Universal Library of Medical and Health Sciences Research Article

ISSN: 3064-6545 | Volume 4, Issue 1

Open Access | PP: 13-26

DOI: https://doi.org/10.70315/uloap.ulmhs.2026.0401003

Evaluation of the Anti-Aging Efficacy of Repeat Juvenile Tablets

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Abstract

Background: *Aging is a physiological decline triggered by various internal and external factors, characterized by organ degeneration and diminished physiological functions. Developing health supplements with anti-aging properties is of significant importance in addressing aging-related functional decline and diseases.*

Methods: *This study utilized 40 male and 40 female 12-month-old aging C57BL/6 mice. Within each sex, mice were randomly assigned to four groups (n=10 per group) based on body weight: a control group, and low, medium, and high-dose groups. Following 12 weeks of continuous administration, tests were sequentially conducted to evaluate memory and learning capabilities, aging-related biomarkers in the brain and liver, and antioxidant capacity.*

Results: *Experimental data from the Morris water maze test indicated that the escape latency (time to reach the platform) for the low, medium, and high-dose Repeat Juvenile groups was significantly lower than that of the control group ($p < 0.05$). Furthermore, supplementation with Repeat Juvenile significantly reduced aging-related biomarkers in the brain and liver while markedly enhancing antioxidant capacity. Finally, in survival assays, supplementation at 1X, 2X, and 5X dosages significantly extended the median survival, mean lifespan, and maximum lifespan ($p < 0.05$) in both male and female Drosophila (fruit fly) survival curves.*

Conclusion: *Repeat Juvenile tablets demonstrate significant antioxidant capacity and a reduction in aging markers in aging mouse models, suggesting substantial health benefits for delaying senescence. It is recommended that a daily supplementation of 3,200 mg for adults may provide efficacious anti-aging benefits.*

INTRODUCTION

Aging is a physiological decline triggered by internal and external factors that is universal, progressive, cumulative, and deleterious (Strehler et al., 1982). This process can be attributed to the random accumulation of damage to macromolecules—such as nucleic acids and proteins—over time, which eventually exceeds the body's innate repair capacity. Such stochastic damage often stems from free radicals, oxidation, or glycation (Moldogazieva et al., 2019). Physiologic decline associated with aging generally manifests in two ways: age-related physiologic deterioration and age-associated diseases, though the two frequently coexist (Amjad et al., 2025).

In recent years, agroproducts, food factors, and phytochemicals have been recognized as vital sources for developing supplements that promote health or even delay senescence. Repeat Juvenile tablets are a multi-ingredient nutraceutical formulation derived from natural sources, designed to delay aging without side effects. The formula combines chicken sternal cartilage hydrolysate, sesame extract, amla extract, and grape skin extract.

Grape skin extract contains high levels of resveratrol, a polyphenolic compound found in red wine, red grape skins, purple grape juice, mulberries, and peanuts. In 2003, Howitz and Sinclair published a landmark study in Nature demonstrating that resveratrol extends the lifespan of yeast (Howitz et al., 2003); subsequent research using nematodes, Drosophila, and mice has yielded similar results.

Amla has gained significant attention in recent anti-aging research due to its abundance of Vitamin C, polyphenols, and tannins, making it a potent natural antioxidant. Amla extract significantly elevates levels of antioxidant enzymes (e.g., SOD, CAT, and GSH) in the brain while reducing oxidative stress markers such as TBARS. Furthermore, it inhibits acetylcholinesterase (AChE), thereby improving memory and learning capabilities (Uddin et al., 2016). Additionally, Amla

Citation: Jia-Xing Wang, Yu-Jou Chien, et al., "Evaluation of the Anti-Aging Efficacy of Repeat Juvenile Tablets", Universal Library of Medical and Health Sciences, 2026; 4(1): 13-26. DOI: https://doi.org/10.70315/uloap.ulmhs.2026.0401003.

regulates SIRT1 (a longevity protein) and protects retinal ganglion cells, indicating broad neuroprotective potential within the central nervous system (Jang et al., 2017).

Regarding chicken sternal cartilage hydrolysate, anti-aging research focuses on the synergistic effects of Type II collagen, chondroitin, and hyaluronic acid. Due to its unique matrix structure, this hydrolysate utilizes small-molecule peptides to act directly on skin fibroblasts, reducing the expression of MMP-1 and MMP-2 while increasing internal hyaluronic acid content, thereby mitigating UV-induced photoaging (Schwartz et al., 2019).

The primary bioactive components in sesame extract are sesame lignans, including sesamin, sesamolin, and sesamol. Research indicates that sesamin can regulate metabolism, combat oxidative stress, and facilitate cellular repair via the Sirtuin 1 (SIRT1) pathway to achieve anti-aging effects (Nakatani et al., 2018).

Based on the aforementioned background, Repeat Juvenile tablets—comprising active ingredients such as resveratrol, polyphenols, and vitamins—are hypothesized to possess significant anti-aging bioactivity. This study aims to provide evidence supporting the senescence-delaying effects of Repeat Juvenile tablets using animal models and analytical methods. By integrating existing literature to establish a basis for dosage selection and mechanistic inference, we hope to advance its development as a health supplement with clinical application potential.

MATERIALS AND METHODS

Experimental Supplement

Repeat Juvenile tablets consist of a proprietary blend containing chicken sternal cartilage hydrolysate, amla extract, grape skin extract, elastin, selenium yeast, vitamin C, vitamin E, vitamin B2, and sesame extract.

Animals and Study Design

A total of 80 C57BL/6 mice (40 males and 40 females, 12 months old) with an average body weight of 30~35g were used. The animals were purchased from the National Laboratory Animal Center (NLAC, Taiwan). All mice were housed in the animal facility of the Institute of Sports Science, National Taiwan Sport University, under controlled conditions: temperature 22 ± 2°C, humidity 60 ± 10%, and a 12-hour light/dark cycle. A standard chow diet (Chow 5001) and water were provided ad libitum.The experimental protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of National Taiwan Sport University (Approval No.: IACUC-10917). The mice were randomly assigned to four groups (n=20 per group, with 10 males and 10 females). (1)Control Group (Vehicle): Administered distilled water, (2)Low-Dose Group (RJ-1X):655.6mg/kg/day, Medium-Dose Group (RJ-2X):1311.2mg/kg/day, High-Dose Group (RJ-5X): 3278mg/kg/day. The intervention lasted for 12 weeks, during which the test samples were administered daily at 09:00 AM via oral gavage. The gavage volume was maintained below 10mL/kg of body weight. For higher volumes, the dose was split into multiple administrations completed within a 6-hour window. Body weight, food intake, and water consumption were recorded throughout the study. After 12 weeks, behavioral tests for memory and learning and subsequent analytical assays were performed.Dosage calculations were based on the 2005 US FDA guidelines (Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers). Given the metabolic differences between species, the human equivalent dose (HED) was converted using a conversion factor of 12.3 for mice.

Physiological Measurements

(A) Body Weight: Measured periodically to compare the initial and final weights.

(B) Food Intake: Daily consumption was recorded to monitor nutritional status.

(C) Water Consumption: Daily water intake was monitored throughout the experimental period.

Animal Memory and Learning Efficacy Test

A reference memory task was employed using the Morris Water Maze. The escape platform was fixed in the third quadrant. Mice were released into the pool from four different starting points in a randomized sequence, with their heads facing the wall. Training Protocol: Four trials per day, each lasting 60~90 seconds. Success Criterion: If a mouse located the platform within 90 seconds, it was allowed to rest on it for 15~30 seconds before returning to its cage for a 30 minute interval between trials. Failure Protocol: If the mouse failed to find the platform within the allotted time, it was manually guided to the platform and allowed to rest for 15~30 seconds.This training phase was conducted over three consecutive days.

Brain Aging Biomarkers

Following sacrifice, brain tissues were surgically excised and stored at -20°C. The following biomarkers were analyzed:

Brain Dopamine Content

Dopamine levels were determined using a commercial ELISA kit (K4219, BioVision, CA, USA) according to the method described by Attia et al. (2021). Briefly, brain tissues 5~10mg were rinsed with ice-cold PBS 0.01M, pH 7.4 to remove residual blood, weighed, and homogenized in PBS on ice. To ensure complete cellular lysis, the homogenates were subjected to ultrasonication or freeze-thaw cycles. The samples were then centrifuged at 5,000 x g for 5 minutes at 4°C, and the supernatant was collected. Standards and samples (50µL each) were added to pre-washed wells, followed by the addition of 50 µL of Biotin-detection antibody. After incubation at 37°C for 45 minutes, the plate was washed three times with 1X wash buffer. Subsequently, 0.1mL of SABC

reagent was added to each well and incubated at 37°C for 30 minutes. Following five additional washes, 90µL of TMB substrate was added, and the plate was incubated in the dark at 37°C for 15~20 minutes. The reaction was terminated by adding 50 µL of stop solution, and the absorbance was measured at 450nm within 20 minutes.

