

Effects of Native Iranian Probiotic Mix on Serum TNF- α Levels and Anxiety-like Behavior in 6-OHDA-Induced Parkinsonian Rats

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ABSTRACT

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons and the presence of both motor and non-motor symptoms. Recent studies suggest that the gut-brain axis and probiotics play important roles in modulating neuroinflammation and behavioral alterations in PD. This study aimed to investigate the effects of an indigenous Iranian probiotic mixture on anxiety-like behaviors and serum TNF- α levels in a 6-hydroxydopamine (6-OHDA) rat model of Parkinson's disease. Fifteen adult male Wistar rats were randomly divided into three groups: control, 6-OHDA + saline, and 6-OHDA + probiotics. Parkinsonism was induced by stereotaxic injection of 6-OHDA (10 μ g in 2 μ L saline with 0.02% ascorbic acid) into the right striatum. The probiotic mixture ($\sim 10^9$ CFU/mL; 1 mL/day) was administered orally for 21 days. Behavioral tests, including apomorphine-induced rotation, elevated plus maze, forced swim test, and cylinder test, were performed. Serum TNF- α levels were measured using ELISA. Probiotic supplementation significantly reduced motor asymmetry and improved anxiety- and depressive-like behaviors compared with the Parkinsonian group ($p < 0.01$). Serum TNF- α concentrations also decreased markedly in the probiotic-treated rats, indicating anti-inflammatory effects. Indigenous Iranian probiotics exhibited neuroprotective and anti-inflammatory properties in the PD model, suggesting their potential as safe, complementary treatments for managing both motor and non-motor symptoms of Parkinson's disease. The use of a combination of indigenous Iranian probiotic strains, each possessing unique biological properties, may represent an advantage over previous studies that investigated only one or a limited number of probiotic species.

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Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting over 10 million people worldwide (Bloem *et al.*, 2021). It is characterized by progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to striatal dopamine depletion and motor dysfunctions such as tremor, bradykinesia,

rigidity, and postural instability. Non-motor symptoms, including anxiety, depression, cognitive impairment, and sleep disturbances, often emerge before motor signs and greatly impair quality of life (Kalia *et al.*, 2015).

The etiology of PD is multifactorial, involving genetic predisposition, environmental toxins, mitochondrial dysfunction, oxidative stress, and chronic inflammation (Schapira *et al.*, 2017).



Among these, oxidative stress plays a central role; excessive reactive oxygen species (ROS) damage cellular macromolecules, leading to neuronal death (Blesa *et al.*, 2022). Experimentally, 6-hydroxydopamine (6-OHDA) reproduces PD pathology by selectively destroying dopaminergic neurons through oxidative mechanisms (Ungerstedt, 1971).

In recent years, the gut-brain axis has gained attention as a key player in neurodegenerative diseases, including PD (Cryan *et al.*, 2019). This bidirectional communication between the gastrointestinal tract and the central nervous system is mediated by neural, immune, and endocrine pathways. Gut microbiota influence brain function by regulating neurotransmitters, immune mediators, and short-chain fatty acids (Foster *et al.*, 2017). Altered gut microbial composition (dysbiosis) has been consistently reported in PD patients (Magistrelli *et al.*, 2024). Dysbiosis promotes intestinal permeability and systemic inflammation, allowing pro-inflammatory molecules such as lipopolysaccharides to reach the brain and exacerbate neuroinflammation (Mulak *et al.*, 2015). Gastrointestinal dysfunctions, notably constipation, often precede motor symptoms, suggesting that gut pathology may initiate or accelerate PD progression (Sampson *et al.*, 2016). Probiotics, defined as live microorganisms that provide health benefits when administered in adequate amounts, can modulate gut-brain communication (Hill *et al.*, 2014). They restore microbial balance, enhance intestinal barrier integrity, produce neuroactive metabolites, and reduce systemic inflammation (Ouweland *et al.*, 2002). Several strains, including *Lactobacillus rhamnosus*, *L. acidophilus*, *Bifidobacterium longum*, and *Bacillus coagulans*, have shown anxiolytic, antidepressant, and cognitive-enhancing properties in preclinical and clinical studies (Bravo *et al.*, 2011; Wang *et al.*, 2016). In PD models, probiotic administration has been reported to mitigate motor impairments, reduce oxidative stress, and protect dopaminergic neurons (Heydari *et al.*, 2025).

