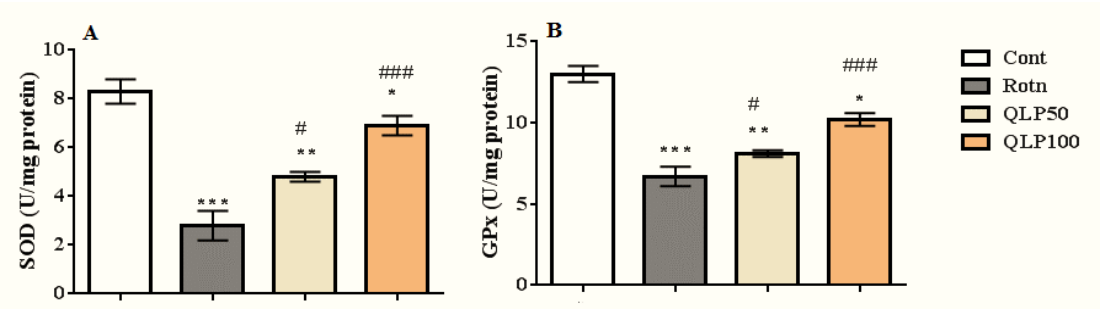

Figure 2. The effects of QLP on antioxidant parameters in rats with Parkinson's. Control healthy (Cont), Control Parkinson (Rotn) and the patient rats treated with 50 mg/kg of and 100 mg/kg of body weight of QLP (QLP50 and QLP100). Superscripts *, ** and *** show significant differences between other groups. Data are represented as mean ± SEM; *p < 0.05; **p < 0.01, ***p < 0.001; two-way ANOVA analysis.

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Figure 2 illustrates the results for the effects of QLP on antioxidant parameters in rats with Parkinson's. The induction of Parkinson decreased the concentrations of GPx (P=0.0001) and SOD (P=0.0001) compared with healthy controls (Cont). It means that Parkinson's could have effects on antioxidant enzymes. The results also showed the treatment with QLP, especially in a higher dose of 100 mg/kg, increased the concentrations of GPx (P=0.0001) and SOD (P=0.0001) Compared with those in the Rotn group. It means the protective role of QLP in the antioxidant system. Figure 3 shows the results for the effects of QLP on the expression of BDNF in rats with Parkinson's. The induction of Parkinson's decreased the expression of BDNF (P=0.0001) compared with healthy controls (Cont). This means that Parkinson's could have adverse effects on the expression of BDNF. The results also showed the treatment with QLP, especially at a higher dose of 100 mg/kg, increased the expression of BDNF (P=0.0001) Compared with those in the Rotn group. It means the protective role of QLP on the expression of BDNF.

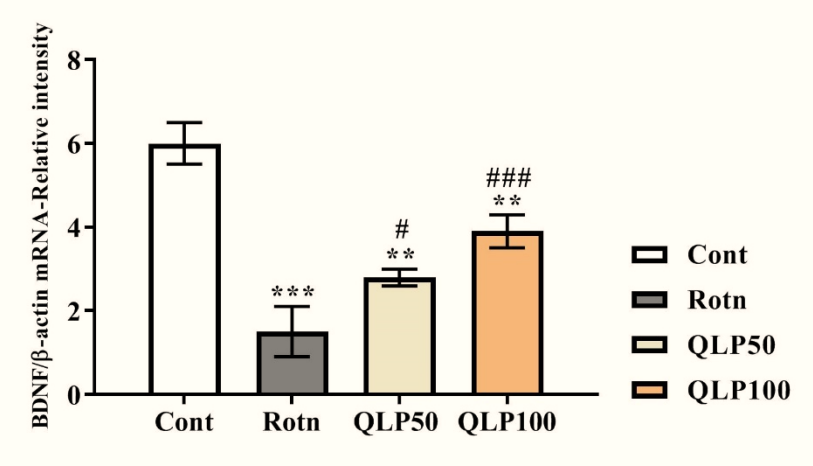

Figure 3. The effects of QLP on the expression of BDNF in rats with Parkinson's. Control healthy (Cont), Control Parkinson (Rotn) and the patient rats treated with 50 mg/kg of and 100 mg/kg of body weight of QLP (QLP50 and QLP100). Superscripts *, ** and *** show significant differences between other groups. Data are represented as mean ± SEM; *p < 0.05; **p < 0.01, ***p < 0.001; two-way ANOVA analysis.

