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Ginkgolide B alleviates Parkinson's disease in rats by resisting oxidative stress and inflammatory response and activating PI3K/Akt signaling pathway

[Ginkgólido B alivia la enfermedad de Parkinson en ratas mediante la resistencia al estrés oxidativo y la respuesta inflamatoria y la activación de la vía de señalización PI3K/Akt]

Chensong Deng[1,*], Qi Yang[2,*] & Wenju Gu[1]

[1]Department of Neurology & [2]Department of Medical Services
Huangshi Central Hospital, Affiliated Hospital of Hubei Polytechnic University, Huangshi, China
*Contributed equally

Abstract: This study explored the alleviative effect of ginkgolide B on Parkinson's disease (PD) in rats. PD model was established in 20 rats, which were then randomly divided into model and treatment group, 10 rats in each group. Other 10 rats were selected as control group. The treatment group was treated with ginkgolide B for four weeks. After treatment, compared with model group, in treatment group the behavior test and learning and memory test indexes were improved, the substantia nigra superoxide dismutase and glutathione peroxidase levels were increased, the substantia nigra malondialdehyde and inflammatory factor levels were decreased, and the substantia nigra phosphorylated phosphatidylinositol-3 kinase (p-PI3K)/phosphatidylinositol-3 kinase (PI3K) and phosphorylated serine-threonine protein kinase (p-Akt)/serine-threonine protein kinase (Akt) ratios were increased (all $p<0.05$). Ginkgolide B can alleviate PD in rats. The action mechanisms may be related to its resisting oxidative stress and inflammatory response and activating PI3K/Akt signaling pathway.

Keywords: Ginkgolide B; Parkinson's disease; Oxidative stress; Inflammatory response; PI3K/Akt.

Resumen: Este estudio exploró el efecto aliviador del ginkgólido B sobre la enfermedad de Parkinson (EP) en ratas. Se estableció modelo de EP en 20 ratas, que luego se dividieron aleatoriamente en un grupo modelo y un grupo de tratamiento, 10 ratas en cada grupo. Otras 10 ratas se seleccionaron como grupo control. El grupo de tratamiento fue tratado con ginkgólido B durante cuatro semanas. Después del tratamiento, en comparación con el grupo modelo, en el grupo de tratamiento los índices de la prueba de comportamiento y la prueba de aprendizaje y memoria mejoraron, los niveles de superóxido dismutasa y glutatión peroxidasa en la sustancia negra aumentaron, los niveles de malondialdehído y factores inflamatorios en la sustancia negra disminuyeron, y las proporciones de fosfatidilinositol-3 quinasa fosforilada (p-PI3K)/fosfatidilinositol-3 quinasa (PI3K) y proteína quinasa serina-treonina fosforilada (p-Akt)/proteína quinasa serina-treonina (Akt) en la sustancia negra aumentaron (todos $p<0.05$). El ginkgólido B puede aliviar la EP en ratas. Los mecanismos de acción pueden estar relacionados con su resistencia al estrés oxidativo y la respuesta inflamatoria, y la activación de la vía de señalización PI3K/Akt.

Palabras clave: Ginkgólido B; Enfermedad de Parkinson; Estrés oxidativo; Respuesta inflamatoria; PI3K/Akt

