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Original Article

Protective Effect of Boric Acid on Oxidative Damage and Cognitive Function in Aging Modeled Rats

Yaşlı Sıçan Modelinde Borik Asidin Oksidatif Hasar ve Bilişsel Fonksiyonlar Üzerine Koruyucu Etkisi

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ABSTRACT

Objective: Aging is a degenerative process. Therefore, the background of our study is to evaluate the effects of boron, one of the important underground resources in Türkiye, on aging and related diseases. This study aimed to assess the antioxidant effect and the cognitive functions of boric acid (BA) in a D-galactose (D-gal)-induced aging model.

Methods: Eight male Wistar rats, each 12 weeks old, were split into four groups at random: control, D-gal, BA and D-gal+BA. An experimental aging model was induced by a single subcutaneous injection of D-gal (150 mg/kg/day), and BA (100 mg/kg/day) was administered by oral gavage for 12 weeks. The novel object recognition test (NORT) and Morris water maze (MWM) were used to evaluate the cognitive ability of rats.

Results: At the end of the experimental period, glutathione (GSH) and malondialdehyde (MDA) levels were assessed in serum and brain tissue. The treatment of D-gal induced aging rats with BA significantly decreased the MDA level ($p<0.05$) and increased the GSH level, although the increase was not significant. Moreover, NORT and MWM tests showed that BA significantly improved ($p<0.05$) cognitive deficits in D-Gal + BA treated rats.

Conclusions: BA prevents D-gal-induced memory deficit by decreasing oxidative stress. Hence, BA was a good candidate for addressing age-related neurodegenerative disorders and cognitive function improvements.

Keywords: Boric acid, D-galactose, aging, oxidative stress, rat

ÖZ

Amaç: Yaşlanma dejeneratif bir süreçtir. Bu nedenle çalışmamızın arka planı, Türkiye'nin önemli yeraltı kaynaklarından biri olan borun yaşlanma ve ilişkili hastalıklar üzerindeki etkilerini değerlendirmektir. Bu çalışma, D-galaktoz (D-gal) kaynaklı yaşlanma modelinde borik asidin (BA) antioksidan etkisini ve bilişsel işlevlerini değerlendirmeyi amaçlamaktadır.

Yöntemler: On iki haftalık erkek Wistar sıçanlar (n=8) rastgele dört gruba ayrıldı; kontrol, D-gal, BA ve D-gal+BA. Deneysel yaşlanma modeli, 12 hafta boyunca D-gal (150 mg/kg/gün) tek doz deri altı enjeksiyonu ve BA (100 mg/kg/gün) oral gavaj uygulanarak oluşturuldu. Sıçanların bilişsel yeteneklerini değerlendirmek için yeni nesne tanıma testi (NORT) ve Morris su labirenti (MWM) testi kullanıldı.

Bulgular: Deneysel periyodun sonunda, serum ve beyin dokusunda glutatyon (GSH) ve malondialdehit (MDA) seviyeleri değerlendirildi. D-gal ile uyarılan yaşlı sıçanların BA ile tedavisi MDA seviyesini anlamlı ölçüde azalttı ($p<0,05$), ancak GSH seviyesini önemli ölçüde artırmadı. Üstelik, NORT ve MWM testleri, BA'nın D-gal +BA ile tedavi edilen sıçanlarda bilişsel eksikliği önemli ölçüde iyileştirdiğini gösterdi ($p<0,05$).

Sonuçlar: Sonuç olarak, BA oksidatif stresi azaltarak D-gal ile uyarılan hafıza eksikliğini önlemektedir. Bu nedenle, BA yaşa bağlı nörodejeneratif bozukluklar ve bilişsel işlevler için iyi bir adaydır.

Anahtar kelimeler: Borik asit, D-galaktoz, yaşlanma, oksidatif stres, sıçan

INTRODUCTION

Aging is a degenerative process that raises the risk of illness and mortality while also causing a time-dependent deterioration in physiological functions. According to studies, the number of functionally competent mitochondria in post-mitotic cells may decrease with age due to progressive membrane damage caused by free radicals and lipid peroxides, which are by-products of oxygen reduction during respiration. Additionally, cellular adenosine triphosphate production may decrease and peroxide production may increase as a result of this

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damage[1]. The majority of intracellular reactive oxygen species (ROS) are assumed to be generated as a byproduct of the respiratory chain's oxidation-reduction processes in the mitochondria[2]. ROS's principal intracellular source is the mitochondria, which can be directly attacked by generated ROS[3]. However, it is widely acknowledged that ROS overproduction and leakage from mitochondria harms proteins, lipids, and nucleic acids, among other cellular constituents. Most ROS generated during aerobic metabolism can be eliminated by a number of antioxidant enzymes and small molecular weight antioxidants found in cells and mitochondria, under normal physiological conditions[4,5].

