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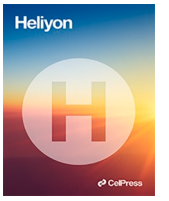

The dosage of curcumin to alleviate movement symptoms in a 6-hydroxydopamine-induced Parkinson's disease rat model

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ABSTRACT

Background: Curcumin is a natural compound with extensive pharmacological effects. This research is to verify the optimal dose and administration duration efficacy of curcumin in alleviating the movement symptoms of Parkinson's disease (PD).

Methods: Wistar rats were divided into six groups including control, model, levodopa treatment and low/middle/high (40/80/160 mg/kg/d) curcumin treatment groups. After stereotactic brain injection of 6-hydroxydopamine (6-OHDA), curcumin was given by intragastric administration for 2 weeks. To evaluate the drug effect, the rats received behavioral tests including apomorphine (APO)-induced rotation test, rotarod test and open field test. Then the rats were sacrificed and the brain slices including substantia nigra pars compacta (SNc) were used for immunofluorescence staining.

Results: After 6-OHDA injection, the model group showed typical movement symptoms including the severe APO-induced rotation to the healthy side, decreased latency in the rotarod with constant or accelerative mode, and decreased total distance and average speed in the open field test. In the results of immunofluorescence staining, the 6-OHDA induced a severe damage of dopaminergic neurons in SNc. The 160 mg/kg/d treatment of curcumin to intervene for 2 weeks alleviated most of the behavioral disorders but the 40/80 mg/kg/d treatment showed limitations. Then, we compared the effect of 1 week intervention to the 2 weeks with 160 mg/kg/d treatment of curcumin to intervene and results indicated that the treatment of 2 weeks could better alleviate the symptoms.

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Conclusions: Curcumin alleviated 6-OHDA-induced movement symptoms in a PD rat model. Additionally, the effect of curcumin against PD indicated dose and duration dependent and the intervention of 160 mg/kg/d for 2 weeks showed optimally therapeutic effect.

1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disease among the elderly, and it is principally characterized by movement deficits including tremors, bradykinesia, gait instability, and rigidity [1,2]. PD is defined by the loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) located in the midbrain, and is also associated with Lewy bodies, in which α-synuclein aggregates [3]. The main choice of clinical treatment is levodopa administration but is often accompanied by attention deficit hyperactivity disorder, decreased efficacy, end-of-dose phenomenon, and a series of complications after 5 years [4]. In addition to drug treatment, deep brain stimulation has been used in recent years to achieve satisfactory clinical results for PD. However, it is suitable for limited patients [5]. Furthermore, stem cell therapy for PD is a novel approach, but its clinical curative effect remains uncertain [6]. Thus, there are limited efficacy and a large number of side effects associated with commonly used first-line medicines and surgical treatment, which indicates that complementary and alternative therapies have become essential to ameliorate symptoms and increase the quality of life for PD patients.

Curcumin, a natural ingredient from the rhizomes of the plant turmeric (*Curcuma longa*), is a prominent polyphenolic compound with the preventive and therapeutic potential to cure neurodegenerative diseases [7]. Modern pharmacological studies have shown that curcumin exerts wide-ranging pharmacological effects, such as anti-inflammatory and anti-oxidant activities, mitochondrial protection, and neuroprotective functions [8,9]. Curcumin is beneficial for improving motor function because it enhances the flexibility of forelimbs [10] and the coordination of movement [11]. It was reported in another study that when the body was in a diseased state which showed movement symptoms due to the decrease in the number of TH-ositive neurons, curcumin can somewhat recover normal motor function; for example, it can do so by increasing movement duration [12]. Recent research has demonstrated that curcumin, as a neuroprotective compound, conferred significant protection to delay the progression of PD [13] by protecting dopaminergic neurons in the substantia nigra and reducing the accumulation of the toxic oligomer α-synuclein in cells [14]. Above all, the neuroprotective functions of curcumin have been preliminarily specific for therapeutic intervention in PD [15].