INTRODUCTION

Parkinson's disease (PD) is the second most common degenerative disease of the central nervous system in the world, often occurring in the elderly. Its clinical symptoms include resting tremors, bradykinesia, muscle rigidity, and abnormal posture and gait, which seriously affect the normal life and physical and mental health of patients (Kalia & Lang, 2015). The pathogenesis of PD is complex, and it is currently believed that multiple factors such as neuroinflammation, oxidative stress, mitochondrial dysfunction, neurotransmitter imbalance, apoptosis, and genetics are involved in the pathological and physiological process of PD (Subramaniam & Chesselet, 2013; Liu *et al.*, 2019; Pajares *et al.*, 2020; Morris *et al.*, 2024). At present, the levodopa drugs are commonly used in clinical practice to treat PD, but these drugs can only alleviate the clinical symptoms and may be accompanied by significant adverse reactions. Therefore, searching for drugs with definite therapeutic effects and minimal adverse reactions for PD has become a current research hotspot. Ginkgolide B is a natural compound extracted from *Ginkgo biloba* leaves. It has the anti-platelet aggregating (Zhang *et al.*, 2018a), anti-inflammatory (Sun *et al.*, 2021), antioxidant (Taguchi *et al.*, 2023), and neuroprotective effects (Nabavi *et al.*, 2015). Ginkgolide B can improve the cerebral blood flow and metabolism by inhibiting the synthesis and release of platelet activating factors, and alleviate the damage of ischemic stroke (Cao *et al.*, 2022). In addition, it has a protective effect on Alzheimer's disease mice (Shao *et al.*, 2022). However, there is limited research on the neuroprotective effect of ginkgolide B on Parkinson's disease, and the mechanism of action is not yet fully understood.

It is reported that the mechanisms of oxidative stress (Jenner, 2003), inflammatory response (Yan *et al.*, 2014) and phosphatidylinositol-3 kinase (PI3K)/serine-threonine protein kinase (Akt) signaling pathway (Goyal *et al.*, 2023) are involved in PD occurrence and progress. Previous studies have found that, Ginkgolide B can exert the neuro-protective effect through the anti-oxidation (Shao *et al.*, 2021), anti-inflammation (Li *et al.*, 2020) and PI3K/Akt signal pathway activation (Zhang *et al.*, 2018b) mechanisms. Therefore, we make a hypothesis that ginkgolide B can alleviate PD in rats by resisting oxidative stress and inflammatory response and activating PI3K/Akt signal pathway, and performed the investigation to verify this.

MATERIALS AND METHODS
Establishment of PD model

Male SD rats (220-250 g) were anesthetized, and fixed in a prone position. After disinfection with iodine and skin preparation, the skin on the head was cut open using a sterile knife, and the fascia and muscles were separated. The position of the anterior fontanelle was accurately determined. The skull was drilled open, and 8 μg 6-hydroxydopamine (6-OHDA) was slowly injected. The skin was sutured, and the penicillin was continuously injected into the abdominal cavity for three days to prevent the infection. After two weeks, the behavior test was conducted, and 20 successfully modeled rats were selected, and they were randomly divided into model and treatment group, 10 rats in each group. Other 10 rats were selected as control group.

Treatment

After modeling, the rats in the treatment group were given 60 mg/kg ginkgolide B by intraperitoneal injection. Rats in the control and model groups were given equal amount of normal saline by intraperitoneal injection. The treatment was performed once per day, for four continuous weeks.

Behavior test

After treatment, the rats were placed in an open experimental box, and were allowed to move freely for 5 min. The number of standing and number of grooming in 5 min, and the number of rotations per minute were counted.

Learning and memory test

Learning and memory of rats were by place navigation experiment and space exploration experiment using the Morris water maze. Firstly, the place navigation experiment was performed. The rats were trained for the four days. The rats facing the pool wall were placed in the pool from the entry in four quadrants. The time of rats successfully reaching the platform within 120 s was recorded as the escape latency. On the fifth day, the platform was removed away. The rats were put into the water. The swimming time and track of rats in the original platform quadrant within one minute were recorded. The platform crossing times were recorded.

Determination of oxidative stress and inflammatory response indexes

Anti-oxidation and anti-inflammation may be the important action mechanisms of levodopa, a typical

drug for treating PD (Prigione *et al.*, 2006; Dorszewska *et al.*, 2014). Therefore, after treatment, the oxidative stress and inflammatory response indexes were determined. After learning and memory test, the rats were executed by decapitation. The brain tissues were taken, and the substantia nigra tissues were separated. The part of substantia nigra tissues was taken, and was homogenized with normal saline. After centrifugation at 3500 rpm for 15 min, the supernatant was obtained. The oxidative stress indexes including superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and malondialdehyde (MDA) and inflammatory response indexes including tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and interleukin 1β (IL-1β) were measured using the corresponding kits.