Protein Carbonyl Content

Oxidatively modified protein carbonyl groups were quantified using a commercial kit (10005020, Cayman Chemical, Ann Arbor, MI, USA) as previously described (Belviranlı et al., 2013). Frozen brain samples (5~10mg) were homogenized (1:5 w/v) in ice-cold potassium phosphate buffer (50 mM KPi, 1.1 mM EDTA, 0.1 mM PMSF, pH 6.7) and centrifuged at 10,000 x g for 15 minutes at 4°C. The supernatant was reacted with 2,4-dinitrophenylhydrazine (DNPH) and TCA, followed by incubation in the dark for 60 minutes. After centrifugation (10,000 x g, 10 minutes, 4°C), the protein pellet was washed three times with an ethanol/ethyl acetate mixture (1:1 v/v) to remove free DNPH. The final pellet was dissolved in guanidine hydrochloride. Protein concentration was verified at 280 nm (using BSA as a standard), and the carbonyl content was determined spectrophotometrically at 360 nm using a molar extinction coefficient of 22,000 $M^{-1}cm^{-1}$. Results are expressed as nmol of protein carbonyl per mg of protein.

Lipid Peroxidation (TBARS) Analysis

Malondialdehyde (MDA) levels were assessed using a TBARS assay kit (10009055, Cayman Chemical, MI, USA) (Chou et al., 2019). Brain samples (5~10 mg) were homogenized in 600 µL of 20 mM Hepes buffer (pH 7.2) using a chilled pestle. The homogenate was further processed at 30,000 rpm for 3~5 seconds. After centrifugation at 10,000 x g for 10 minutes at 4°C, the absorbance of the supernatant was measured at 362 nm.

Mitochondrial DNA Damage (8-oxodG) Determination

The levels of 8-hydroxy-2'-deoxyguanosine (8-oxodG) in brain tissue were measured using a commercial kit (589320, Cayman Chemical, MI, USA) (Okudan et al., 2016). Tissues (5~10 mg) were homogenized (1:15 w/v) in a specific buffer (137 mM NaCl, 0.27 mM KCl, 10 mM Na_2HPO_4, 0.18 mM KH_2PO_4, 1 mM EDTA, pH 6.7) and centrifuged at 10,000 x g for 10 minutes at 4°C. The supernatant was isolated and stored at -80°C until analysis. Samples were reacted with DNPH or HCl (control), precipitated with TCA (20% and 10%), and incubated in the dark. After centrifugation, the absorbance was measured spectrophotometrically at 375 nm to quantify oxidative damage according to the Levine method.

Bioactive Indicators of Liver Tissue Aging

Following sacrifice, liver tissues were surgically removed, and identical anatomical regions from each mouse were collected and stored at -20°C for subsequent analysis.

Protein Carbonyl Content in Liver

The concentration of oxidatively modified protein carbonyl groups was determined using a commercial kit (10005020, Cayman Chemical, Ann Arbor, MI, USA) based on the method by Belviranlı et al. (2013). Frozen liver samples (5~10 mg) were homogenized (1:5 w/v) in ice-cold potassium phosphate buffer (50 mM KPi, 1.1 mM EDTA, 0.1 mM PMSF, pH 6.7) and centrifuged at 10,000 x g for 15 minutes at 4°C. The supernatant was mixed with 2,4-dinitrophenylhydrazine (DNPH) and TCA, then incubated in the dark at room temperature for 60 minutes. After centrifugation (10,000 x g, 10 minutes, 4°C), the protein pellet was washed three times with an ethanol/ethyl acetate mixture (1:1 v/v) to remove unreacted DNPH. The pellet was then dissolved in guanidine hydrochloride. Protein purity was assessed by the 280 nm absorbance ratio using BSA as a standard. If the ratio was >1, protein carbonyl content was quantified spectrophotometrically at 360 nm using a molar extinction coefficient of 22,000 $M^{-1}cm^{-1}$. Results are expressed as nmol of protein carbonyl per mg of protein.

Lipid Peroxidation (TBARS) Analysis in Liver

Malondialdehyde (MDA) levels were assessed using a TBARS assay kit (10009055, Cayman Chemical, MI, USA) (Chou et al., 2019). Liver samples (5~10 mg) were homogenized in 600 µL of 20 mM Hepes buffer (pH 7.2) using a chilled pestle. The homogenate was processed at 30,000 rpm for 3~5 seconds and centrifuged at 10,000 x g for 10 minutes at 4°C. The absorbance was recorded at 362 nm at room temperature.

Mitochondrial DNA Damage (8-oxodG) Determination in Liver

The levels of 8-hydroxy-2'-deoxyguanosine (8-oxodG) were determined using a commercial kit (589320, Cayman Chemical, MI, USA). Tissues (5~10 mg) were homogenized (1:15 w/v) in buffer (137 mM NaCl, 0.27 mM KCl, 10 mM Na_2HPO_4, 0.18 mM KH_2PO_4, 1 mM EDTA, pH 6.7) and centrifuged at 10,000 x g for 10 minutes at 4°C. Supernatants were collected and stored at -80°C until analysis. Carbonyl content was quantified according to the Levine method. Briefly, DNPH or HCl was added to each sample, followed by multiple washes with ethanol/ethyl acetate. Samples were then precipitated with 20% and 10% TCA in the dark. After centrifugation, the absorbance was measured at 375 nm.

Antioxidant Biochemical Assays

At the end of the experiment, mice were euthanized via CO_2 inhalation. Blood samples were collected via cardiac puncture into EDTA-containing tubes and immediately centrifuged at 1,000 x g for 10 minutes at 4°C. Plasma and red blood cells were separated and stored at -70°C until analysis.

Superoxide Dismutase (SOD) Activity

SOD activity was measured using a commercial kit (706002, Cayman Chemical, MI, USA). Each well was filled with 200 µL of diluted radical detector and 10 µL of plasma. The

reaction was initiated by adding 20 µL of diluted xanthine oxidase, followed by incubation at room temperature for 30 minutes. Absorbance was recorded at 440~460 nm using a spectrophotometer (Tecan Sunrise with Magellan Standard software).

Catalase (CAT) Activity

CAT activity was assessed using a commercial kit (707002, Cayman Chemical, MI, USA). Wells were filled with 100 µL of assay buffer, 30 µL of methanol, and 20 µL of plasma. The reaction was initiated by adding 20 µL of hydrogen peroxide (H_2O_2) and shaken for 20 minutes at room temperature. The reaction was terminated with 30 µL of potassium hydroxide, followed by the addition of Catalase Purpald (30 µL). After 10 minutes of shaking, potassium periodate (10 µL) was added for 5 minutes. Absorbance was read at 540 nm.

Glutathione Peroxidase (GPx) Activity

GPx activity was determined using a commercial kit (703102, Cayman Chemical, MI, USA). Samples were mixed with 100 µL of assay buffer, 50 µL of GPx co-substrate mixture, and 20 µL of plasma. The reaction was initiated with 20 µL of cumene hydroperoxide. Absorbance at 340 nm was recorded once per minute for 5 consecutive time points to calculate the kinetic rate.

Glutathione Reductase (GRd) Activity

GRd activity was measured using a commercial kit (703202, Cayman Chemical, MI, USA). Assay buffer (100 µL), GSSG (20 µL), and plasma (20 µL) were added to the wells. The plate was shaken briefly, and absorbance at 340 nm was monitored every minute for at least 5 time points.

Statistical analysis

The data are expressed as the mean ± standard deviation (SD). Statistical comparisons among groups were made using one-way analysis of variance (ANOVA), followed by Duncan's post hoc test. A p-value of less than 0.05 was considered statistically significant. All statistical analyses were done using SAS software (SAS Institute, Cary, NC, USA).

RESULTS

Body Weight and Dietary Records

The changes in body weight, water consumption, and Repeat Juvenile (RJ) administration during the experimental period are presented in Tables 1 and 2. In both male and female aging mice, body weights in all four groups showed a steady and stable increase throughout the rearing and experimental period. This indicates that supplementation with RJ at 1X, 2X, and 5X dosages did not induce adverse side effects such as weight loss. Furthermore, no significant differences in body weight were observed between the four groups at either the baseline or the conclusion of the study. As shown in Tables 1 and 2, there were no significant changes in the average daily food intake among the four groups in either sex over the 12-week trial. Consequently, continuous 12-week supplementation with RJ at 1X, 2X, and 5X dosages does not significantly impact the water or food consumption of the animals.