However, the ideal drug action time and the most effective dose of curcumin to mitigate movement symptoms of PD remain controversial. And in a large number of animal experiments, the intervention dose and period of curcumin are not uniform, which limits the reliability of the research conclusions. As a consequence, using a PD animal model to determine the most optimal dosage and intervention period for curcumin is a critical and necessary preclinical procedure. In this study, we used a recognized rat model with movement symptoms induced by 6-hydroxydopamine (6-OHDA) [16] to verify curcumin's protective efficacy at different doses and time gradients. Combined with the behavioral tests and histological evidences, we aimed to determine the onset time and optimal dose of curcumin against 6-OHDA damage.

2. Experimental procedure

2.1. Animals

For these experiments, 38 male Wistar rats (280–320 g, 6 weeks old) were purchased from Vital River Laboratories (Beijing, China) [Laboratory Animal Production License No. SCXK (Jing) 2016-0006]. The animals were randomly divided into six groups: control group; model group; low, medium, and high doses of curcumin groups; and levodopa group, and two animals died during surgery and 6 animals per group for the rest of the study. The rats were separately housed in cages that allowed free movement. Water was provided, and they received 10–20 g of feed every day. The rats were subject to controlled temperatures (22 ± 2 °C) with a 12-h light/dark cycle (lights on from 09:00 to 21:00 h) in a specific pathogen-free (SPF) barrier environment [Laboratory Animal Use License No. SYXK (Lu) 2017-0022]. Before the experiment, the rats were adapted to the new laboratory environment for 7 days. During the experiment, according to international animal experimentation standards, all measures were taken to alleviate the pain of the rats. The animal study was reviewed and approved by the Ethics Review Board of the Shandong University of Traditional Chinese Medicine [No. SDUTCM20210806007, 2021.8.1–2024.12.31].

2.2. 6-OHDA lesion

In this study, the rats were deeply anesthetized using isoflurane (3% for induction and 1.5–2.0% for maintenance). A small incision was made to expose the skull, and a cranial drill was used to create a hole in the left side of the skull at the following coordinates: AP: −2.16 mm, ML: −2.1 mm, and DV: 8.4/8.65 mm. Except for the rats in the control group, the rats were slowly injected with 3 μL of 6-OHDA (4 μg/μL, 1 μl/min; H4381, Sigma, USA) at two depths using a Hamilton syringe, according to our previous research [17]. The rats in the control group were injected with the same volume of saline. The syringe was maintained in the same position for more than 5 min to completely deliver the drug.

