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Synergistic effects of *Ginkgo biloba* and voluntary exercise on oxidative stress and antioxidant markers in Parkinson's disease in mice model

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ABSTRACT

Background & Aim: Parkinson's disease (PD) is a neurodegenerative disorder marked by the degeneration of dopaminergic neurons in the substantia nigra. Inflammation and oxidative stress contribute significantly to its progression. This study assessed the effects of voluntary exercise and *Ginkgo biloba* supplementation on oxidative stress in a PD mouse model, using thirty female C57BL/6 mice induced with PD via MPTP.

Experimental: The study included a pre-test and post-test phase with an eight-week intervention. Mice in the exercise group used spinning wheels daily, while those in the *Ginkgo biloba* group received 80 mg plant extract via gavage. A combination group followed both methods, and a control group received a placebo. Biochemical assessments were conducted after fasting, and results were analyzed with one-way ANOVA.

Results: Findings showed that expression levels of SIRT1 and NRF2 as well as SOD concentration were significantly lower ($P<0.05$) in the PD model compared to control but increased after interventions. Malondialdehyde (MDA) levels were elevated in the PD group but decreased following the interventions, with the greatest improvements in the combination group, indicating a synergistic effect in alleviating Parkinson symptoms.

Recommended applications/industries: Complimentary medicine identified *Ginkgo biloba* and voluntary exercise are recognized as effective methods to prevent and improve neurodegenerative disorder. Based on present results, *Ginkgo biloba* extract and voluntary exercise improved SIRT1 and NRF2 as well as SOD and MDA concentration in Parkinson condition. Furthermore, consuming the *Ginkgo biloba* along with voluntary exercise might recover oxidative stress pathway and regulate the hub genes networks.

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder primarily characterized by the degeneration of dopaminergic neurons within the substantia nigra, a region critical for regulating movement. The depletion of these neurons disrupts dopamine signaling pathways, resulting in a constellation of motor symptoms, including bradykinesia, muscle rigidity, and tremors. An extensive body of research has established the central role of inflammation, oxidative stress, and free radical production in the etiology of PD, with these factors accelerating neuronal deterioration and symptom progression (Xiao *et al.*, 2023). The prevalence of PD in the United States and Western Europe is estimated to be approximately 1 to 2 cases per 1,000 individuals, highlighting its significant burden on public health (Umehara *et al.*, 2024).

Oxidative stress arises when reactive oxygen species (ROS) overwhelm the cell's antioxidant defenses, leading to cellular damage, particularly of lipids and proteins, which ultimately contributes to cell death. Notably, oxidative stress can precede the clinical manifestations of neurodegeneration, suggesting its early involvement in disease pathology. Antioxidant defenses within the central nervous system, particularly in dopaminergic neurons, rely on small-molecule antioxidants such as vitamins E and C, as well as larger enzymatic antioxidants such as superoxide dismutase (SOD) and glutathione, to mitigate ROS-induced damage (Murakami *et al.*, 2023).

The brain's phospholipid-rich structure and high polyunsaturated fatty acid (PUFA) content make it particularly vulnerable to oxidative damage. In PD, a notable reduction in PUFA levels within the substantia nigra and a corresponding increase in malondialdehyde (MDA) serve as markers of lipid peroxidation, underscoring oxidative stress as a pivotal pathological factor (Winiarska-Mieczan *et al.*, 2020). Studies indicate that regular physical exercise, known for its neuroprotective effects, can modulate oxidative conditions, promoting brain health and resilience against neurodegeneration (Lee *et al.*, 2020). Exercise fosters neurogenesis and angiogenesis, which are crucial for sustaining cognitive health. Specifically, neurotrophic factors such as BDNF and vascular endothelial growth factor (VEGF) are instrumental in promoting neuronal survival, synaptic plasticity, and overall brain function, thus reinforcing cognitive resilience against neurodegenerative disorders (Moujalled *et al.*, 2021).