Neuroinflammation, driven by activated microglia, is a hallmark of PD. Among pro-inflammatory mediators, tumor necrosis factor- α (TNF- α) plays a central role (McCoy *et al.*, 2008). While TNF- α normally regulates immune

and apoptotic pathways, its chronic overproduction leads to neuronal injury and synaptic dysfunction (Bradley, 2008). Elevated TNF- α levels in the substantia nigra and cerebrospinal fluid of PD patients support its pathogenic role (Boka *et al.*, 1994). Blocking TNF- α signaling has been shown to protect dopaminergic neurons in animal models (Ferber *et al.*, 2004). Thus, TNF- α serves as both a biomarker and a potential therapeutic target in PD. Accumulating evidence indicates that probiotics can downregulate inflammatory cytokines, including TNF- α , in both peripheral and central systems. *Lactobacillus reuteri* and *Bifidobacterium longum* have been reported to lower TNF- α levels in models of stress and inflammation (Savignac *et al.*, 2013), while human trials show similar anti-inflammatory effects in metabolic and intestinal disorders (Furrie *et al.*, 2005).

Previous studies have demonstrated that indigenous Iranian probiotic strains, including *L. acidophilus*, *L. paracasei*, *L. rhamnosus*, *L. reuteri*, *B. coagulans*, and *B. longum*, possess antioxidant and immunomodulatory properties. Therefore, these strains offer a valuable model for exploring microbiota-based strategies against neuroinflammation. Although the neuroprotective potential of probiotics has been increasingly studied, their impact on non-motor symptoms and inflammatory biomarkers in PD remains poorly understood. Most existing research focuses on motor recovery, leaving behavioral aspects such as anxiety underexplored (Pont-Sunyer *et al.*, 2015). Moreover, the specific effects of indigenous probiotic combinations on TNF- α levels have not been evaluated in PD models. The present study aimed to assess the effects of an Iranian indigenous probiotic mixture on anxiety-like behavior and TNF- α levels in 6-OHDA-induced parkinsonian rats. By integrating behavioral testing with biochemical analysis, this study seeks to clarify the therapeutic potential of probiotics in modulating both neuroinflammatory and neuropsychiatric aspects of PD.

Materials and Methods

Animals and housing

Thirty-six adult male Wistar rats (200 \pm 20 g, 8-10 weeks old) were obtained from the Animal House

of Islamic Azad University, Tehran Central Branch. The animals were housed individually in standard polycarbonate cages (40× 25× 20 cm) with sterilized wood shavings as bedding. Environmental conditions were carefully controlled: A 12 h light/dark cycle (lights on at 7:00 a.m.), ambient temperature maintained at 22± 2 °C, and relative humidity at 55-65%. Rats had ad libitum access to standard rodent chow and filtered tap water. All animals were acclimatized to laboratory conditions for at least one week prior to experimentation.

Animal care and experimental protocols complied with the guidelines of the National Institutes of Health (NIH) for the care and use of laboratory animals (National Research Council, 2011) and were approved by the Institutional Ethics Committee of Islamic Azad University. Every effort was made to minimize animal suffering and reduce the number of animals used.

Experimental design and groups

The rats were randomly divided into three groups: Control group (Sham): Rats underwent no surgical procedure and received no oral gavage treatment. (n= 5); Parkinsonian group (6-OHDA + saline): Rats received unilateral intrastriatal injection of 6-hydroxydopamine (6-OHDA) and were subsequently administered normal saline by oral gavage for three weeks. (n= 5); Probiotic-treated Parkinsonian group (6-OHDA + probiotics): Rats received unilateral 6-OHDA lesions and were treated with a probiotic mixture by oral gavage daily for three weeks. (n= 5). This experimental design enabled comparison between healthy controls, parkinsonian rats without treatment, and parkinsonian rats receiving probiotic intervention.

Parkinsonism induction

Parkinsonism was induced by stereotaxic injection of 6-hydroxydopamine (6-OHDA), a dopaminergic neurotoxin. Rats were anesthetized with intraperitoneal ketamine (60 mg/kg) and xylazine (40 mg/kg), and anesthesia depth was verified by loss of pedal reflex. Each animal was positioned in a stereotaxic apparatus (Stoelting Co., USA), and the scalp was disinfected with povidone-iodine.