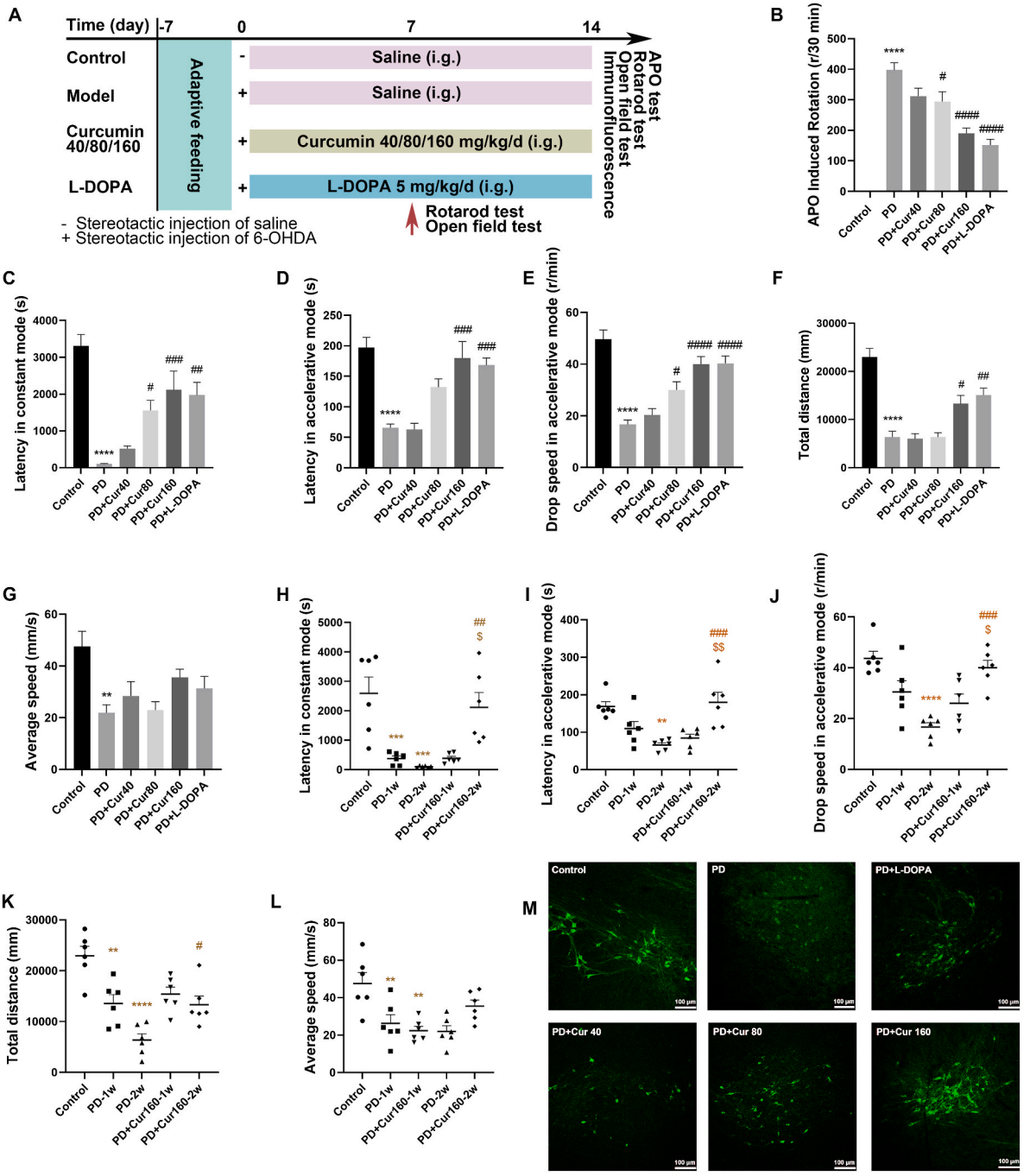

Fig. 1. Experiment schedule and results of the rat model of Parkinson's disease establishing, treatment and behavioral tests. Data are shown as mean ± standard error of the mean (SEM). (A) After 7 days of adaptive feeding, all rats were injected with 6-hydroxydopamine except for the control group by brain stereotaxic technique. Open field test and rotation experiment were performed at 1 week after operation. In the Curcumin group (including low, middle and high dose) and the L-DOPA group, all rats were performed by intragastric administration for 2 weeks. Then, all rats were carried on the APO induced rotation experiment, open field test, rotation experiment and the immunofluorescence of tyrosine hydroxylase 2 weeks after the administration. (B) The results of APO induced rotation after 2 weeks in intragastric administration, n = 6. (C) The latency of rotation in constant speed mode after 2 weeks of intragastric administration, n = 6. (D) The latency of rotation experiment in accelerative speed after 2 weeks of intragastric administration, n = 6. (E) The drop speed of rotation experiment in accelerative speed after 2 weeks of intragastric administration, n = 6. (F) The total distance of open field test, n = 6. (G) The average speed of open field test, n = 6. (H) The latency of rotation experiment in constant speed mode of rats in the high dose curcumin (160 mg/kg/d) group, n = 6. (I) The latency of rotation experiment in accelerative speed mode of rats in the high dose curcumin (160 mg/kg/d) group, n = 6. (J) The drop speed of rotation experiment in accelerative speed mode of rats in the high dose curcumin (160 mg/kg/d) group, n = 6. (K) The total distance of open field test of rats in the high dose curcumin

(160 mg/kg/d) group, n = 6. (L) The average speed of open field test of rats in the high dose curcumin (160 mg/kg/d) group, n = 6. (M) Representative figure of the immunofluorescence detection of rats in brain slices containing substantia nigra pars compacta in the control, model, L-DOPA and curcumin (40/80/160 mg/kg/d) group, n = 3. $^{**}p < 0.01$, $^{***}p < 0.001$, $^{****}p < 0.0001$ compared to the control group, $\#p < 0.05$, $\#\#p < 0.01$, $\#\#\#p < 0.001$, $\#\#\#\#p < 0.0001$ compared to the PD-2W group, $\$p < 0.05$, $\$\$p < 0.01$ compared the PD + Cur160-1W group.