Western blotting
It is reported that, levodopa can alleviate PD by activating the PI3K/Akt signal pathway (Alkholifi *et al.*, 2023). Therefore, after treatment, the expression of PI3K/Akt signal pathway related proteins was determined. The part of substantia nigra tissues was taken, and was homogenized on ice. The lysis buffer was added for lysing the tissue in an ultrasonic instrument. After centrifugeing at 15000 rpm for 15 min, the total protein was extracted. The BCA method was used to determine the protein concentration, followed by Western blot protein analysis. The separation and concentration gels were prepared, followed by electrophoresis, membrane transferring, and blocking. The primary antibodies of PI3K, phosphorylated-PI3K (p-PI3K), Akt,

phosphorylated-Akt (p-Akt), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) were added, followed by incubation overnight at 4ºC. The secondary antibody sheep anti-rabbit IgG was added, followed by incubation room temperature for 2 h. The antibody hybridization and color development were performed. Image J software was used to analyze the scanned image. The relative expression level of target protein was presented as the ratio of target protein strip integral optical density to GAPDH strip integral optical density. The p-PI3K/PI3K and p-Akt/Akt ratios were calculated.

Statistical analysis
SPSS 22.0 software was used to perform the statistical analysis. Data were presented as the mean $\pm$ SD. Grouped data were analyzed using a one-way analysis of variance followed by LSD-t test. $p < 0.05$ was considered as statistically significant.

RESULTS
Behavior test results
As shown in Table No. 1, a significant decrease in number of standing and number of grooming and significant increase in number of rotations per minute were observed in model and treatment groups than control group, respectively ($p < 0.05$). When comparing to model group, in treatment group the number of standing and number of grooming were significantly increased, respectively ($p < 0.05$), and the number of rotations per minute was significantly decreased ($p < 0.05$).

Table No. 1
Comparison of behavior test results among three groups (n = 10)

Group	Standing (times)	Grooming (times)	Rotations (times/min)
Control	15.28 ± 2.67	7.04 ± 1.32	0.00 ± 0.00
Model	8.19 ± 1.54[*]	3.21 ± 0.55[*]	11.05 ± 1.25[*]
Treatment	13.32 ± 2.01[*#]	5.38 ± 1.03[*#]	5.29 ± 0.65[*#]
F	29.698	35.632	461.623
P	< 0.001	< 0.001	< 0.001

[*]$p < 0.05$ compared to control group, [#]$p < 0.05$ compared to model group

Learning and memory test results
Morris water maze test results showed that, when comparing to control group, in model and treatment groups the escape latency of rats was significantly increased, respectively ($p < 0.05$), and the platform crossing times were significantly decreased,

respectively ($p < 0.05$). The escape latency in treatment group was significantly lower than model group ($p < 0.05$), and the platform crossing times in treatment group were significantly higher than model group ($p < 0.05$) (Table No. 2).

Table No. 2
Comparison of learning and memory test results among three groups (n=10)

Group	Escape latency (s)	Platform crossing times
Control	15.32 ± 2.56	3.52 ± 0.56
Model	$28.05 \pm 4.28^{*}$	$0.63 \pm 0.13^{*}$
Treatment	$22.18 \pm 5.33^{*\#}$	$2.72 \pm 0.43^{*\#}$
F	22.857	129.610
P	< 0.001	< 0.001

$^{*}p<0.05$ compared to control group, $^{\#}p<0.05$ compared to model group

Oxidative stress indexes

Table 3 showed that, a significant decrease in substantia nigra SOD and GSH-Px levels a significant increase in substantia nigra MDA level were observed in model and treatment groups than control group, respectively ($p<0.05$). When comparing to model group, in treatment group the SOD and GSH-Px levels were significantly increased, respectively ($p<0.05$), and the MDA level was significantly decreased ($p<0.05$).