Long-term (LT) consumption of D-galactose (D-gal), present in a variety of foods including milk and dairy products, chocolate, and honey, has been demonstrated to induce alterations that mimic the aging process that occurs naturally in animals[6]. D-galactokinase or galactose-1-phosphate uridyltransferase usually metabolizes D-gal in mammals; However, aberrant metabolism is brought on by excessive D-gal. During this process, D-gal is changed into galactitol, which can build up inside the cell and cause osmotic stress and ROS. The reduced form of nicotine adenine dinucleotide phosphate causes a decrease in glutathione (GSH) reductase activity, while excess D-gal also leads to the production of galactitol by aldose reductase activity. Consequently, the cell experiences a build-up of free radical species, including hydrogen peroxide, leading to severe oxidative damage. Furthermore, galactose oxidase can catalyze the conversion of large concentrations of D-gal to aldose hydroperoxides, which form ROS and superoxide anions. Cellular damage and oxidative stress are caused by all of these metabolic mechanisms[7,8].

Boron, a bioactive non-metal, is in group 3A in the periodic table. Boric acid (BA) is found in nature as the sassolite mineral. It is stated that when dietary boron compounds are taken orally, they are rapidly biotransformed into BA in the gastrointestinal tract, and almost all of them are absorbed as BA and transported to the tissues via the blood[9]. BA is a dynamic trace element needed by many organisms, including humans, for biological and metabolic activities and plays significant roles. But its exact biochemical mode of action is still unknown. It is generally hypothesized that it could affect vital biochemical processes such as oxidative stress, energy metabolism, endocrine activities, and the metabolism of bones and minerals. Dietary BA sources are plant-based and are mostly found in fruits such as dried apricots, raisins, almonds, hazelnuts, avocados, chickpeas, quince, wine, vine leaves, parsley, and peaches[10,11]. BA interacts with hydroxyl groups in serine structures, with N in histidine's imidazole group, or with cis-hydroxyl groups on the ribosyl segments of nucleotides and with serine proteases in both humans and higher animals. These interactions may affect the regulation of specific metabolic pathways and enzymatic activity of serine proteases or oxidoreductases that require pyridine or flavin nucleotides[10].

Studies have shown that BA has antioxidant effects, strengthens the immune system, regulates energy metabolism and calcium, plays a role in bone growth and wound healing, increases mental performance, the amount of reduced GSH in the body, and reduces oxidative damage[12,13]. Since it has been used safely in previous experimental studies, we used 100 mg/kg for the BA dose in our study. The acute LD_{50} value of BA was found to be 3450 mg/kg for mice and 2660 mg/kg for rats using biochemical analyses[14,15].

In this study, we assessed BA's protective effects on oxidative stress and cognitive functioning using a mimetic aging model.

MATERIALS and METHODS

Chemicals

D-gal and BA were purchased from Sigma-Aldrich (St. Louis, MO, USA).

Animal Studies

Thirty-two male Wistar albino rats, aged three months, were used in the investigation. The rats were housed in typical cages with a 12-hour light and dark cycle at a temperature of 22±2 °C. Standard pellet feed was given to the rats on an ad libitum basis. This investigation was conducted in the laboratory of the Üsküdar University Experimental Research Unit. The Üsküdar University Animal Experiments Ethics Committee approved the study protocol (approval no: 2021-10, date: 24.12.2021).

Experimental Procedure

The animals were divided into four groups. The eight rats in the control group were fed commercial rat chow. At the same time, the animals in the D-gal group (n=8) received 150 mg/kg/day of D-gal subcutaneously (s.c.); The animals in the BA group (n=8) received 100 mg/kg/day of BA by oral gavage; and the animals in the D-gal+BA group (n=8) received a combination of D-gal (150 mg/kg/day) by s.c. injection and BA (100 mg/kg/day) by oral gavage during 12 weeks. In our study, the BA dose was estimated by Kar et al.[14] using a specific reference, while the D-gal dose was determined by Çoban et al.[16].