Meta-analyses have consistently demonstrate that exercise plays a vital role in PD management by improving physical performance, health-related quality of life, muscle strength, balance, and gait, which are essential for maintaining functional independence in PD patients (He *et al.*, 2020). Among the different exercise modalities, voluntary treadmill running, forced treadmill activity, and resistance training are frequently employed in clinical and research settings to explore their distinct effects on neuroprotection and cognitive function. Voluntary exercise, in particular, has shown profound benefits for neurobehavioral outcomes in animal studies, offering a less stressful, cognitively supportive alternative to forced exercise. Considering the link between oxidative stress and PD pathophysiology, voluntary exercise has emerged as a promising, potentially superior strategy for alleviating PD symptoms (Liu *et al.*, 2020).

Ginkgo biloba has garnered attention for its potent antioxidant properties. This plant contains diverse bioactive compounds, notably terpene lactones and flavonoids, which contribute to its neuroprotective capacity (Sivanandy *et al.*, 2021). The evidence suggests that *Ginkgo biloba* supplementation may enhance cognitive function by reducing oxidative stress and increasing brain-derived neurotrophic factor (BDNF) (Jankovic and Lang, 2021).

This research examines the efficacy of voluntary exercise and *Ginkgo biloba* supplementation as a natural treatment approach for managing Parkinson's disease.

2. Materials and Methods

2.1. Preparation of extract

The *Ginkgo biloba* (100 g) was dissolved in 666 mL of methanol and subjected to sonication for 15 min, after which 1200 mL of ethyl was added, followed by an additional sonication for 30 min. After ultra-filtration, the extract was subsequently dried using a vacuum pump at 75 °C for 24 h. The purified product was dissolved in boiling ethanol-water (17% w/w), decolorized with activated carbon for 5 min, and subsequently filtered. The purified product was combined with a $Na_2S_2O_5$ solution, and 2 g of Ginkgolide B was added into the mixture and dissolved by heating. The solution was subsequently concentrated using filtering. The EGb concentrate was pH-adjusted to 7 using $NaHCO_3$ prior to autoclave sterilization (Wang *et al.*, 2017).

2.2. Animal study

Thirty female C57BL/6 mice, aged 3–4 months with an average weight of 24 ± 2 grams, were selected for this study. The mice were housed under standard laboratory conditions (temperature 23 ± 2 °C, humidity 65 ± 5%, 12-hour light/12-hour dark cycle) with ad libitum access to food and water. Following a seven-day acclimatization period, which was designed to minimize environmental stress and ensure a stable baseline, the mice were randomly assigned to one of five groups, each balanced for age, weight. This randomization reduced potential bias and provided uniform conditions for the subsequent experimental phases.

The groups included: 1) Healthy Control Group , which was administered normal saline as a vehicle control; 2) Disease Control Group which received intraperitoneal injections of MPTP (12 mg/kg in 200 µL PBS) for two consecutive days to induce Parkinsonian pathology (Zhang *et al.*, 2018) 3). An Exercise-Only Group (EX) in which the mice performed voluntary exercise; 4) Supplement-Only Group (SUPP) which was administered *Ginkgo biloba* extract (20 mg/kg body weight) by gavage (Adebayo *et al.*, 2022); 5) Combined Treatment Group (SUPP+EX), which received both voluntary exercise and *Ginkgo biloba* supplementation. Each treatment was administered following established protocols, two models of Parkinson's pathology, and to assess intervention efficacy under controlled conditions.

2.3. qPCR real-time assay

After two months, tissue samples were collected under approved ethical guidelines (IR.IAU.KHUISF.REC.1402, 382). The mice were anesthetized with ketamine, and tissue biopsies were conducted with precision. The samples were frozen in liquid nitrogen and stored at -80 °C to preserve molecular integrity. For RNA extraction, 50 mg of tissue was homogenized in TRIzol reagent, followed by the addition of 200 µL of chloroform. After vigorously shaking for 15 seconds and incubating on ice for 5 minutes, the mixture was centrifuged at 12,000 rpm for 15 minutes at 4 °C. The RNA-containing upper phase was carefully collected, ensuring minimal interface disruption. Cold isopropanol was then added to precipitate the RNA, and the mixture was gently inverted and incubated on ice for 15 minutes, followed by 12,000 rpm centrifugation at 4 °C. The regulation RNA pellet was washed with 1 mL of 75% ethanol and centrifuged at 7,500 rpm for 8 minute. After supernatant was decanted, the residual ethanol was evaporated by placing the pellet under foam hood. The RNA pellet was dissolved in 50 µL of DEPC-treated water, vortexed briefly, and incubated at 60 °C for 10 minutes. The RNA purity and concentration were measured spectrophotometrically at 260 and 280 nm, with a 260/280 absorbance ratio indicating RNA integrity. To ensure high-quality RNA for downstream applications, 1 µg of RNA was treated with DNase I (in the presence of DNase buffer and an RNase inhibitor) at 37 °C for 30 minutes. After inactivation with EDTA at 65 °C for 10 minutes, reverse transcription was performed via the RevertAid First Strand cDNA Synthesis Kit (Takara Bio) with random hexamers and oligo (dT) primers. This approach enables comprehensive cDNA synthesis, Which is suitable for multiple applications, including PCR and qPCR, facilitating the study of gene expression changes associated with Parkinsonian pathology and therapeutic interventions (Safavi *et al.*, 2025). For the voluntary exercise intervention, the mice had access to a running wheel (Andisheh Sanat Engineering Company) within their cages for one hour per day, five days per week, over four weeks. This setup allowed for the precise measurement of exercise distance, Which was automatically recorded by a computer, ensuring reliable data on physical activity levels.