Table No. 3
Comparison of oxidative stress indexes among three groups (n=10)

Group	SOD (U/mg)	GSH-Px (U/mg)	MDA (nmol/mg)
Control	105.21 ± 20.84	16.07 ± 1.73	2.44 ± 0.78
Model	$67.85 \pm 11.30^{*}$	9.06 ± 1.78	$4.98 \pm 0.52^{*}$
Treatment	$87.18 \pm 14.26^{*\#}$	$13.63 \pm 1.23^{*\#}$	$3.16 \pm 0.43^{*\#}$
F	13.683	49.503	48.333
P	< 0.001	< 0.001	< 0.001

$^{*}p<0.05$ compared to control group, $^{\#}p<0.05$ compared to model group. SOD, superoxide dismutase;
GSH-Px, glutathione peroxidase; MDA, malondialdehyde

Inflammatory response indexes

When comparing to control group, in model and treatment groups the substantia nigra TNF-α, IL-6 and IL-1β levels were significantly increased, respectively ($p<0.05$). Each index in treatment group was significantly lower than model group ($p<0.05$) (Table No. 4).

Table No. 4
Comparison of inflammatory response indexes among three groups (n=10)

Group	TNF-α (pg/mg)	IL-6 (pg/mg)	IL-1β (pg/mg)
Control	87.84 ± 16.23	12.05 ± 2.63	22.32 ± 4.27
Model	$278.16 \pm 37.19^{*}$	$32.15 \pm 6.18^{*}$	$67.30 \pm 9.32^{*}$
Treatment	$145.94 \pm 28.53^{*\#}$	$19.20 \pm 5.04^{*\#}$	$43.15 \pm 7.94^{*\#}$
F	115.993	44.166	90.411
P	< 0.001	< 0.001	< 0.001

$^{*}p<0.05$ compared to control group, $^{\#}p<0.05$ compared to model group. TNF-α, tumor necrosis factor α;
IL-6, interleukin 6; IL-1β, interleukin 1β

Substantia nigra p-PI3K/PI3K and p-Akt/Akt ratios

Table No. 5 showed that, a significant decrease in substantia nigra p-PI3K/PI3K and p-Akt/Akt ratios were presented in model and treatment groups than control group, respectively ($p<0.05$). When comparing to model group, each index in treatment group was significantly increased ($p<0.05$).

Table No. 5
Comparison of substantia nigra p-PI3K/PI3K and p-Akt/Akt ratios among three groups (n=10)

Group	p-PI3K/PI3K	p-Akt/Akt
Control	0.82 ± 0.15	0.92 ± 0.16
Model	$0.15 \pm 0.03^{*}$	$0.34 \pm 0.05^{*}$
Treatment	$0.46 \pm 0.07^{*\#}$	$0.72 \pm 0.15^{*\#}$
F	119.187	51.462
P	< 0.001	< 0.001

*$p<0.05$ compared to control group, #$p<0.05$ compared to model group. PI3K, phosphatidylinositol-3 kinase; p-PI3K, phosphorylated phosphatidylinositol-3 kinase PI3K; Akt, serine-threonine protein kinase; p-Akt, phosphorylated-serine-threonine protein kinase.