Using the bregma as a reference, a small burr hole was drilled, and 6-OHDA (10 µg in 2 µL saline

containing 0.02% ascorbic acid) was unilaterally injected into the right striatum at the following coordinates relative to bregma (Paxinos & Watson, 1998): AP -0.5 mm, ML +2.5 mm, DV -7.2 mm. The solution was infused at 0.5 µL/min using a 5 µL Hamilton microsyringe. After injection, the needle remained in place for 3 minutes to prevent backflow before slow withdrawal.

The incision was closed with sutures, and topical tetracycline ointment was applied to avoid infection. Rats recovered in a warmed chamber and were monitored daily. Sham-operated controls underwent the same procedure but received saline instead of 6-OHDA.

Probiotic preparation and administration

The probiotic mixture contained six indigenous Iranian strains: “*Lactobacillus acidophilus*, *Lactobacillus paracasei*, *Lactobacillus rhamnosus*, *Lactobacillus reuteri*, *Bacillus coagulans*, *Bifidobacterium longum*” (Probiotic code: IS-506). Each strain was cultured in de Man, Rogosa, and Sharpe (MRS) broth under anaerobic conditions at 37°C. The cultures were harvested during the logarithmic growth phase, washed twice with sterile phosphate-buffered saline (PBS), and adjusted to a final concentration of ~10⁹ CFU/mL. Equal volumes of each strain were mixed to prepare the probiotic cocktail fresh daily. Probiotic-treated rats received 1 mL of the mixture by oral gavage once daily for 21 consecutive days using a flexible gavage needle. Control and 6-OHDA + saline groups received 1 mL of sterile normal saline (0.9% NaCl) by gavage.

Apomorphine-induced rotation test

Two weeks post-surgery, rotational behavior was assessed to confirm successful lesioning. Rats were injected subcutaneously with apomorphine hydrochloride (0.5 mg/kg). Each animal was placed individually in a transparent cylindrical chamber (22 cm diameter × 26 cm height), and rotations were counted for 30 min. Net contralateral rotations (turns away from the lesioned side) were recorded. More than seven rotations per minute were considered indicative of successful parkinsonism induction (Ungerstedt, 1971).

Elevated plus maze

The plus maze (EPM) test was performed on day 22 to evaluate anxiety-like behavior. The apparatus consisted of two open arms (50× 10 cm), two closed arms (50× 10× 40 cm), and a central platform (10× 10 cm), elevated 50 cm above the floor. Each rat was placed at the center facing an open arm and allowed to explore for 5 min. The percentage of time spent in open arms (OAT%) and the percentage of open arm entries (OAE%) were calculated. Reduced exploration of open arms was interpreted as increased anxiety (Carobrez *et al.*, 2005).

TNF- α analysis

On day 25, animals were anesthetized with ketamine/xylazine, and blood samples were collected via cardiac puncture. Serum was separated by centrifugation at 3000 rpm for 15 min at 4°C and stored at -80°C until analysis. Serum TNF- α levels were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (ZellBio GmbH, Germany; Cat. No. ZB-10764C), following the manufacturer’s protocol. Briefly, standards and samples (40 μ L) were added to microplate wells pre-coated with TNF- α antibody, followed by horseradish peroxidase-conjugated secondary antibody. After incubation and washing, chromogenic substrates A and B were added, and the reaction was stopped with sulfuric acid. Absorbance was measured at 450 nm using a microplate reader (Biotek, USA). TNF- α concentrations were calculated from the standard curve and expressed in pg/mL.

Statistical analysis

Data were analyzed using GraphPad Prism version 10.4.1 (GraphPad Software, Boston, MA, USA). All results were expressed as mean± standard error of the mean (SEM). Normality was assessed using the Shapiro-Wilk test. Differences among groups were analyzed by one-way analysis of variance (ANOVA), followed by Tukey’s post hoc test for multiple comparisons. For non-parametric data, the Kruskal-Wallis test was used. A $p < 0.05$ was considered statistically significant.

Results

General observations

All animals recovered uneventfully from surgical procedures, and no mortality was recorded during

the course of the study. Rats in the 6-OHDA-lesioned groups exhibited typical parkinsonian features, including bradykinesia, rigidity, and reduced spontaneous activity, as compared to control rats. Body weight changes during the experimental period did not significantly differ between groups (data not shown).