2.3. Drug administration

After the surgery, the rats received intragastric administration at 9:00 every day for 14 consecutive days. The rats in the low-, medium-, and high-dose curcumin groups received 40 mg/kg, 80 mg/kg, and 160 mg/kg curcumin (C805205, Macklin, China, purity >98%), respectively, and the rats in the levodopa group were given 5 mg/kg levodopa (D807434, Macklin, China, purity >99%). All the drugs were dissolved in 0.9% saline. The rats in the control and model groups were given an equal volume of saline.

2.4. Behavioral analysis

Behavioral tests were performed between 10:00 and 18:00 according to the schedule in Fig. 1A. The apomorphine (APO)-induced healthy side rotation test was only performed on day 14.

In the APO test, rats was injected with apomorphine hydrochlorid (1 mg/kg, intramuscularly; PHR2621, Sigma, USA). The rotation number toward the healthy side (contralateral to the 6-OHDA injection side) was counted within 30 min [18].

In the rotarod test, all rats received a 3-day training period before the official test. Rats were placed on a rotating rod with a constant speed (10 r/min), and the rotation lasted for 60 s every day during the training. On the test day, the rats were placed on the rotating rod at a constant speed (20 r/min), and the running latency was recorded. Four hours later, the rats were tested in an accelerative mode (from 10 r/min to 70 r/min), and the speed at which the rats fell off the rod and the running latency were recorded within 300 s. Each rat was tested four times at 10-min intervals, and the mean value was used for statistical analysis.

In the open field test (OFT), each rat were placed in the centre area of a 100 × 100 cm square apparatus and allowed to move freely for 6 min. With the XR-Super Maze tracking system from Shanghai Xinsoft Information Technology (Shanghai, China), the total distance and the average speed of animals were calculated by analyzing the trajectory recorded by a camera.

2.5. Immunofluorescence staining

After the behavioral tests, rats were randomly selected for examination of SNc brain slices after fluorescence immunolabeling staining with tyrosine hydroxylase (TH) [19]. Rats were anesthetized with isoflurane, and heart perfusion with pre-chilled 1× PBS and 4% paraformaldehyde (PFA) was performed. Then, the brain was completely removed and stored at 4 °C. After 48 h of 4% PFA fixation and 4 days of 30% sugar water sedimentation treatment, SNc brain slices were cut (40 μm, −20 °C) using a freezing microtome (CM1950, Leica, Germany). 3 animals in each group were used for Immunofluorescence staining. After continuous coronal sectioning of the substantia nigra, one of every two brain slice was selected for staining, and at least 6 brain slices from each animal were used in this experiment. The key experimental steps included blocking the brain slices for 2 h with goat serum blocking solution, treating the brain slices with primary antibody (1:500 Tyrosine Hydroxylase E2L6M Rabbit mAb #58844, Cell Signaling Technology, USA), incubating at 4 °C for 12 h, then treating with the secondary antibody (1:500 Goat Anti-Rabbit IgG H&L Alexa Fluor® 488 pre-adsorbed, Abcam, UK), and incubating at room temperature for 2 h. The brain slices were mounted on slides and protected with a cover glass. Then, confocal laser scanning microscopy (LSM880+Fast Airyscan, Carl Zeiss AG, Germany) was performed to observe the fluorescence effect using a 20 × objective lens (scale bar = 100 μm), a filter with a hydrogen ion laser, and a 488-nm emission.

2.6. Statistical analysis

Data analysis was conducted using GraphPad Prism 9 (GraphPad Software, La Jolla, CA, USA). Statistics were performed using one-way analysis of variance (ANOVA), followed by Tukey's test after the Kolmogorov–Smirnov test for normality. Brown-Forsythe and Welch ANOVA were used when the square deviation was not equal. *P*-values less than 0.05 were considered statistically significant. The data are represented as the mean ± standard error.