Table 1. Changes in body weight and food intake of male aging mice during the experimental period.

Characteristics-Male	Vehicle	RJ-1X	RJ-2X	RJ-5X
Initial BW (g)	33.0± 2.7	33.1± 1.7	33.2± 1.7	33.3± 1.3
1st wk BW	33.6± 2.9	33.6± 1.8	33.4± 1.7	33.5± 1.3
2nd wk BW	33.8± 3.0	33.7± 1.9	33.5± 1.7	33.7± 1.2
3rd wk BW	33.9± 2.9	33.8± 1.9	33.6± 1.7	33.8± 1.2
4th wk BW	34.0± 2.9	33.9± 1.8	33.7± 1.7	33.9± 1.2
5th wk BW	34.1± 1.1	34.0± 1.8	33.9± 1.7	34.0± 1.3
6th wk BW	34.2± 2.9	34.1± 1.8	34.0± 1.6	34.1± 1.3
7th wk BW	34.3± 2.9	34.2± 1.8	34.0± 1.7	34.2± 1.3
8th wk BW	34.4± 3.0	34.3± 1.8	34.0± 1.7	34.3± 1.3
9th wk BW	34.6± 3.0	34.3± 1.8	34.1± 1.7	34.4± 1.3
10th wk BW	34.7± 3.1	34.5± 1.8	34.2± 1.7	34.4± 1.3
11th wk BW	34.9± 3.2	34.8± 1.7	34.3± 1.7	34.5± 1.3
12th wk BW	35.0± 3.2	35.1± 1.8	34.5± 1.6	34.7± 1.3
13th wk BW	35.2± 3.3	35.4± 1.9	34.9± 1.6	34.9± 1.5
Final BW (g)	35.4± 3.3	35.6± 1.9	35.7± 1.9	35.5± 1.6
Water intake (mL/mice/day)	5.4± 0.4	5.4± 0.3	5.4± 0.3	5.4± 0.6
Diet intake (g/mice/day)	4.5± 0.3	4.6± 0.3	4.5± 0.2	4.5± 0.4

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Table 2. Changes in body weight and food intake of female aging mice during the experimental period.

Characteristics-Female	Vehicle	RJ-1X	RJ-2X	RJ-5X
Initial BW (g)	26.8 ± 1.7	27.0 ± 1.7	27.0 ± 1.2	26.9 ± 1.5
1st wk BW	27.0 ± 1.8	27.3 ± 1.2	27.2 ± 1.1	27.1 ± 1.5
2nd wk BW	27.3 ± 1.8	27.5 ± 1.3	27.3 ± 1.1	27.2 ± 1.5
3rd wk BW	27.4 ± 1.8	27.6 ± 1.3	27.4 ± 1.1	27.3 ± 1.5
4th wk BW	27.5 ± 1.8	27.7 ± 1.3	27.5 ± 1.1	27.4 ± 1.5
5th wk BW	27.6 ± 1.8	27.8 ± 1.3	27.5 ± 1.2	27.5 ± 1.5
6th wk BW	27.6 ± 1.8	27.9 ± 1.3	27.6 ± 1.2	27.6 ± 1.5
7th wk BW	27.7 ± 1.8	27.9 ± 1.5	27.7 ± 1.2	27.7 ± 1.5
8th wk BW	27.8 ± 1.8	28.0 ± 1.3	27.8 ± 1.2	27.8 ± 1.5
9th wk BW	27.8 ± 1.8	28.1 ± 1.3	27.9 ± 1.1	27.9 ± 1.5
10th wk BW	28.0 ± 1.8	28.1 ± 1.2	28.1 ± 1.4	28.0 ± 1.5
11th wk BW	28.1 ± 1.8	28.3 ± 1.3	28.3 ± 1.4	28.3 ± 1.6
12th wk BW	28.4 ± 1.8	28.5 ± 1.3	28.6 ± 1.5	28.4 ± 1.6
13th wk BW	28.7 ± 1.9	28.8 ± 1.4	29.0 ± 1.6	28.8 ± 1.5
Final BW (g)	29.2 ± 1.9	29.1 ± 1.4	3.7 ± 1.6	29.3 ± 1.4
Water intake (mL/mice/day)	3.6 ± 0.3	3.6 ± 0.3	4.9 ± 0.3	3.7 ± 0.3
Diet intake (g/mice/day)	4.9± 0.5	5.0 ± 0.3	± 0.5	5.0 ± 0.5

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Enhancement of Learning and Memory Efficacy

The results regarding memory and learning capabilities are shown in Figure 1A. For male aging mice, the average escape latency (time to reach the platform from different quadrants) on Day 1 for the control, 1X, 2X, and 5X RJ groups was 44.3±10.5, 31.1±10.4, 30.9±7.2, and 25.1±4.8 seconds, respectively. Compared to the control group, escape latencies in the RJ groups were significantly reduced by 29.8% (p=0.0015), 30.2% (p=0.0014), and 43.3% (p<0.0001). On Day 2, latencies were 31.6±6.9, 23.0±8.2, 20.1±4.5, and 17.8±3.7 seconds, showing significant reductions of 27.2% (p=0.0031), 36.4% (p=0.0001), and 43.7% (p<0.0001). On Day 3, latencies further decreased by 26.9% (p=0.0007), 41.3% (p=0.0005), and 54.1% (p<0.0001), respectively. The overall three-day average escape latency (Figure 1B) for the male control and RJ groups was 33.4±7.4, 23.9±8.1, 21.7±4.8, and 18.0±3.9 seconds, indicating significant improvements of 28.4%, 35.0%, and 46.1% (p≤0.0018).

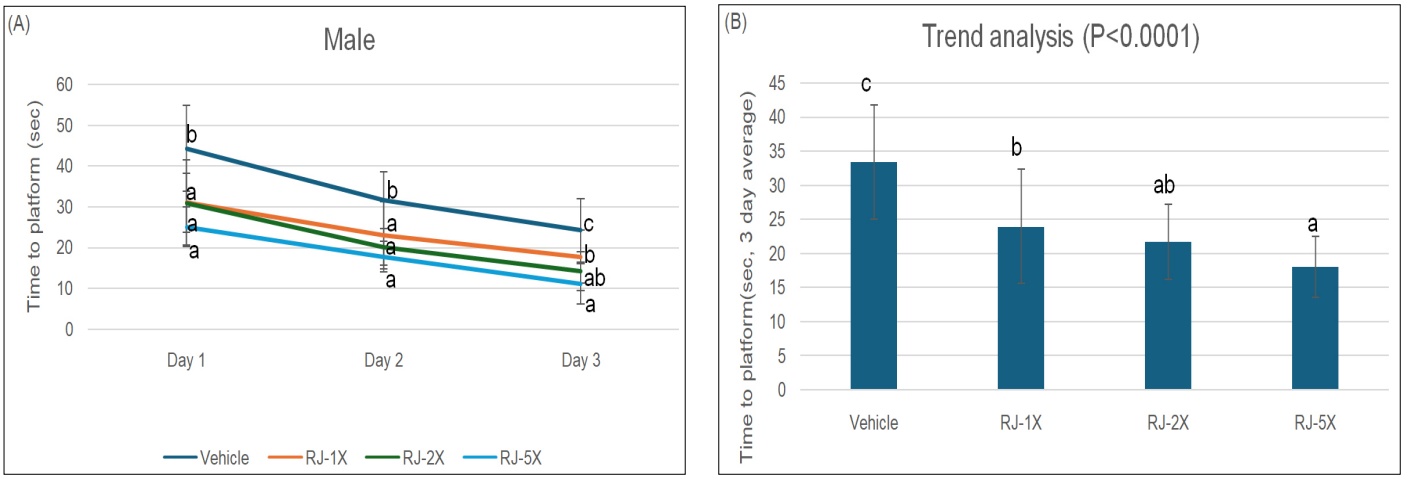


Figure 1. Effects of Repeat Juvenile (RJ) supplementation on learning and memory capabilities in male aging mice during the Morris water maze test: (A) Daily escape latency over three consecutive days; (B) Mean escape latency over the three-day period.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c) above the bars indicate significant differences ($p < 0.05$).

In female aging mice (Figure 2A), Day 1 escape latencies for the control and RJ groups (1X, 2X, 5X) were 49.0±6.8, 34.2±4.7, 30.8±5.3, and 25.0±5.9 seconds, respectively, representing significant decreases of 30.2%, 37.1%, and 49.0% ($p<0.0001$ for all). On Day 2, the RJ groups exhibited significant reductions of 31.8%, 45.6%, and 54.2% ($p<0.0001$ for all). On Day 3, the latencies significantly dropped by 29.7% ($p=0.0007$), 42.0% ($p=0.0005$), and 54.1% ($p<0.0001$). The overall three-day average latency (Figure 2B) for the female control and RJ groups was 38.4±5.3, 26.6±3.5, 22.6±3.9, and 18.5±4.0 seconds, respectively. Compared to the control, RJ supplementation significantly shortened the average exploration time by 30.7%, 41.1%, and 51.8% ($p<0.0001$ for all).