2.4. ELISA assay

Blood samples were taken from the right ventricle of each mouse. Serum was extracted by centrifugation at 1600 g for 15 min at 4 °C. The concentrations of SOD (ab285309, Abcam) and MDA (MBS741034, mybiosource) were determined using enzyme-linked immunosorbent assay as per the manufacturers' recommendations (Abedpoor *et al.*, 2024; Abedpoor *et al.*, 2025; Safavi *et al.*, 2025; Safavi *et al.*, 2024).

2.5. Statistical analysis

All data are presented as the means ± standard deviations (SDs). One-way analysis of variance (ANOVA) was used to compare the mean values across the groups. In cases where the data were not normally distributed, the Kruskal-Wallis test was applied. The Bonferroni correction was employed for posthoc comparisons between each pair of groups. Pearson's linear regression analysis was conducted with a 95% confidence interval (CI). All the statistical analyses were performed via SPSS software (version 28). A p-value of less than 0.05 was considered statistically significant. Graphs were generated via GraphPad Prism (version 8.4.3) (Safavi *et al.*, 2024)

3. Results and discussion

We assessed data normality via the using the Shapiro-Wilk test, Which is appropriate for sample sizes under 50. Except for MDA, all data demonstrated normal distributions. The mean ± standard deviation (SD) values for each group and factor are detailed in (Figure 1).

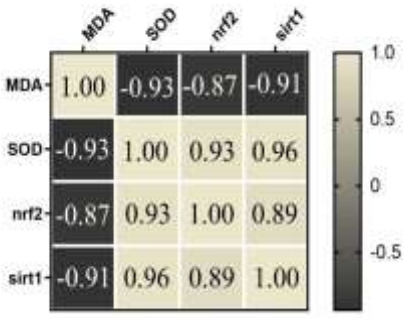

Figure 1. Effects of interventions on oxidative stress and antioxidant biomarkers in experimental groups. MDA: malondialdehyde, SOD: superoxide dismutase, nrf2: nuclear factor erythroid 2–related factor 2, and sirt1: sirtuin.

Our findings revealed that eight weeks of voluntary exercise led to significant differences in MDA levels across the study groups. Specifically, significant differences were observed between the supp+ex and ex, supp+ex and supp, supp+ex and PD, supp+ex and CON, ex and CON, supp and CON, and PD and CON groups (P<0.001). Further analysis also showed significant differences between the ex and PD (p=0.003) and PD and supp groups (p=0.001), whereas no significant difference was found between the ex and supp groups (p=1.00) (Figure 2A).

The levels of MDA (malondialdehyde), a biomarker of lipid peroxidation, were significantly elevated (P<0.05) in the Parkinson's disease group; these levels were reduced after the combined intervention, indicating that voluntary exercise and *Ginkgo biloba* supplementation may effectively mitigate oxidative stress and bolster antioxidant capacity in this disease model (Li *et al.*, 2023).