3. Results

3.1. The typical motor symptoms of PD were induced by 6-OHDA

In all of the behavioral tests, the rats in the PD model group exhibited significant movement symptoms compared to the control group due to the damage caused by 6-OHDA. Two weeks after 6-OHDA injection, apomorphine (APO) induced severe contralateral rotation in 30 min ($p < 0.0001$) (Fig. 1B). As shown in Fig. 1C–E, the rats in the PD group exhibited shorter latencies in the rotation test, whether at a constant speed or in accelerative mode, and the rotation speed at which the rats droped from the rod in accelerative mode was lower ($p < 0.0001$). And in the OFT (Fig. 1F–G), rats in PD group showed lower total distance and decreased average speed ($p < 0.0001$) and ($p < 0.01$). This movement symptoms became significantly severe 2 weeks after the injection compared to the results 1 week after the surgery. It can be concluded from the results in Fig. 1H-L that in the 2-week test, the rats were only able to grip at lower

rotation speeds before they were forced to release the rod due to the accelerative rotation ($p < 0.0001$). And the total distance and average speed in OFT were also getting lower. Furthermore, pathological evidence proved the success of the PD rat model because there was a decrease in TH-stained neurons under the objective lens at 20 × magnification in the model group (Fig. 1M). This indicated that 6-OHDA clearly induced the typical motor symptoms of PD, and the movement symptoms were simulated more representatively 2 weeks after the injection.

3.2. The effective time and dose of curcumin to significantly alleviate PD motor symptoms were determined

Compared to the model group, it was verified that the middle ($p < 0.05$), and high doses of curcumin and levodopa treatment alleviated abnormal movement in the APO-induced rotation test ($p < 0.0001$) (Fig. 1B). In the rotation experiment, the middle and high doses of curcumin and levodopa treatment increased the latencies of PD model rats at a constant speed ($p < 0.05$), ($p < 0.001$) and ($p < 0.01$) (Fig. 1C). Furthermore, the rats that received high doses of curcumin and that received levodopa treatment showed increased latencies at an accelerative speed ($p < 0.001$) (Fig. 1D). Additionally, the rotation speeds at which rats released the rod were significantly increased with middle, high doses of curcumin and with levodopa treatment ($p < 0.05$), ($p < 0.0001$) and ($p < 0.0001$) (Fig. 1E). And in OFT (Fig. 1F–G), rats with high dose of curcumin and levodopa treatment had higher total distance compared to rats in PD group ($p < 0.05$) and ($p < 0.01$). From the immunofluorescent staining results in Fig. 1M, the high dose of curcumin treatment could protect dopaminergic (TH-positive) neurons from the 6-OHDA damage, which provided the histological evidence.

We found a possible dose-dependent effect of curcumin in alleviating the movement symptoms caused by 6-OHDA, where a comparatively ideal protective effect was observed for the rats that received the high dose (160 mg/kg/d) of curcumin. There was no significant statistical difference between the low-dose curcumin group and the model group, and there was only few effect on movement in the medium-dose curcumin group. However, there was a clear alleviative effect observed for the rats in the high-dose curcumin group that was similar to that of the levodopa group (Fig. 1B–G).

Based on the conclusion above, we then explored the most effective intervention period at the dose of 160 mg/kg/d. Fig. 1H–L shows that movement symptoms in PD rats were partly alleviated 1 week after curcumin administration. Two weeks after intragastric administration of high-dose curcumin, the latencies of the PD model rats were significantly increased at a constant speed and at accelerative speeds ($p < 0.01$) (Fig. 1H) and ($p < 0.001$) (Fig. 1I). The rotation speeds at which the rats released the rod were also evidently increased in accelerative mode ($p < 0.001$) (Fig. 1J). Additionally, the total distance in OFT was increased with drug treatment for 2 weeks ($p < 0.05$) (Fig. 1K). With further analysis, we found that the latencies of rats were significantly increased after 2 weeks in the constant mode and the accelerative mode compared with 1 week of intragastric administration, and the drop speed in accelerative mode also had a significant difference ($p < 0.05$) (Fig. 1H), ($p < 0.01$) (Fig. 1I) and ($p < 0.05$) (Fig. 1J). Combining the results above, we determined that the most optimal therapeutic dose of curcumin was 160 mg/kg/d, and the administration duration to alleviate symptoms in a 6-OHDA-induced PD rat model was 2 weeks.

4. Discussion

In this study, we evaluated the effect of curcumin treatment in attenuating the movement symptoms caused by 6-OHDA in PD model rats using classical behavioral test methods, including the APO-induced rotation test, the rotarod test and the OFT. The results indicated that the most optimal dose of curcumin to alleviate PD-related symptoms was 160 mg/kg/d, and the effect was obvious after intragastric treatment for 2 weeks.