Apomorphine-induced rotation test

Two weeks following the unilateral 6-OHDA lesion, apomorphine challenge induced robust contralateral rotations in lesioned rats, confirming successful establishment of the parkinsonian model. 6-OHDA + saline group: Rats displayed a mean net rotation of 8.9 ± 0.6 turns/min, which was significantly higher than the control group (0.7 ± 0.2 turns/min, $p < 0.001$); 6-OHDA + probiotic group: The mean rotation rate was 4.1 ± 0.5 turns/min, significantly lower than the saline group ($p < 0.01$), but still elevated compared to controls ($p < 0.05$). This finding suggests that probiotic supplementation partially mitigated dopaminergic neuron loss and improved striatal function (Fig. 1)

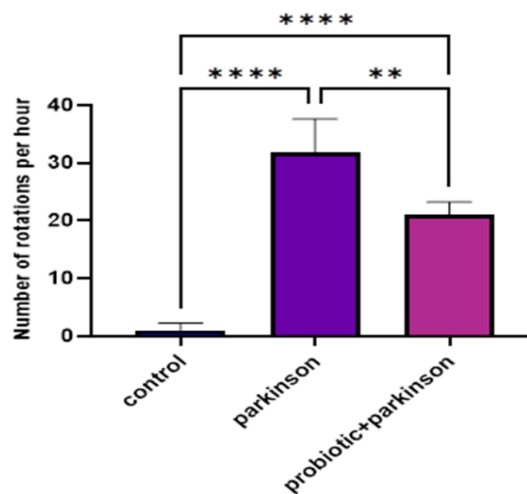


Fig. 1. Comparison of groups in the number of net rotations: Analysis of the results of the apomorphine rotation test showed that the number of net rotations in the Parkinson's group was significantly higher than the control group. Also, the number of net rotations in the pretreatment group was significantly reduced compared to the Parkinson's group. Results are expressed as mean± SEM (n=10). $p < 0.001$ **** is Parkinson's group compared to control and $p < 0.05$ probiotic compared to control group.

Elevated plus maze

The EPM test was conducted on day 22 to evaluate anxiety-like behavior. Control group: Rats spent $42.3\% \pm 3.1$ of the total test time in open arms and exhibited $38.7\% \pm 2.4$ of total entries into open arms; 6-OHDA + saline group: Rats demonstrated pronounced anxiety-like behavior, spending only $18.6\% \pm 2.9$ of the time in open arms ($p < 0.001$ vs. control) and showing $16.9\% \pm 2.7$ open arm entries; 6-OHDA + probiotic group: Probiotic-treated rats exhibited significant improvement, spending $33.8\% \pm 3.5$ of the time in open arms ($p < 0.01$ vs. saline group) and showing $29.4\% \pm 2.1$ open arm entries (Fig. 2 and 3). However, these values remained slightly lower than those of controls. These results indicate that probiotic treatment alleviated anxiety-like behaviors in parkinsonian rats.

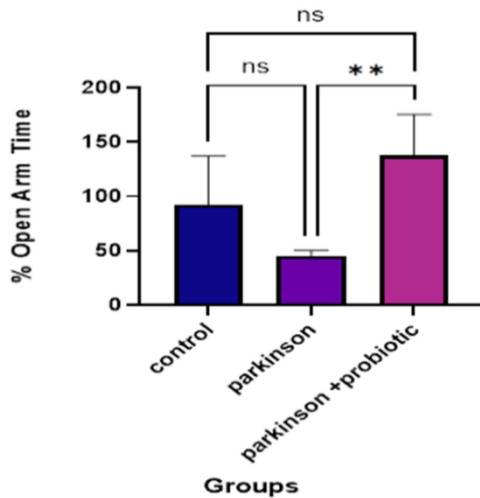


Fig. 2. Percentage of time spent in the open arms of the elevated plus maze among experimental groups. Data are presented as mean \pm SEM.

Serum TNF- α levels

ELISA analysis of serum samples revealed marked differences among groups. Control group: TNF- α concentration was 18.4 ± 2.3 pg/mL; 6-OHDA + saline group: Levels rose significantly to 42.7 ± 3.1 pg/mL ($p < 0.001$ vs. control), consistent with neuroinflammation; 6-OHDA + probiotic group: TNF- α concentration was significantly reduced to 24.9 ± 2.8 pg/mL ($p < 0.01$ vs. saline group), approaching control values (Fig. 4). These results indicate that probiotic treatment effectively attenuated systemic inflammation associated with parkinsonism.