4. Discussion

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by the death of dopaminergic neurons in the substantia nigra pars compacta., oxidative stress and perturbed protein homeostasis increase manifestations in older adults [22]. PD is characterized by the gradual loss of dopaminergic neurons in the SN within the midbrain, which is usually accompanied by the accumulation of Lewy bodies in neuronal cell bodies and Lewy neurites in neuronal processes, and α-synuclein is an important protein component of Lewy bodies [17]. The results showed that Parkinson's had negative effects on behavioral responses. The FST has been used for assessing the behavioral responses in animal models [16]. Several studies have reported the negative effects of Parkinson's on behavioral responses in terms of FST [16, 23, 24]. The mechanism of Parkinson's behavioral responses could be attributed to its effects on serotonin because the disorder reduces serotonin levels and increases the sensitivity of patients to depression [16]. The results showed the treatment with QLP improved behavioral responses. The results are in agreement with other studies on the effects of Quercetin on behavioral responses [25, 26]. There are studies linking the relationship between antioxidants and behavioral responses [27, 28]. Our findings showed QLP a natural flavonoid, has multiple pharmacological activities. However, it has not been established whether QLP can protect against dopaminergic neuron death by inhibiting ferroptosis. In this study, we the effects were also explored using PD mouse models. as an antioxidant in a system based on findings for SOD and GPx. Seemingly, QLP prevents the oxidation of serotonin and tryptophan in the brain

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site and improves behavioral responses. Our findings showed negative effects of the disorder on latency time, which is in agreement with other studies [17]. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophic factor family and promotes neuroprotection and neuroregeneration. Changed levels of BDNF in the circulation and central nervous system (CNS) have been shown to be associated with the pathogenesis of neurodegenerative diseases, including PD [21]. Brain-derived neurotrophic factor (BDNF) and its receptors are widely distributed throughout the central nervous system, which can promote the survival and growth of neurons and protect neurons. Other possible mechanisms for the effects of the disorder on behavioral responses could be attributed to the concentration of BDNF. It was reported a close relation between the expression of BDNF and locomotor activities [15] was approved in the current study. Parkinson's disease reduced the activities of antioxidant response element BDNF, which could be attributed to the effects of rotenone on the antioxidant system. Rotenone works as an inhibitor for mitochondrial complex I activity in the brain region [29] that increases oxidants and reduces antioxidants [30, 31]. In this study, both enzymes were antioxidants and may scavenge free radicals in the brain region. The results for the effects of disease on the antioxidant system are in agreement with other studies [15, 32, 33]. QLP is an antioxidant and inhibits oxidation [12, 13]. In sum, QLP works as an antioxidant and inhibits the depletion of other antioxidants. Higher concentrations of QLP may supply higher antioxidants in the brain, which results in higher concentrations of GPx and SOD. Our research findings confirmed that Parkinson's decreases the expression of BDNF, which is related to the previous studies [9, 15, 34]. BDNF helps to increase the survival of dopaminergic neurons and dopaminergic neurotransmission and improves motor performance [9]. QLP increased the expression of BDNF which is in agreement with other studies [35, 36]. The mechanism of QLP in the increase of BDNF is not still elucidated. Other studies reported that plant derivations induce phosphorylation of cAMP and increase the expression of BDNF [37].

5. Conclusions

In conclusion, Parkinson had hallmark impacts on behavioral responses of immobility time, retention latency and climbing and the activities of SOD and GPx and also the expression of BDNF. However, the treatment with QLP decreased the negative effects of Parkinson's on behavioral responses, antioxidant responses and concentrations of BDNF. In sum, QLP can be used for the prevention and treatment of Parkinson's after confirmation by clinical studies on humans. This study provides an important reference for explaining the potential mechanisms underlying PD pathogenesis and developing new therapeutic targets.

Author Contributions: All authors contributed toward data analysis, drafting, and revising the paper and agreed to be responsible for all the aspects of this work. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare that there are no competing interests in this work.

References:

1. Bloem BR, Okun MS, Klein C. Parkinson's disease. The Lancet. 2021;397(10291):2284-303. https://doi.org/10.1016/S0140-6736(21)00218-X
2. Tolosa E, Garrido A, Scholz SW, Poewe W. Challenges in the diagnosis of Parkinson's disease. The Lancet Neurology. 2021;20(5):385-97. https://doi.org/10.1016/S1474-4422(21)00030-2
3. Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. The Lancet Neurology. 2020;19(2):170-8. https://doi.org/10.1016/S1474-4422(19)30287-X
4. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. Jama. 2020;323(6):548-60. https://doi.org/10.1001/jama.2019.22360

[DOI: 10.58209/neurolife.2023.31]