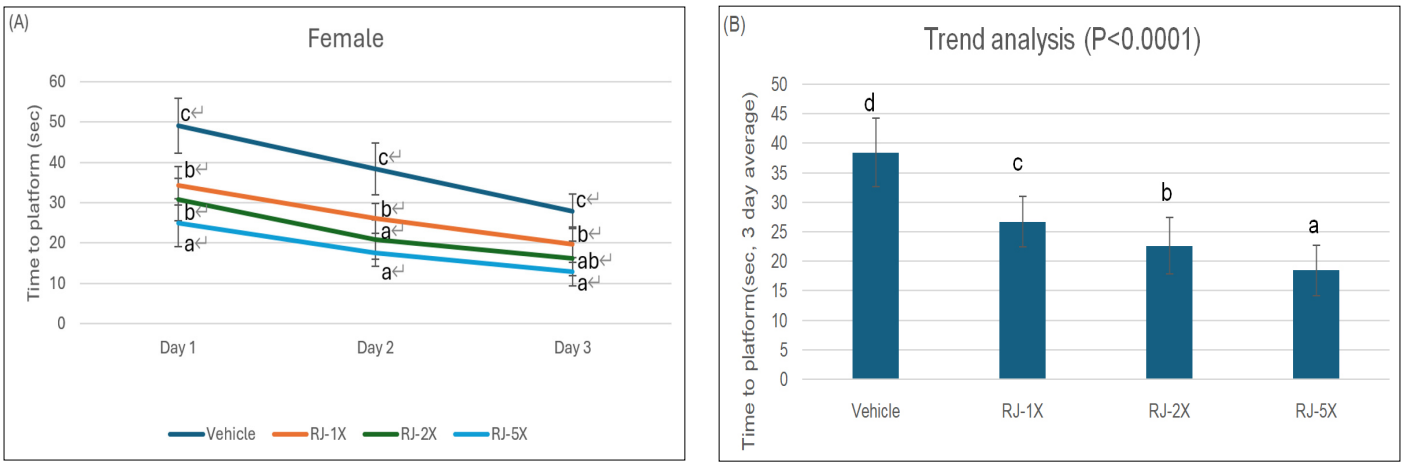


Figure 2. Effects of Repeat Juvenile (RJ) supplementation on learning and memory capabilities in female aging mice during the Morris water maze test: (A) Daily escape latency over three consecutive days; (B) Mean escape latency over the three-day period.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c, d) above the bars indicate significant differences ($p < 0.05$).

Effects of RJ Supplementation on Brain Dopamine Content

At the end of the experiment, brain tissues were collected to analyze dopamine levels. As shown in Figure 3A, the brain dopamine content in male aging mice for the vehicle control, 1X, 2X, and 5X RJ groups was 65.24±4.22, 72.24±4.52, 76.32±2.49, and 78.22±2.60 ng/mL, respectively. Compared to the control group, supplementation with RJ at 1X, 2X, and 5X dosages significantly increased brain dopamine levels by 1.11-fold, 1.17-fold, and 1.20-fold ($p < 0.0001$), respectively. Similarly, in female aging mice (Figure 4A), the brain dopamine content for the control, 1X, 2X, and 5X RJ groups was 70.43±2.61, 74.84±2.88, 76.59±3.14, and 84.60±6.55 ng/mL, respectively. Relative to the control group, RJ supplementation significantly elevated dopamine levels by 1.06-fold ($p = 0.0220$), 1.09-fold ($p = 0.0019$), and 1.20-fold ($p < 0.0001$) for the respective dosage groups.

Effects of RJ Supplementation on Brain Protein Carbonyl Content

At the conclusion of the study, brain tissues were analyzed for protein carbonyl content, a primary indicator of oxidative protein modification. As shown in Figure 3B, the brain protein carbonyl levels in male aging mice for the control, 1X, 2X, and 5X RJ groups were 5.78±0.58, 3.69±0.77, 2.18±0.62, and 2.11±0.68 nmol/mg protein, respectively. Compared to the control group, RJ supplementation significantly reduced brain protein carbonyl levels by 36.2%, 62.3%, and 63.5% ($p < 0.0001$). For female aging mice (Figure 4B), the levels were 6.31±1.12, 2.71±0.59, 2.30±0.85, and 2.18±0.49 nmol/mg protein, respectively, representing significant reductions of 57.1%, 63.5%, and 65.5% ($p < 0.0001$).

Effects of RJ Supplementation on Brain Lipid Peroxidation (TBARS)

Brain TBARS levels were quantified to assess lipid peroxidation in the central nervous system. In male aging mice (Figure 3C), TBARS concentrations for the control and RJ groups (1X, 2X, 5X) were 4.12±0.64, 3.25±0.34, 3.17±0.33, and 3.12±0.38 nmol/mg protein, respectively. RJ supplementation significantly lowered brain TBARS content by 21.1%, 23.1%, and 24.3% ($p < 0.0001$). In female aging mice (Figure 4C), TBARS levels were 5.38±0.65, 4.30±0.48, 4.21±0.53, and 4.16±0.45 nmol/mg protein, showing significant reductions of 20.1%, 21.7%, and 22.7% ($p < 0.0001$).

Effects of RJ Supplementation on Brain 8-hydroxy-2'-deoxyguanosine (8-OHdG)

The impact of RJ on mitochondrial DNA damage in the brain was evaluated via 8-OHdG levels. In male aging mice (Figure 3D),

8-OHdG concentrations in the control and RJ groups (1X, 2X, 5X) were 776.7±60.1, 695.3±75.6, 641.1±69.8, and 571.4±23.1 pg/mL DNA, respectively. This equates to significant reductions of 10.5% ($p = 0.0049$), 17.5% ($p < 0.0001$), and 26.4% ($p < 0.0001$). For female aging mice (Figure 4D), the levels were 689.6±63.5, 621.8±16.8, 601.2±45.3, and 533.3±48.7 pg/mL DNA. RJ supplementation significantly decreased 8-OHdG levels by 9.8% ($p = 0.0025$), 12.8% ($p = 0.0002$), and 22.7% ($p < 0.0001$).