Discussion

The present study investigated the effects of a mixture of indigenous Iranian probiotics on anxiety-like behavior and TNF- α levels in a rat model of Parkinson's disease (PD) induced by 6-hydroxydopamine (6-OHDA).

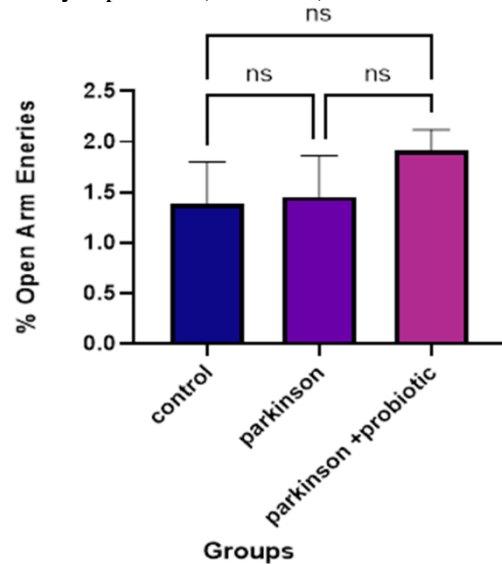


Fig. 3. Comparison of the percentage of times of entering the open arm between the control group and the Parkinson's group, as well as comparison of the Percentage of open-arm entries in the elevated plus maze among experimental groups. Each column represents the Mean \pm S.E.M.

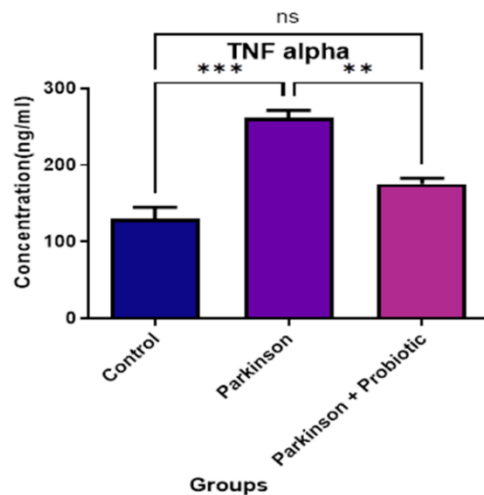


Fig. 4. Serum TNF- α concentrations in control, Parkinsonian, and probiotic-treated Parkinsonian rats. Data are presented as mean \pm SEM. *** $p < 0.001$ versus control; $p < 0.01$ versus Parkinsonian group.

Our results demonstrated that probiotic supplementation significantly ameliorated motor

deficits, reduced anxiety- and depressive-like behaviors, and decreased serum TNF- α levels compared with untreated parkinsonian rats. These findings highlight the therapeutic potential of probiotics as modulators of neuroinflammation and behavioral symptoms in PD.

Rotational behavior induced by apomorphine is a classical measure of dopaminergic neuron integrity. In this study, 6-OHDA-lesioned rats exhibited marked contralateral rotations, confirming substantial dopaminergic damage. Probiotic supplementation significantly reduced rotational asymmetry, suggesting partial neuroprotection. This result is consistent with the findings, which reported that oral administration of *Lactobacillus rhamnosus* and *Bifidobacterium animalis lactis* improved motor performance and protected dopaminergic neurons in a PD model. Similarly, Sun *et al.* (2018) observed that probiotics enhanced locomotor activity in MPTP-treated mice through modulation of gut microbiota and short-chain fatty acid production. Collectively, these studies support the hypothesis that probiotics may influence dopaminergic pathways indirectly via anti-inflammatory and antioxidant effects.