Despite these insights, the exact mechanisms underpinning dopamine neuron loss in the substantia nigra in Parkinson's disease remain elusive (Gong *et al.*, 2024). However, extensive evidence supports a crucial role for oxidative stress and reactive oxygen species (ROS) in the disease's progression (Ahmad *et al.*, 2008). The antioxidant properties and neuroprotective effects of EGb761, a *Ginkgo biloba* leaf extract, align with the results of this study (Biernacka *et al.*, 2023). The neuroprotective effects of EGb761 are hypothesized to be due to its ability to inhibit monoamine oxidase (MAO), an enzyme responsible for dopamine metabolism and free radical production (Liu *et al.*, 2024). Their findings suggest EGb761 as a candidate for reducing oxidative stress and slowing neurodegeneration, with possible inhibition of neurotoxic compounds such as 6-hydroxydopamine, MPTP, and MPP.

The current study, consistent with this body of research, found that voluntary exercise and *Ginkgo biloba* supplementation over eight weeks reduced MDA levels in Parkinsonian mice, providing further evidence of the potential for these interventions to counteract oxidative stress (Chen *et al.*, 2020). Additional research on EGb761 and related compounds indicated its ability to protect neuronal integrity through various mechanisms (Rojas *et al.*, 2012). For instance, GBDP, a *Ginkgo biloba*-derived preparation, was shown to be neuroprotective against dopaminergic cell loss and cognitive impairment in models treated with MPTP and other neurotoxins (Zang *et al.*, 2023). Laboratory findings suggest that the neuroprotective effects of GBDP may be mediated through the Akt/GSK3β pathway, underscoring a possible mechanistic link between these Ginkgo biloba components and neuroprotection (Zang *et al.*, 2023).

In examining SOD levels, we observed statistically significant differences among the groups. Significant pairwise differences were identified between the supp+ex and PD, ex and CON, supp and CON, and PD and CON groups (P<0.001). Additional differences were noted between the supp+ex and CON (p=0.02) and ex and PD (p=0.01) groups. However, comparisons between supp+ex and ex (p=1.00), ex and supp (p=1.00), supp+ex and supp (p=0.05), and supp and PD (p=0.41) showed no statistical significance (Figure 2B). Following the eight-week voluntary exercise program, NRF2 levels demonstrated notable group differences. Significant differences emerged between the supp+ex and ex, supp+ex and supp, supp+ex and PD, ex and PD, ex and CON, supp and PD, and supp and CON groups (P<0.001). By contrast, comparisons between supp+ex and CON (p=0.76) and ex and supp (p=0.21) did not yield statistically significant results (Figure 2C). Lastly, our analysis of SIRT1 gene expression revealed statistically significant differences across study groups post-exercise. Significant differences were found between the supp+ex and supp, supp+ex and PD, supp+ex and CON, ex and PD, ex and CON,

supp and CON, and PD and CON groups (P<0.001). Additionally, the supp+ex and ex (p=0.002) and ex and supp (p=0.01) comparisons showed significance (Figure 2D).