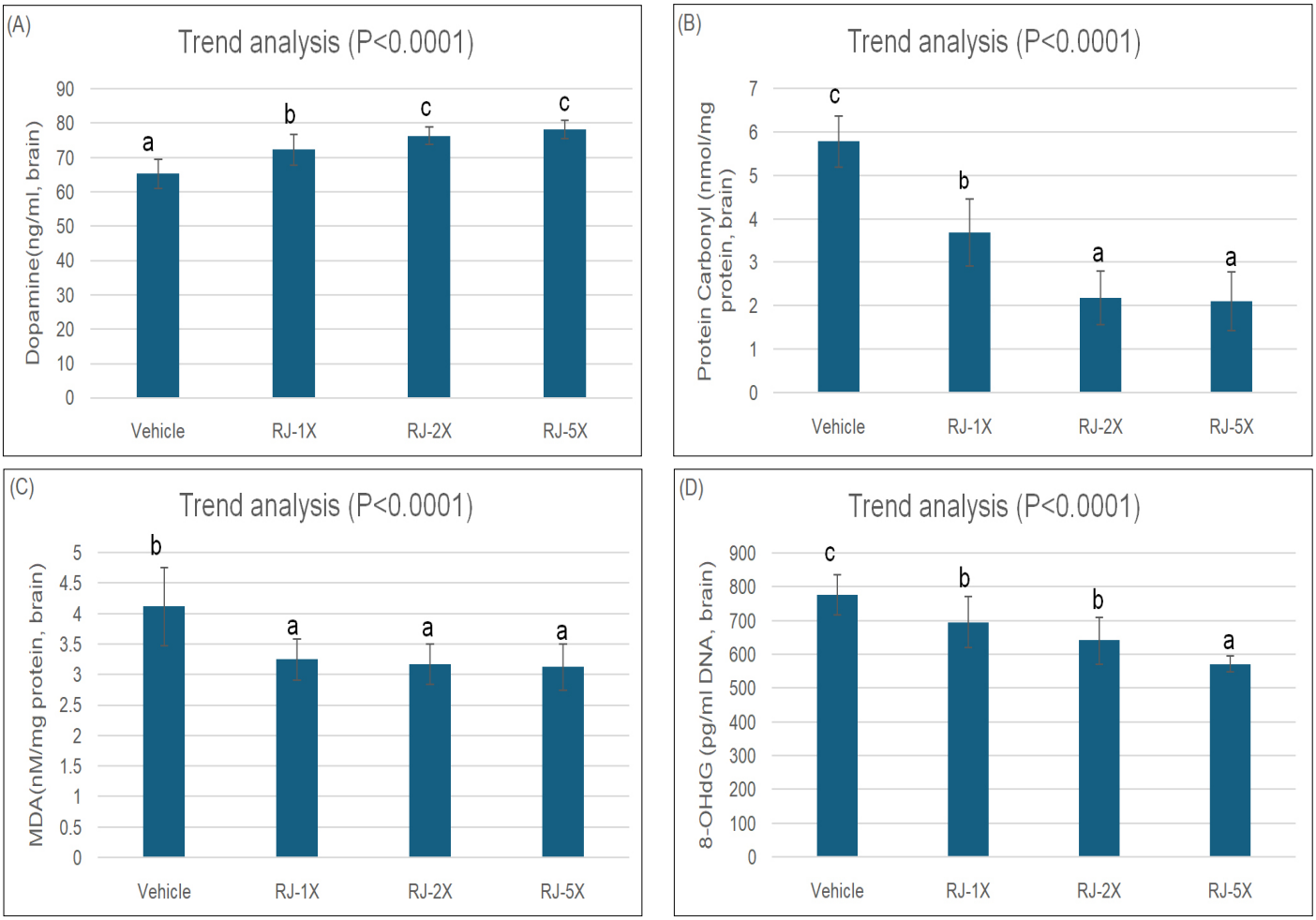
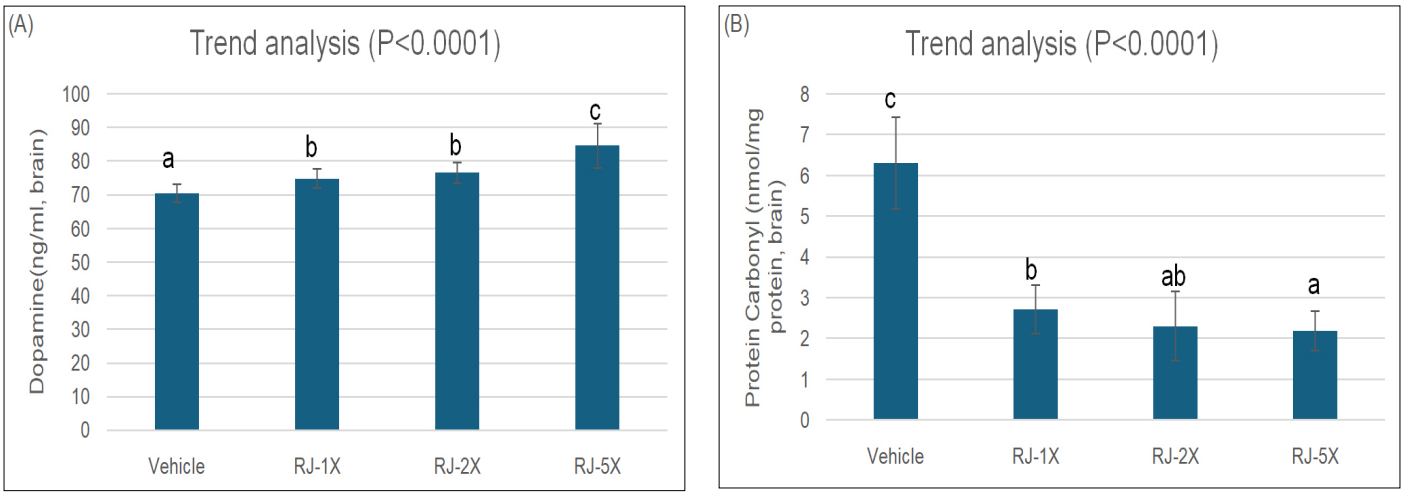
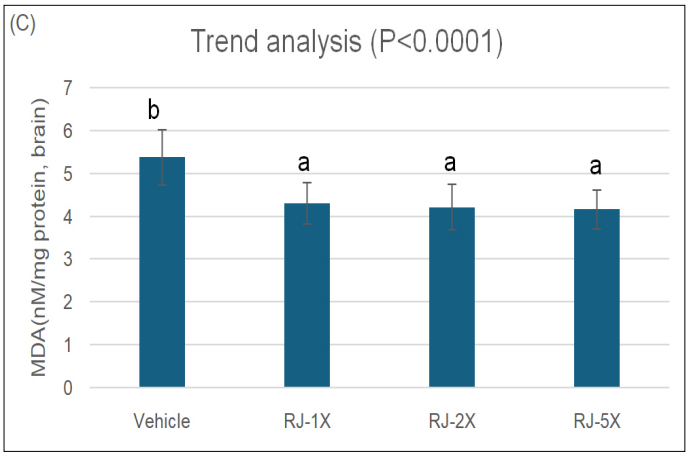


Figure 3. Effects of Repeat Juvenile (RJ) supplementation on brain aging biomarkers in male aging mice: (A) Brain dopamine content; (B) Brain protein carbonyl content; (C) Brain malondialdehyde (MDA) levels; and (D) Brain 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c) above the bars indicate significant differences ($p < 0.05$).





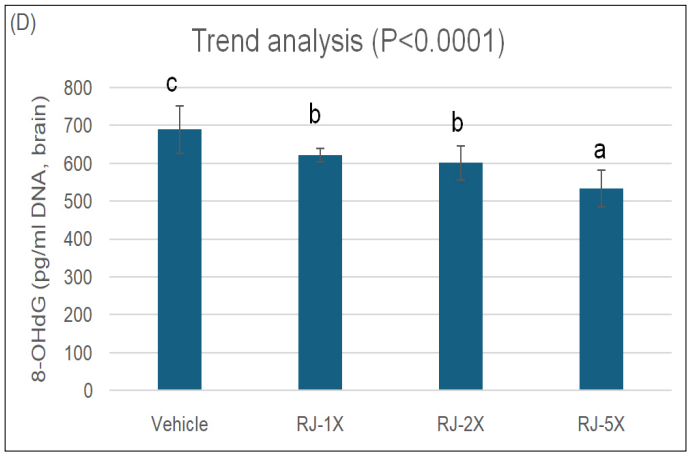


Figure 4. Effects of Repeat Juvenile (RJ) supplementation on brain aging biomarkers in female aging mice: (A) Brain dopamine content; (B) Brain protein carbonyl content; (C) Brain malondialdehyde (MDA) levels; and (D) Brain 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c) above the bars indicate significant differences ($p < 0.05$).

Effects of RJ Supplementation on Liver Protein Carbonyl Content

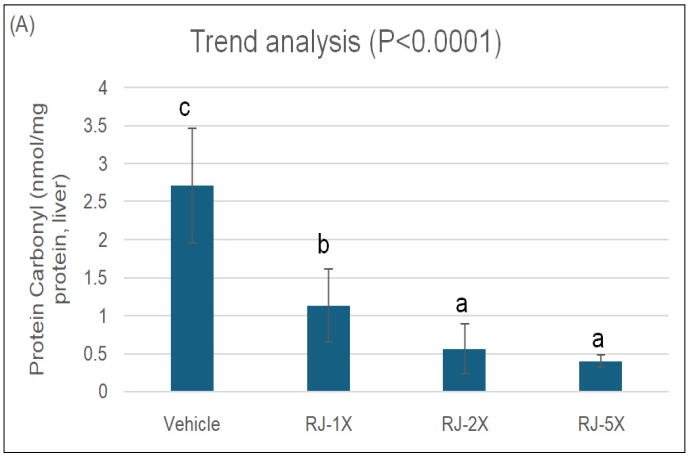
At the conclusion of the experiment, liver tissues were analyzed for protein carbonyl content, a marker of oxidative protein modification. As shown in Figure 5A, the liver protein carbonyl levels in male aging mice for the vehicle control, 1X, 2X, and 5X RJ groups were 2.71±0.75, 1.13±0.48, 0.56±0.33, and 0.40±0.08 nmol/mg protein, respectively. Compared to the control group, RJ supplementation at 1X, 2X, and 5X dosages significantly reduced liver protein carbonyl levels by 58.3%, 79.3%, and 85.2% ($p < 0.0001$). Similarly, in female aging mice (Figure 6A), the levels were 2.58±0.71, 1.08±0.46, 0.53±0.31, and 0.39±0.07 nmol/mg protein, respectively, representing significant reductions of 58.1%, 79.5%, and 84.9% ($p < 0.0001$).