Non-motor symptoms such as anxiety and depression are among the most disabling aspects of PD, often preceding motor dysfunction (Pont-Sunyer *et al.*, 2015). In our study, 6-OHDA-lesioned rats displayed heightened anxiety in the elevated plus maze, consistent with previous reports. Probiotic-treated rats showed significant improvements in both assays, suggesting anxiolytic and antidepressant-like effects (Bravo *et al.*, 2011), and provided seminal evidence that ingestion of *Lactobacillus rhamnosus* regulated GABA receptor expression in the brain and reduced stress-induced corticosterone levels, thereby influencing emotional behavior. More recently, Wang *et al.* (2016) systematically reviewed clinical and preclinical studies, concluding that probiotics exert consistent anxiolytic and antidepressant effects across diverse models. The observed behavioral improvements in our study may thus be mediated by probiotics' capacity to modulate neurotransmitter systems, including serotonin and GABA, in addition to reducing systemic inflammation.

A key finding of our study was the significant reduction in serum TNF- α levels in probiotic-treated parkinsonian rats. TNF- α is a central mediator of neuroinflammation and has been implicated in dopaminergic neuronal death (McCoy *et al.*, 2008). Elevated TNF- α levels in PD patients and animal models have been consistently reported (Boka *et al.*, 1994). Our data confirm this pattern and demonstrate that probiotics can effectively downregulate TNF- α levels. The anti-inflammatory effects of probiotics have been widely documented. For example, they showed that probiotic supplementation decreased circulating TNF- α and C-reactive protein in patients with type 2 diabetes. In a preclinical model, Savignac *et al.* (2014) found that *Bifidobacterium longum* reduced stress-induced TNF- α elevations. These findings align with our results, supporting the hypothesis that probiotics suppress systemic inflammation, thereby alleviating neuroinflammatory cascades in PD.

Mechanistically, probiotics may reduce TNF- α via: 1- Restoration of gut barrier integrity, preventing endotoxin leakage; 2- Modulation of gut microbiota composition, favoring anti-inflammatory taxa; 3- Production of metabolites such as butyrate that inhibit NF- κ B signaling, a key regulator of TNF- α transcription (Chang *et al.*, 2014).

The dual improvement in both motor and non-motor symptoms observed in our study underscores the holistic benefits of probiotic intervention. Traditional dopaminergic therapies such as levodopa primarily address motor symptoms but have limited efficacy for anxiety and depression (Connolly *et al.*, 2014). Probiotics, by targeting systemic inflammation and gut-brain communication, may offer broader therapeutic benefits. This integrated approach resonates with the concept of the "microbiota-gut-brain axis," which posits that microbial metabolites influence central nervous system function through immune, endocrine, and neural pathways (Cryan *et al.*, 2019). By modulating this axis, probiotics may simultaneously improve motor control, emotional regulation, and immune balance.

Our findings have important translational implications. First, they suggest that probiotic supplementation could serve as a safe and

accessible adjunct therapy for PD patients, potentially reducing the reliance on high doses of dopaminergic drugs and mitigating associated side effects. Second, indigenous strains tailored to local populations may offer enhanced efficacy due to host-microbe coadaptation (Khalesi *et al.*, 2014). Finally, the reduction in TNF- α highlights a measurable biomarker that could be used to monitor probiotic efficacy in clinical trials.

Conclusion

The present study demonstrated that supplementation with a mixture of indigenous Iranian probiotics exerted significant beneficial effects in a rat model of Parkinson's disease induced by 6-hydroxydopamine. Probiotic treatment not only improved motor deficits, as evidenced by reduced apomorphine-induced rotations and attenuated forelimb asymmetry, but also alleviated non-motor symptoms including anxiety- and depressive-like behaviors. Moreover, probiotics effectively lowered serum TNF- α levels, highlighting their anti-inflammatory potential. These findings suggest that probiotics act through multiple mechanisms, including modulation of the gut-brain axis, restoration of microbial balance, reinforcement of intestinal barrier integrity, and downregulation of pro-inflammatory cytokines. Importantly, the dual improvement of both motor and non-motor features indicates that probiotics may represent a holistic therapeutic strategy, complementing conventional dopaminergic treatments. From a translational perspective, probiotics offer a safe, accessible, and cost-effective intervention with minimal side effects. However, clinical validation in human PD populations is essential before routine application. Future research should focus on long-term efficacy, optimal formulations, and individualized interventions based on gut microbiota profiles. In conclusion, our results provide preliminary evidence that indigenous probiotic mixtures can serve as promising adjunct therapies for Parkinson's disease, targeting both neuroinflammation and behavioral dysfunctions.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interests

The authors declare no conflict of interest.

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