It was reported in previous studies [20] that curcumin mitigates or confers a protective effect on movement symptoms in PD animal models. However, there has been no coincident conclusion regarding the ideal dosage of curcumin or optimal treatment duration that should be used to obtain the greatest therapeutic effect. For example, PD model rats were treated with curcumin at 40 mg/kg/d for 21 days, and the results showed that it could afford neuroprotection and inhibit α-synuclein aggregation [21]. In research using a PD mouse model induced with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), curcumin intraperitoneal injection at 50 mg/kg/d for 5 consecutive prevented degeneration by inhibiting the mitochondrial dysfunction caused by MPTP [22]. The same dosage of 50 mg/kg/d was used in another PD rat model, but the duration was 10 consecutive days [23]. In a rotenone-induced PD rat model, curcumin was intraperitoneally injected at 200 mg/kg/d for 3 weeks [7], and in another study using a rotenone-induced PD rat model, curcumin was orally administered at 80 mg/kg/d for 12 days [10]. In pathology, curcumin was expected to protect, at least partially, the dopaminergic nigrostriatal neurons in 6-OHDA-lesioned animals based on previous reports of neuroprotection in animal models of PD induced by 6-OHDA [15,24–28]. Similarly in a recent study, curcumin improved parkinsonian disability scores in unilaterally 6-OHDA-injected rats through autophagy induction, but failed to improve TH levels in the lesioned striatum [15].

The interventional dosage of curcumin used in PD animal models widely differed in previous studies; this inconsistency has limited the study of the drug and even restricted its clinical application. In addition, most of the previous studies failed to specify the basis of the dosage and intervention duration they chose. In our research, we established a rat model of PD using 6-OHDA lesions, which is a classic method. In addition, our group has performed a series of research studies using this model [17,29]. The 6-OHDA-induced model produces sustained motor deficit and mimics the numerous features of PD patients due to its selective damage toward dopaminergic neurons [30]. A newer clinical trials indicated an absence of positive effects in PD patients regarding the use of curcumin [31], conducted a pilot, randomized, triple-blind, placebo-controlled, add-on trial, eligible patients were randomly assigned to either the curcumin (n = 30, 80 mg/day) or placebo (n = 30) groups and they were tracked for nine months, the results showed that curcumin is not clinically effective in these patients. Therefore, it is essential to determine the effective dose of curcumin against PD.

Before conducting mechanism studies examining the use of curcumin against PD, it is essential to confirm the most optimal dosage

and duration that can alleviate the typical movement symptoms caused by 6-OHDA toxicity. With the APO-induced rotation test, the rotarod test and the OFT, curcumin at 160 mg/kg/d for 2 weeks was sufficient to protect the dysfunctions in our PD rat model. This will provide a reliable reference basis for the curcumin dosage to use in PD-related studies. Additionally, we have not observed any side effects on rats over the whole schedule in our experiment. Moreover, according to a previous research, the curcumin is safe for adults with the dose up to 12 g per day [32]. So we have reason to believe the safety of this drug in the dosage of 160 mg/kg/d in rats for future clinical applications in the prevention and treatment of Parkinson's disease. And the treatment was given by intragastric administration, which is convenient and suitable for most people.

A limitation of this study is that the mechanism affected by curcumin to alleviate behavioral disorders for PD has not yet been explored. There have been multitudinous reports describing the use of curcumin against PD, and the results show that curcumin scavenged the inhibited inflammatory cytokines [33], prevented α-synuclein aggregation [34] to reduce the damage to dopamine neurons, and created a balance between the formation and neutralization of reactive oxygen species to decrease oxidative stress [35].

According to previous reports, curcumin is a multi-targeted compound, delaying the movement symptoms and the pathological progression of Parkinson's disease may be the result of a combination of factors. Therefore, in our next study, we will verify the most closely related mechanism of PD and explore new molecular targets, which will satisfy the demand to discover new approaches to prevent, delay, or ideally reverse the process of PD.

Author contribution statement

Xiaoyu Liu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Hao Zhang: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.
Chuanfen Li: Performed the experiments; Analyzed and interpreted the data.
Zhibin Chen, Qian Gao, Muxuan Han, Feng Zhao, Dan Chen: Performed the experiments.
Qiuyue Chen, Minghui Hu: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.
Zifa Li, Sheng Wei, Xiwen Geng: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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