5. Duarte-Jurado AP, Gopar-Cuevas Y, Saucedo-Cardenas O, Loera-Arias MdJ, Montes-de-Oca-Luna R, Garcia-Garcia A, et al. Antioxidant therapeutics in Parkinson's disease: current challenges and opportunities. Antioxidants. 2021;10(3):453. https://doi.org/10.3390/antiox10030453
6. Hemmati-Dinarvand M, Valilo M, Kalantary-Charvadeh A, Sani MA, Kargar R, Safari H, et al. Oxidative stress and Parkinson's disease: conflict of oxidant-antioxidant systems. Neuroscience Letters. 2019;709:134296. https://doi.org/10.1016/j.neulet.2019.134296
7. He J, Zhu G, Wang G, Zhang F. Oxidative stress and neuroinflammation potentiate each other to promote progression of dopamine neurodegeneration. Oxidative medicine and cellular longevity. 2020;2020. https://doi.org/10.1155/2020/6137521
8. Lu B, Nagappan G, Lu Y. BDNF and synaptic plasticity, cognitive function, and dysfunction. Neurotrophic factors. 2014:223-50. https://doi.org/10.1007/978-3-642-45106-5_9
9. Palasz E, Wysocka A, Gasiorowska A, Chalimoniuk M, Niewiadomski W, Niewiadomska G. BDNF as a promising therapeutic agent in Parkinson's disease. International journal of molecular sciences. 2020;21(3):1170. https://doi.org/10.3390/ijms21031170
10. Almeida AF, Borge GIA, Piskula M, Tudose A, Tudoreanu L, Valentová K, et al. Bioavailability of quercetin in humans with a focus on interindividual variation. Comprehensive reviews in food science and food safety. 2018;17(3):714-31. https://doi.org/10.1111/1541-4337.12342
11. Boots AW, Haenen GR, Bast A. Health effects of quercetin: from antioxidant to nutraceutical. European journal of pharmacology. 2008;585(2-3):325-37. https://doi.org/10.1016/j.ejphar.2008.03.008
12. Xie X, Shen Q, Cao L, Chen Y, Ma L, Xiao Q, et al. Depression caused by long-term stress regulates premature aging and is possibly associated with disruption of circadian rhythms in mice. Physiology & behavior. 2019;199:100-10. https://doi.org/10.1016/j.physbeh.2018.11.011
13. Aytac Z, Kusku SI, Durgun E, Uyar T. Quercetin/β-cyclodextrin inclusion complex embedded nanofibres: Slow release and high solubility. Food chemistry. 2016;197:864-71. https://doi.org/10.1016/j.foodchem.2015.11.051
14. Abd El-Fattah AI, Fathy MM, Ali ZY, El-Garawany AE-RA, Mohamed EK. Enhanced therapeutic benefit of quercetin-loaded phytosome nanoparticles in ovariectomized rats. Chemico-Biological Interactions. 2017;271:30-8. https://doi.org/10.1016/j.cbi.2017.04.026
15. Anusha C, Sumathi T, Joseph LD. Protective role of apigenin on rotenone induced rat model of Parkinson's disease: Suppression of neuroinflammation and oxidative stress mediated apoptosis. Chemico-biological interactions. 2017;269:67-79. https://doi.org/10.1016/j.cbi.2017.03.016
16. Shin M-S, Kim T-W, Lee J-M, Sung Y-H, Lim B-V. Treadmill exercise alleviates depressive symptoms in rotenone-induced Parkinson disease rats. Journal of exercise rehabilitation. 2017;13(2):124. https://doi.org/10.12965/jer.1734966.483
17. Hadadianpour Z, Fatehi F, Ayoobi F, Kaeidi A, Shamsizadeh A, Fatemi I. The effect of orexin-A on motor and cognitive functions in a rat model of Parkinson's disease. Neurological research. 2017;39(9):845-51. https://doi.org/10.1080/01616412.2017.1352185
18. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. Journal of biological chemistry. 1951;193:265-75. https://doi.org/10.1016/S0021-9258(19)52451-6
19. Devasagayam TP, Tarachand U. Decreased lipid peroxidation in the rat kidney during gestation. Biochemical and biophysical research communications. 1987;145(1):134-8. https://doi.org/10.1016/0006-291X(87)91297-6
20. Marklund S, Marklund G. Involvement of the superoxide anion radical in the autoxidation of pyrogallol and a convenient assay for superoxide dismutase. European journal of biochemistry. 1974;47(3):469-74. https://doi.org/10.1111/j.1432-1033.1974.tb03714.x
21. Rotruck J, Pope A, Ganther HE, Swanson A, Hafeman DG, Hoekstra W. Selenium: biochemical role as a component of glutathione peroxidase. Science. 1973;179(4073):588-90. https://doi.org/10.1126/science.179.4073.588

[DOI: 10.58209/neurolife.2023.31]