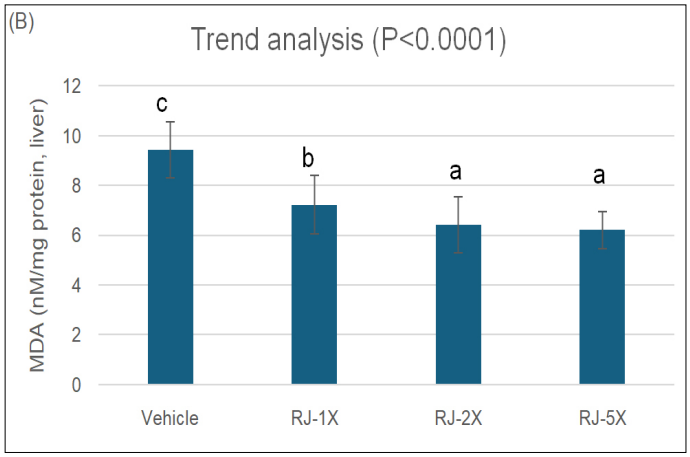
Effects of RJ Supplementation on Liver Lipid Peroxidation (TBARS)

Liver TBARS content was measured to evaluate lipid peroxidation. In male aging mice (Figure 5B), TBARS levels for the control and RJ groups (1X, 2X, 5X) were 9.42±1.13, 7.22±1.17, 6.41±1.12, and 6.21±0.74 nmol/mg protein, respectively. RJ supplementation significantly decreased TBARS levels by 23.3%, 32.0%, and 34.1% ($p < 0.0001$). In female aging mice (Figure 6B), the TBARS levels were 10.69±1.15, 7.93±0.77, 6.27±0.97, and 6.13±1.25 nmol/mg protein, showing significant reductions of 25.8%, 41.3%, and 42.7% ($p < 0.0001$).

Effects of RJ Supplementation on Liver 8-hydroxy-2'-deoxyguanosine (8-OHdG)

The impact on mitochondrial DNA damage was assessed via liver 8-OHdG levels. In male aging mice (Figure 5C), 8-OHdG concentrations in the control and RJ groups (1X, 2X, 5X) were 636.0±55.8, 531.0±44.7, 522.3±39.1, and 522.0±21.7 pg/mL DNA, respectively. This equates to significant reductions of 16.5%, 17.9%, and 17.9% ($p < 0.0001$). For female aging mice (Figure 6C), the levels were 592.8±69.9, 511.5±49.8, 439.0±47.7, and 385.8±62.9 pg/mL DNA. Supplementation significantly reduced 8-OHdG by 13.7% ($p = 0.0036$), 25.9% ($p < 0.0001$), and 34.9% ($p < 0.0001$).





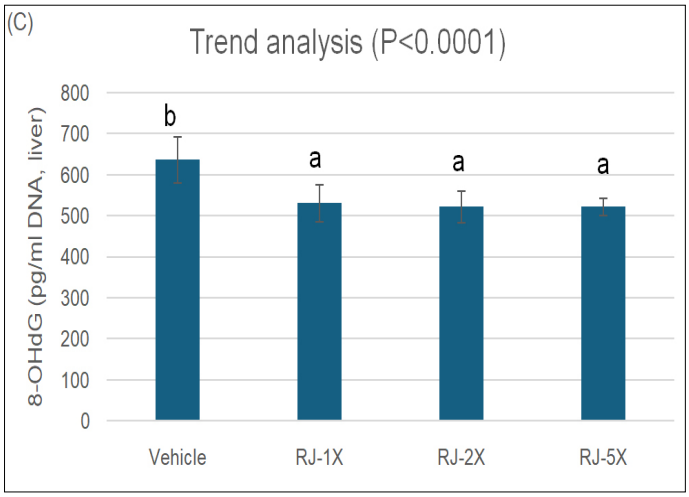


Figure 5. Effects of Repeat Juvenile (RJ) supplementation on liver aging biomarkers in male aging mice: (A) Liver protein carbonyl content; (B) Liver malondialdehyde (MDA) levels; and (C) Liver 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c) above the bars indicate significant differences ($p < 0.05$).

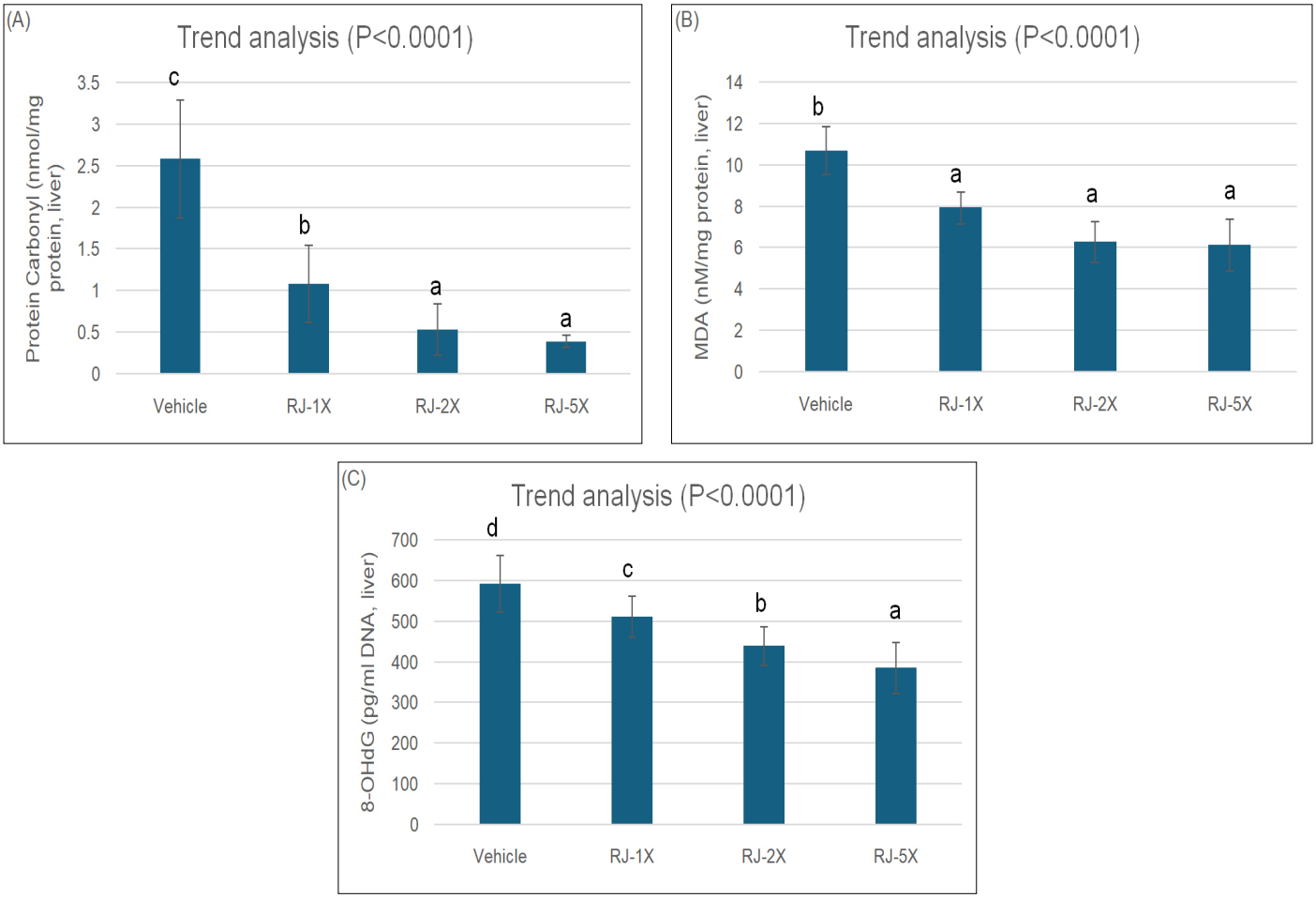


Figure 6. Effects of Repeat Juvenile (RJ) supplementation on liver aging biomarkers in female aging mice: (A) Liver protein carbonyl content; (B) Liver malondialdehyde (MDA) levels; and (C) Liver 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c, d) above the bars indicate significant differences ($p < 0.05$).

Effects of RJ Supplementation on Superoxide Dismutase (SOD) Activity

SOD activity in the blood was analyzed to evaluate systemic antioxidant capacity. As shown in Figure 7A, SOD activity in male aging mice for the control and RJ groups (1X, 2X, 5X) was 0.68±0.17, 0.86±0.14, 1.00±0.24, and 1.08±0.47 U/mg protein, respectively. Compared to the control, RJ supplementation significantly enhanced SOD activity by 1.26-fold ($p = 0.0385$), 1.47-fold ($p = 0.0005$), and 1.59-fold ($p < 0.0001$). In female aging mice (Figure 8A), SOD activity was 0.65±0.10, 0.88±0.09, 1.19±0.18, and 1.35±0.16 U/mg protein. Supplementation significantly increased activity by 1.35-fold ($p = 0.0006$), 1.83-fold ($p < 0.0001$), and 2.08-fold ($p < 0.0001$).