Novel Object Recognition Test

The novel object recognition test (NORT) uses identical objects with varying colors and shapes in four stages to assess the short-term (ST) and long-term visual memory of rats: habituation, retention, ST memory, and LT memory sessions. The animals were accustomed to an empty apparatus during the habituation stage, after which two identical objects were placed there. Two hours later, the ST memory phase began, replacing one object with another. After 24 hours, the LT memory phase began, replacing the object changed in the previous phase with another object. To avoid odor interference between tests, ethyl alcohol was used to clean the objects and test apparatus. The capacity of rats to distinguish between familiar and new objects was measured using the discrimination index (DI) and recognition index (RI). These indexes suggest that healthy animals should spend more time examining unfamiliar objects. The reference was used to calculate DI and RI[17].

Morris Water Maze

Morris Water Maze (MWM) is one of the preferred tests when evaluating learning and memory performance (especially hippocampus-dependent). The iterative process of teaching the platform's location is known as the learning phase. During the testing phase, the elevated platform's previously taught position should be identified, and the platform should be guided to its previously taught position. There are guiding clues placed throughout the tank to aid in the learning process. Water fills the tank, which has a 150 cm diameter and a 60 cm height. Measurements are taken via video and the image is transferred to the monitor via the camera system mounted on the tank (SMART 3.0)[18].

The platform is positioned in a randomly chosen quadrant (northwest, northeast, southwest, or southeast) created by dividing the final image. The rats were let go into the water from their assigned quadrants for five days, and they had up to 120 seconds to locate the platform. Rats that could not find the platform were directed to the platform and removed, and then kept on the platform for 15 seconds. On the 6th day, the rats were left in the water, the platform was removed, and measurements were made using the system.

Preparation of Serum and Brain Tissue Samples

After the 12-week trial was over, blood was drawn from the rats' hearts, and they were then given intramuscular injections of the anesthetic Xylazine (8-10 mg/kg) and ketamine (80-100 mg/kg). After being centrifuged for ten minutes at 3,000 rpm, blood samples were kept at -80 °C. After the brain tissues were swiftly removed, they were gently washed in saline solution (0.9%) and homogenized in cold 0.15 M KCl (10%; W/v). The homogenates were then centrifuged for 15 minutes at 4 °C at 10,000 × g.

Determination of Glutathione Level

The amount of GSH in blood and a homogenized brain tissue sample was determined according to Serdaroğlu Kaşıkçı and Gökalp[19] using metaphosphoric acid for protein precipitation and 5.5'-dithiobis-2-nitrobenzoic acid for color development.

Determination of Malondialdehyde Level

Malondialdehyde (MDA) was assessed as a measure of lipid peroxidation (LPO) in serum and homogenized brain tissue samples. LPO was determined, according to Coban et al.[16], by measuring the MDA content with thiobarbituric acid.

Statistical Analysis

For statistical analysis, GraphPad Prism version 10.0.0 for Windows (GraphPad Software, Boston, Massachusetts USA, www.graphpad.com) was utilized. The one-way ANOVA test was used to compare the groups, and the LSD test was used for post-hoc pair comparison. The p-values denote different levels of significance: less than 0.05 indicates significant, less than 0.01 indicates highly significant, and less than 0.001 indicates very highly significant, respectively.

RESULTS

The effects of BA on the levels of GSH and MDA in serum are displayed in Figure 1.

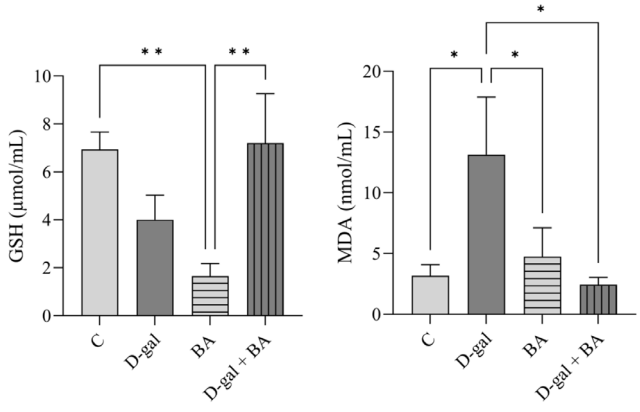

Figure 1. Effects of BA administration on serum GSH and MDA levels in D-gal treated rats.