22. Raza C, Anjum R. Parkinson's disease: Mechanisms, translational models and management strategies. Life sciences. 2019;226:77-90. https://doi.org/10.1016/j.lfs.2019.03.057
23. Luo XF, Zhang BL, Li JC, Yang YY, Sun YF, Zhao H. Lateral habenula as a link between dopaminergic and serotonergic systems contributes to depressive symptoms in Parkinson's disease. Brain research bulletin. 2015;110:40-6. https://doi.org/10.1016/j.brainresbull.2014.11.006
24. Dalla Vecchia D, Kanazawa LKS, Wendler E, Hocayen PdAS, Vital MABF, Takahashi RN, et al. Ketamine reversed short-term memory impairment and depressive-like behavior in animal model of Parkinson's disease. Brain Research Bulletin. 2021;168:63-73.
https://doi.org/10.1016/j.brainresbull.2020.12.011
25. Mzhelskaya KV, Shipelin VA, Shumakova AA, Musaeva AD, Soto JS, Riger NA, et al. Effects of quercetin on the neuromotor function and behavioral responses of Wistar and Zucker rats fed a high-fat and high-carbohydrate diet. Behavioural Brain Research. 2020;378:112270.
https://doi.org/10.1016/j.bbr.2019.112270
26. Silvestro S, Bramanti P, Mazzon E. Role of quercetin in depressive-like behaviors: Findings from animal models. Applied Sciences. 2021;11(15):7116. https://doi.org/10.3390/app11157116
27. Huang Q, Liu H, Suzuki K, Ma S, Liu C. Linking what we eat to our mood: a review of diet, dietary antioxidants, and depression. Antioxidants. 2019;8(9):376.
https://doi.org/10.3390/antiox8090376
28. Vaváková M, Ďuračková Z, Trebatická J. Markers of oxidative stress and neuroprogression in depression disorder. Oxidative Medicine and Cellular Longevity. 2015;2015.
https://doi.org/10.1155/2015/898393
29. Xiong N, Huang J, Zhang Z, Zhang Z, Xiong J, Liu X, et al. Stereotaxical infusion of rotenone: a reliable rodent model for Parkinson's disease. PloS one. 2009;4(11):e7878.
https://doi.org/10.1371/journal.pone.0007878
30. Sherer TB, Richardson JR, Testa CM, Seo BB, Panov AV, Yagi T, et al. Mechanism of toxicity of pesticides acting at complex I: relevance to environmental etiologies of Parkinson's disease. Journal of neurochemistry. 2007;100(6):1469-79. https://doi.org/10.1111/j.1471-4159.2006.04333.x
31. Marella M, Seo BB, Nakamaru-Ogiso E, Greenamyre JT, Matsuno-Yagi A, Yagi T. Protection by the NDI1 gene against neurodegeneration in a rotenone rat model of Parkinson's disease. PLoS One. 2008;3(1):e1433. https://doi.org/10.1371/journal.pone.0001433
32. Khan Z, Ali SA. Oxidative stress-related biomarkers in Parkinson's disease: A systematic review and meta-analysis. Iranian journal of neurology. 2018;17(3):137.
https://doi.org/10.18502/ijnl.v17i3.373
33. Romuk EB, Szczurek W, Oleś M, Gabrysiak A, Skowron M, Nowak P, et al. The evaluation of the changes in enzymatic antioxidant reserves and lipid peroxidation in chosen parts of the brain in an animal model of Parkinson disease. Advances in Clinical and Experimental Medicine. 2017;26(6):953-9.
https://doi.org/10.17219/acem/63999
34. Rahmani F, Saghazadeh A, Rahmani M, Teixeira AL, Rezaei N, Aghamollaii V, et al. Plasma levels of brain-derived neurotrophic factor in patients with Parkinson disease: a systematic review and meta-analysis. Brain research. 2019;1704:127-36. https://doi.org/10.1016/j.brainres.2018.10.006
35. Fang K, Li H-R, Chen X-X, Gao X-R, Huang L-L, Du A-Q, et al. Quercetin alleviates LPS-induced depression-like behavior in rats via regulating BDNF-related imbalance of Copine 6 and TREM1/2 in the hippocampus and PFC. Frontiers in pharmacology. 2020;10:1544. https://doi.org/10.3389/fphar.2019.01544
36. Ma Z-X, Zhang R-Y, Rui W-J, Wang Z-Q, Feng X. Quercetin alleviates chronic unpredictable mild stress-induced depressive-like behaviors by promoting adult hippocampal neurogenesis via FoxG1/CREB/BDNF signaling pathway. Behavioural Brain Research. 2021;406:113245. https://doi.org/10.1016/j.bbr.2021.113245
37. Sharma P, Kumar A, Singh D. Dietary flavonoids interaction with CREB-BDNF pathway: an unconventional approach for comprehensive management of epilepsy. Current neuropharmacology. 2019;17(12):1158-75. https://doi.org/10.2174/1570159X17666190809165549

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