Effects of RJ Supplementation on Catalase (CAT) Activity

Blood samples were collected at the end of the experiment to analyze CAT activity. As shown in Figure 7B, the CAT activity in male aging mice for the vehicle control, 1X, 2X, and 5X RJ groups was 0.60±0.08, 0.73±0.09, 0.79±0.15, and 0.85±0.14 U/mg protein, respectively. Compared to the control group, CAT activity in the 1X, 2X, and 5X RJ groups was significantly enhanced by 1.22-fold ($p = 0.0209$), 1.32-fold ($p = 0.0017$), and 1.42-fold ($p < 0.0001$). As shown in Figure 8B, CAT activity in female aging mice for the control and RJ groups (1X, 2X, 5X) was 0.59±0.10, 0.73±0.13, 0.85±0.12, and 1.08±0.13 U/mg protein, representing significant increases of 1.24-fold ($p = 0.0185$), 1.44-fold ($p < 0.0001$), and 1.83-fold ($p < 0.0001$).

Effects of RJ Supplementation on Glutathione Peroxidase (GPx) Activity

As illustrated in Figure 7C, the GPx activity in male aging mice for the control and RJ groups (1X, 2X, 5X) was 12.50±1.54, 15.14±2.11, 21.44±2.44, and 23.94±2.72 U/mg protein, respectively. RJ supplementation significantly increased GPx activity by 1.21-fold ($p = 0.0125$), 1.72-fold ($p < 0.0001$), and 1.92-fold ($p < 0.0001$). For female aging mice (Figure 8C), the GPx activity levels were 18.46±1.31, 21.18±2.19, 24.25±1.32, and 25.22±1.90 U/mg protein, showing significant enhancements of 1.15-fold ($p = 0.0012$), 1.31-fold ($p < 0.0001$), and 1.37-fold ($p < 0.0001$).

Effects of RJ Supplementation on Glutathione Reductase (GRd) Activity

The GRd activity in male aging mice for the control and RJ groups (1X, 2X, 5X) was 0.24±0.07, 0.32±0.06, 0.32±0.06, and 0.47±0.10 U/mg protein, respectively (Figure 7D). Supplementation significantly boosted GRd activity by 1.33-fold ($p = 0.0317$), 1.33-fold ($p = 0.0197$), and 1.96-fold ($p < 0.0001$). In female aging mice (Figure 8D), the GRd activity was 0.26±0.04, 0.35±0.06, 0.44±0.07, and 0.62±0.07 U/mg protein. Compared to the control group, the RJ-supplemented groups exhibited significant increases of 1.35-fold ($p = 0.0037$), 1.69-fold ($p < 0.0001$), and 2.38-fold ($p < 0.0001$).

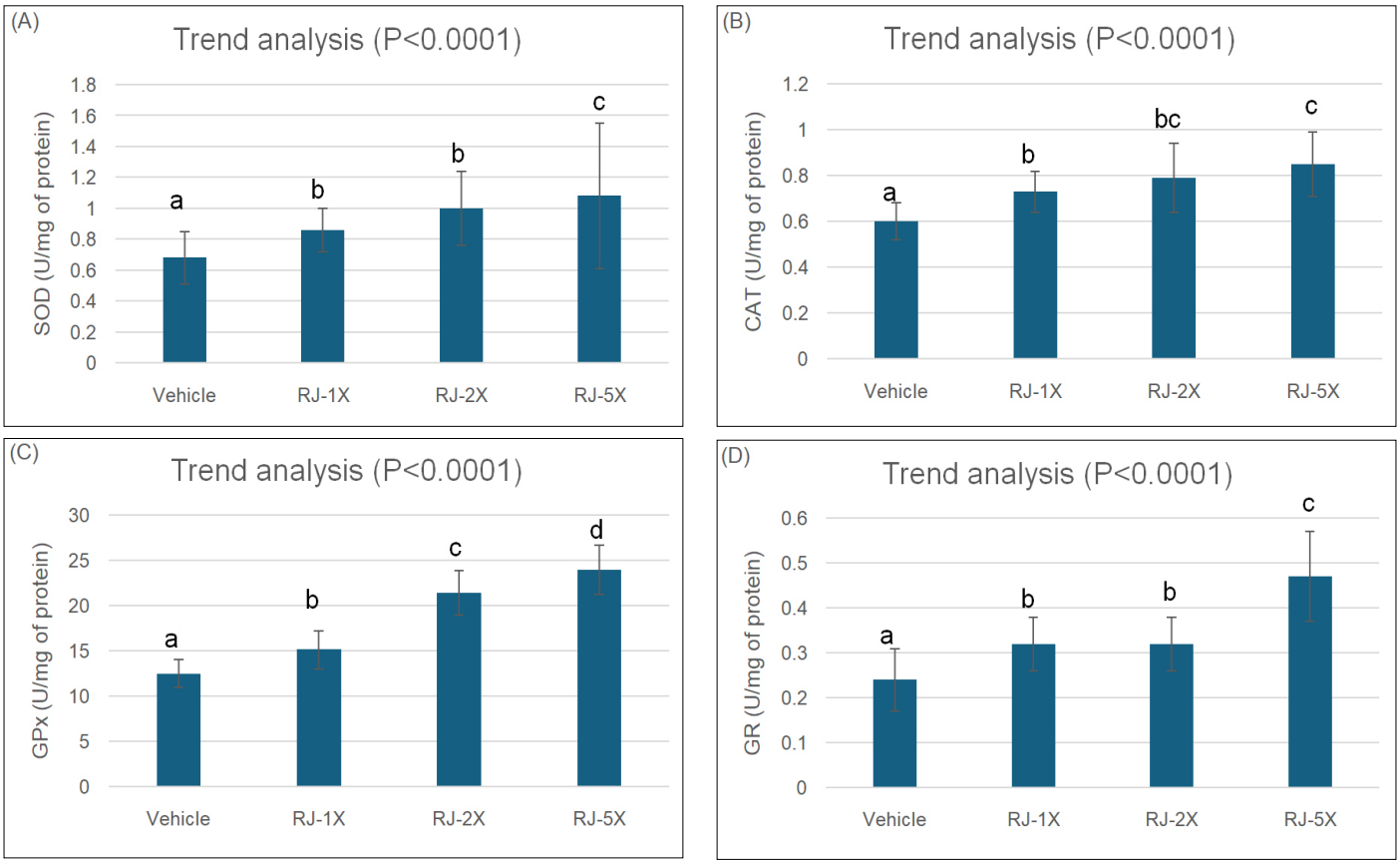


Figure 7. Effects of Repeat Juvenile (RJ) supplementation on plasma antioxidant biochemical parameters in male aging mice: (A) Plasma SOD activity; (B) Plasma CAT activity; (C) Plasma GPx activity; and (D) Plasma GRd activity.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c, d) above the bars indicate significant differences ($p < 0.05$).