DISCUSSION

At present, the pathogenesis of PD is not clear, and clinical treatment mainly involves drug intervention. Conventional drugs include levodopa, anticholinergic drugs, etc., which promote the enhancement of dopamine effect and aid in nerve endings dopamine synthesis (LeWitt, 2015; Nawaz *et al.*, 2022). However, these drugs may lead to a significant increase in adverse reactions in patients, affecting the treatment effectiveness. 6-OHDA plays an important role in the preparation of PD models in rats, mainly because it has toxic effects on the substantia nigra and striatal neurons, producing a large amount of hydrogen peroxide through oxidation (Simola *et al.*, 2007). Therefore, our study used 6-hydroxydopamine to prepare PD model of rats. It is reported that, the ginkgo biloba extract has the protective effect onPD (Tanaka *et al.*, 2013). Ginkgolide B is one component in ginkgo biloba extract. This study explored the alleviative effect of ginkgolide B on PD. Results showed that, after four weeks of treatment, compared with model group, in treatment group the number of standing and number of grooming were significantly increased, the number of rotations per minute was significantly decreased, the escape latency was significantly decreased, and the platform crossing times were significantly increased. This suggests that the ginkgolide B treatment can improve the behavior and learning and memory ability of PD rats. The result of our study further verifies the findings of above reported study.

Oxidative stress and inflammatory response are the important pathological and physiological foundation of PD. Study has shown that the level of oxidative stress significantly increases in the early stages of damage to dopaminergic neurons (Guo *et al.*, 2018). The substantia nigra of the brain tissue in PD rats is in an oxidative stress state, with decreased SOD and GSH-Px levels and increased MDA level, causing the antioxidant stress system dysfunction, leading to damage to dopaminergic neurons and ultimately damaging the neural function (Wang *et al.*, 2022). TNF-α, IL-6 and IL-1β are the pro-inflammatory factors, which can activate the microglia, increase their activity, and then induce the damage to dopaminergic neurons. On the other hand, they can bind to the dopaminergic neuron-related receptors to induce the cell apoptosis, thereby exacerbating the PD condition (Zhang *et al.*, 2020). Results of our study showed that, after treatment, compared with model group, in treatment group the substantia nigra SOD and GSH-Px levels were significantly increased, and the substantia nigra MDA, TNF-α, IL-6 and IL-1β levels were significantly decreased. It is suggested that the ginkgolide B treatment can resist the oxidative stress and inflammatory response in brain tissue of PD rats, thus alleviating the nerve damage. In study of Hu *et al.* (2010), the hydrogen sulfide can mitigate the neurodegeneration in PD rats via the anti-oxidative stress and anti-inflammation mechanisms. This is basically consistent with the findings of our study.

PI3K/Akt signaling pathway is one of the most important intracellular signaling pathways, which can regulate the cell apoptosis, autophagy, proliferation, neural remodeling, and cell survival, playing a critical role in the nervous system (Han *et al.*, 2022). PI3K can connect the extracellular signals with cellular response effects. It is activated by phosphorylation. The p-PI3K can activate the Akt through phosphorylation. Akt is located downstream of this signaling pathway, and its activation has important effects on cell growth and metabolism (Hou *et al.*, 2023). Research has shown that the PI3K/Akt signaling pathway can regulate the cell apoptosis and microglial activation, inhibit the

neuroinflammation, and prevent the accumulation of reactive oxygen species, thereby providing the neuroprotective effects on dopaminergic neurons (Arthur *et al.*, 2023). The substantia nigra p-PI3K/PI3K and p-Akt/Akt ratios are the important indexes to reflect the nerve damage of PD rats. Results of our study showed that, after treatment, when comparing to model group, the substantia nigra p-PI3K/PI3K and p-Akt/Akt ratios in treatment group were significantly increased. This suggests that ginkgolide B can activate the substantia nigra PI3K/Akt signaling pathway and promote the protein phosphorylation, thereby exerting the neuroprotective effect in PD rats. Salama *et al.* (2020), have found that, crocin shows the promising neuroprotective effects on PD rats via activation of PI3K/Akt signal pathway. Jin *et al.* (2022), have also found that, curcumin can improve PD via activating /PI3K/Akt

signaling pathway. These findings further confirm the action mechanism of ginkgolide B on PD in our study.

CONCLUSIONS
In conclusion, ginkgolide B can improve the behavior and learning and memory ability of PD rats. The action mechanisms may be related to its resisting oxidative stress and inflammatory response and activating PI3K/Akt signaling pathway. This study can provide a new strategy for the prevention and treatment of PD.

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