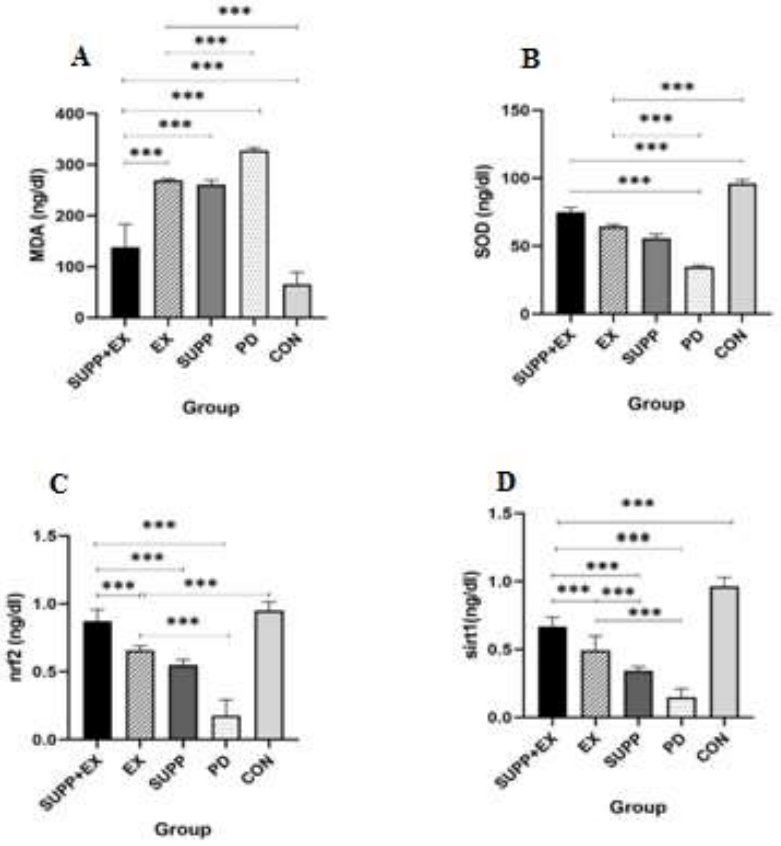

Figure 2. Effects of interventions on oxidative stress and antioxidant biomarkers in experimental groups.
The bar graphs represent the mean ± standard deviation of MDA (malondialdehyde), SOD (superoxide dismutase), NRF2 (nuclear factor erythroid 2–related factor 2), and SIRT1 (sirtuin 1) levels across different groups. The groups include CON (Control), PD (Parkinson's disease), SUPP (*Ginkgo biloba* supplementation, 20 mg/kg), EX (Voluntary exercise), and SUPP+EX (*Ginkgo biloba* supplementation + Voluntary exercise).
Statistical analysis was performed using one-way ANOVA followed by Bonferroni's post hoc test. Significant differences are denoted by *** (P<0.001), indicating distinct variations between the groups for each biomarker.

The correlation analysis revealed significant relationships among the studied biomarkers (Figure 3 A-F). Specifically, a strong negative correlation was observed between SOD and MDA levels (-0.93), NRF2 and MDA levels (-0.87), and SIRT1 and MDA levels (-0.91), indicating an inverse association between oxidative stress markers and antioxidant defense and regulatory proteins (Figure 3A-C). In contrast, positive correlations were noted between NRF2 and SOD levels (0.93), SIRT1 and SOD levels (0.96), and SIRT1 and NRF2 levels (0.89), highlighting a synergistic relationship among these antioxidant and regulatory factors (Figure 3D-F). These findings underscore the interconnected roles of SOD, NRF2, and SIRT1 in counteracting oxidative damage, which may provide insight into therapeutic mechanisms for mitigating oxidative stress in neurodegenerative conditions.