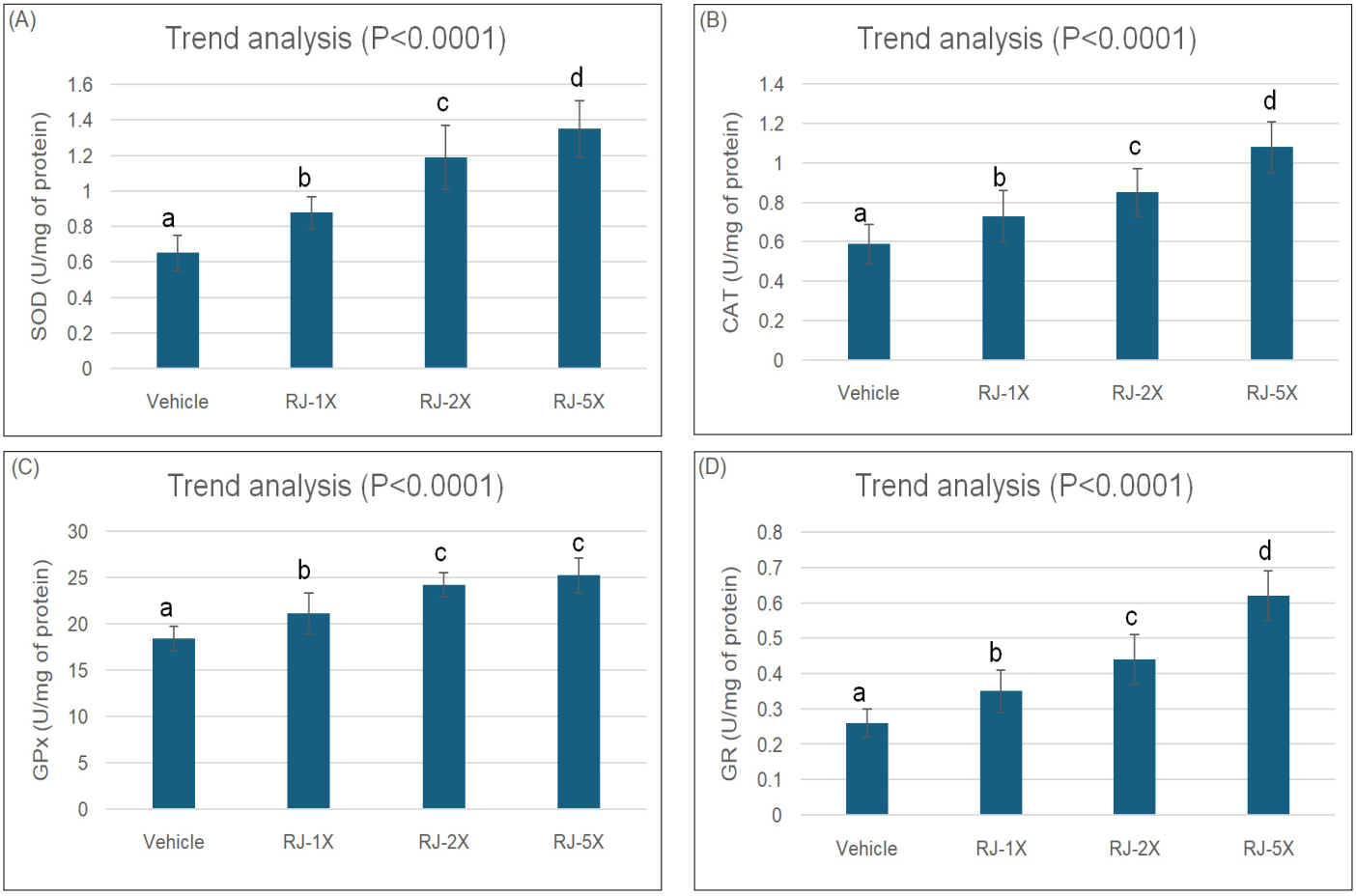


Figure 8. Effects of Repeat Juvenile (RJ) supplementation on plasma antioxidant biochemical parameters in female aging mice: (A) Plasma SOD activity; (B) Plasma CAT activity; (C) Plasma GPx activity; and (D) Plasma GRd activity.

Experimental animals were randomly assigned to four groups (n=10 per group): (1) Vehicle (control group); (2) RJ-1X (recommended human dose of Repeat Juvenile tablets); (3) RJ-2X (2X human dose); and (4) RJ-5X (5X human dose). All data are expressed as mean ± SD. The energy density of the standard laboratory diet (Chow 5001) was 3.36 kcal/g.

Different letters (a, b, c, d) above the bars indicate significant differences ($p < 0.05$).

DISCUSSION

In this study, supplementation with Repeat Juvenile (RJ) tablets at 1X, 2X, and 5X the recommended human equivalent dose (3,200 mg/day) significantly enhanced learning and memory capabilities, reduced aging biomarkers in the brain and liver, and increased antioxidant enzyme activities, thereby demonstrating substantial anti-aging efficacy. Chicken sternal cartilage hydrolysate is rich in chondroitin, hyaluronic acid, glucosamine, and Type II collagen. While Type II collagen is widely recognized for its anti-inflammatory properties and its role in treating osteoarthritis (Orhan et al., 2021), research regarding its anti-aging potential remains relatively scarce. Previous studies have indicated that Type II collagen can enhance the body's antioxidant capacity by increasing SOD and GSH activities while reducing MDA content. Furthermore, it mitigates inflammatory responses by modulating inflammatory cytokines and significantly reducing protein carbonyl content (Yan et al., 2020), which helps protect the brain from oxidative damage. Given that antioxidants such as icariin, N-tert-butyl-α-phenylnitrone, and vitamins C and E have been shown to improve memory and protect the brain from oxidative stress by increasing monoamines (He et al., 2010), it can be inferred that Type II collagen supplementation may also contribute to elevated dopamine levels in the brain, thereby improving learning and memory performance.

Resveratrol (3,4',5-trihydroxystilbene; $C_{14}H_{12}O_3$), a polyphenol found in grapes, berries, and peanuts, exhibits multiple bioactivities, including antioxidant, immunomodulatory, antimicrobial, anticancer, and antidiabetic effects, as well as cardiovascular disease (CVD) prevention and senescence delay (Zhang et al., 2021). As an antioxidant, resveratrol acts through a dual mechanism: it increases the activity of antioxidant enzymes and serves as a direct free radical

scavenger (Izzo et al., 2021). It stimulates Nrf2 (Nuclear factor erythroid-2-related factor) activity and promotes SOD and CAT expression, thereby inhibiting the production of reactive oxygen species (ROS) and reducing oxidative stress. Prior research indicated that supplementation with 500 mg/day of resveratrol significantly increases SOD and total antioxidant capacity while lowering MDA concentrations. Additionally, it elevates other antioxidant enzymes such as GPx and Glutathione S-transferases (GST) (García-Martínez et al., 2021). Regarding its anti-aging mechanisms, resveratrol stimulates the longevity factor Sirtuin 1 (Sirt1) and modulates the Akt/mTOR pathway to inhibit mitochondrial ROS, enhance mitochondrial biogenesis, and improve overall mitochondrial function. Furthermore, resveratrol modulates NF-κB and Sirt1 to decrease levels of inflammatory markers such as IL-1β, TNF-α, and MCP-1. By upregulating Sirt1, resveratrol promotes FoxO1 and inhibits the p53 protein, thereby regulating the activity of pro-apoptotic proteins (Bim, Bax) and anti-apoptotic proteins (Bcl-2) to reduce programmed cell death (Zhou et al., 2021).

Sesame seeds contain substantial amounts of vitamin B1, dietary fiber, and protein, as well as essential minerals such as iron, calcium, magnesium, copper, zinc, and phosphorus (Pathak et al., 2014). Beyond these valuable constituents, sesame is an excellent source of vitamin E, a phenylpropanoid derivative. Its chemical structure features a hydroxyl (-OH) group, which provides reducing power and the ability to donate electrons (Neelam et al., 2020). The presence of a saturated hydroxy chain within its pentacyclic structure confers both reducing and lipophilic properties to vitamin E (Ciarcià et al., 2022). Furthermore, literature indicates that sesame contains 50–60% high-quality oil, which is rich in bioactive compounds such as polyunsaturated fatty acids (PUFAs), lignans, tocopherols, and phytosterols (Pathak et al., 2014). These active components have been found to offer extensive health benefits, including anti-adipogenic, anti-atherosclerotic, anti-inflammatory, antioxidant, anticancer, cholesterol-lowering, anti-degenerative, and cardioprotective effects (Orsavova et al., 2015).

In the present study, supplementation with Repeat Juvenile tablets led to a reduction in aging biomarkers and a significant enhancement of antioxidant capacity and memory/learning capabilities in aging mice. This improvement may be attributed to the synergistic effects of the formulation's integral components—including resveratrol, chicken sternal cartilage hydrolysate, and sesame extract. Together, these ingredients enhance antioxidant defenses and suppress the secretion of aging-related biomarkers, ultimately leading to improved cognitive function and delayed senescence.

In summary, the senescence-delaying effects of Repeat Juvenile tablets are likely achieved through three primary pathways: (1) enhancement of systemic antioxidant capacity, (2) mitigation of inflammation, and (3) reduction in the secretion of aging biomarkers. Consequently, this research confirms that Repeat Juvenile tablets possess the efficacy to improve memory and learning capabilities and delay aging, positioning them as a promising potential health supplement for anti-aging applications.

CONCLUSION

The results of this study demonstrate that 12 weeks of continuous supplementation with Repeat Juvenile (RJ) tablets:

1. Enhances learning and memory capabilities.
2. Reduces aging-related biomarkers in the brain.
3. Diminishes oxidative aging markers in the liver.
4. Strengthens overall systemic antioxidant capacity.

Based on dose-conversion calculations, a daily intake of 3,200 mg of Repeat Juvenile tablets for adults is recommended to provide health benefits for delaying senescence and promoting healthy aging.

ACKNOWLEDGMENT

This research was founded by HealthTake Co., Ltd.

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