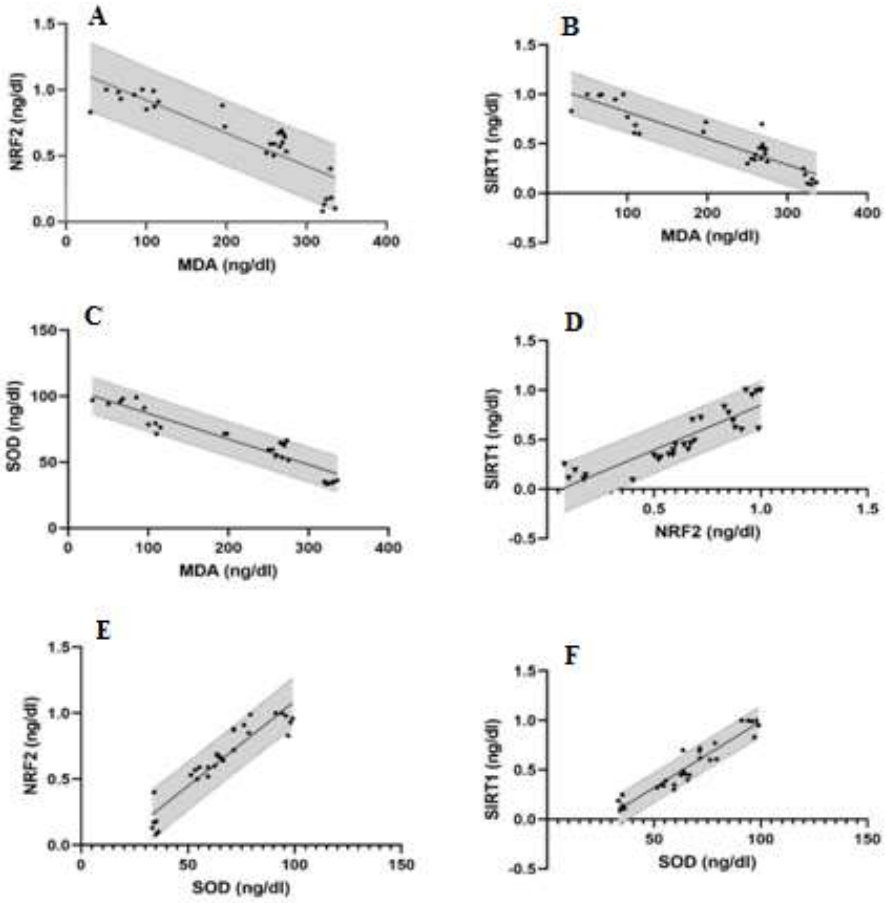

Figure 3. Relationships between MDA, NRF2, SOD, and SIRT1 levels.

The primary findings of this study reveal a marked reduction in SOD (superoxide dismutase), SIRT1 (Sirtuin 1), and NRF2 (nuclear factor erythroid-related factor 2) levels in mice with Parkinson's disease compared to the control group. This reduction underscores the potential role of these antioxidant and regulatory factors in the pathogenesis of Parkinson's disease, suggesting their involvement in oxidative stress and the associated neurodegenerative processes characteristic of this condition (Surendran and Rajasankar, 2010). Notably, following voluntary exercise and *Ginkgo biloba* supplementation, the concentrations of SOD, SIRT1, and NRF2 in the Parkinsonian mice approximated those observed in the control group.

These findings are supported by studies demonstrating that compounds like kaempferol, quercetin, and isoramantine in Ginkgo biloba exhibit potent anti-inflammatory and neuroprotective properties. Given the distinct profiles of GBDP and EGb761 (Nowak *et al.*, 2021), future studies should explore the differential efficacy of these compounds in clinical contexts. This study also corroborates previous findings that physical exercise confers neuroprotective benefits in Parkinson's disease models (Dauer and Przedborski, 2003). High-intensity exercise has been shown to increase neurotrophic factors, such as BDNF and GDNF, in the substantia nigra and striatum, enhancing motor function in animals treated with MPTP or 6-OHDA (Zaychik *et al.*, 2021).

The results of this study, which showed an increase in SOD, SIRT1, and NRF2 levels following voluntary exercise and *Ginkgo biloba* supplementation, further substantiate the potential synergistic effects of these interventions in mitigating Parkinsonian symptoms. This synergism was particularly evident in the combined intervention group, suggesting that exercise and supplementation could be an effective adjunct to pharmacological therapies. Future research should consider variations in age, dose, and intervention

duration, as well as explore mechanisms by which voluntary exercise and *Ginkgo biloba* supplementation may offer neuroprotection against Parkinson's disease. Future research should assess the effects of different exercise protocols in conjunction with Parkinson's standard pharmacological treatments. It is essential to explore and compare the impact of various intensities and durations of voluntary exercise, along with combined and resistance training protocols. Additionally, studies should examine the physiological changes associated with diverse exercise regimens tailored to different age groups and physical conditions. Given the cross-sectional nature of this study, further longitudinal research is needed to evaluate the long-term effects of *Ginkgo biloba* supplementation in this context. SOD, a critical antioxidant enzyme, mitigates harmful reactive oxygen species (ROS) and reduces oxidative stress, which is a central factor in Parkinson's disease progression. SIRT1, a protein associated with aging and stress resilience, contributes to neuroprotection by enhancing mitochondrial function. NRF2 supports cellular defense against oxidative damage by promoting the expression of antioxidant proteins. Additionally, the decrease in MDA, a marker of lipid peroxidation, suggests reduced oxidative injury to cell membranes. Together, exercise and Ginkgo biloba appear to regulate these key molecules, potentially decelerating disease progression.

4. Conclusion

This study indicated that integrating voluntary exercise and *Ginkgo biloba* supplementation may provide a viable neuroprotective approach for Parkinson's disease. Elevations in SOD, SIRT1, and NRF2, together with diminished MDA levels, signify less oxidative stress and improved cellular protection. The molecular alterations indicated a deceleration of disease progression via enhanced antioxidant activity and mitochondrial function. Future studies ought to investigate diverse exercise regimes, intensities, and durations, particularly in conjunction with established treatments, while taking into account age and physical condition. Comprehensive longitudinal studies are required to evaluate the enduring effects of *Ginkgo biloba.*

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