*p<0.05, **p<0.01, C: Control, D-gal: D-galactose, BA: Boric acid, MDA: Malondialdehyde, GSH: Glutathione

Although not statistically significant, the D-gal group's serum GSH levels dropped in comparison to the control group. However, it was demonstrated that BA raised serum GSH in comparison to D-gal+BA (p=0.0046) and lowered its levels in comparison to the control group (p=0.0066). In addition, when compared to the control group (p=0.0169), the D-gal group was shown to have higher serum MDA levels; In contrast, the BA (p=0.0401) and D-gal+BA (p=0.0111) groups had lower MDA levels (Figure 1).

Figure 2 shows the impact of BA on brain homogenates' levels of GSH and MDA. GSH levels were found to be lower in the D-gal group compared with the control group (p=0.0276). Conversely, it was shown that the D-gal+BA group had higher GSH levels. There were increases in GSH levels in both the D-gal+BA and BA groups as compared to the Control group (p=0.0049, p=0.0014) (Figure 2).

Furthermore, MDA levels were found to be higher in the D-gal group than in the control group (p<0.0001). However, the BA (p=0.0039) and D-gal+BA (p<0.0001) group's MDA levels were found to be lower than those of D-gal. The D-gal group that received BA had lower MDA levels compared to the group that received only BA (p=0.0083) (Figure 2).

In comparison to the control group, subjects treated with D-gal were found to have a lower ST RI (p=0.0414) (Figure 3).

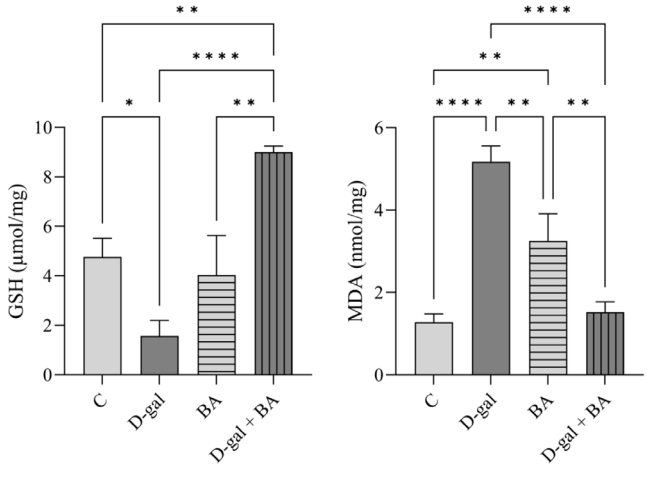

Figure 2. Effects of BA administration on brain homogenates GSH and MDA levels in D-gal treated rats.

*p<0.05, **p<0.01, ****p<0.0001, C: Control, D-gal: D-galactose, BA: Boric acid

It was shown that there was a decrease in the ST DI of D-gal compared to the control group (p=0.0466), whereas it was increased in the BA group (p=0.0237) (Figure 4).

When D-gal and the Control group's times to reach the platform in the Morris water tank were compared, it was found that the D-gal's time increased (p<0.0001), but the BA and the D-gal+BA groups' times decreased (p<0.0001) (Figure 5).

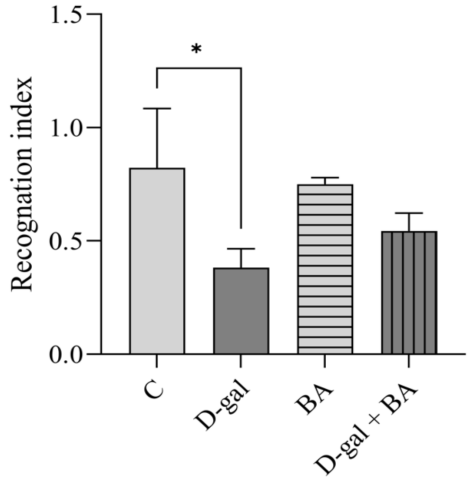

Figure 3. Short-term recognition index in the new object recognition test.

*p<0.05, C: Control, D-gal: D-galactose, BA: Boric acid

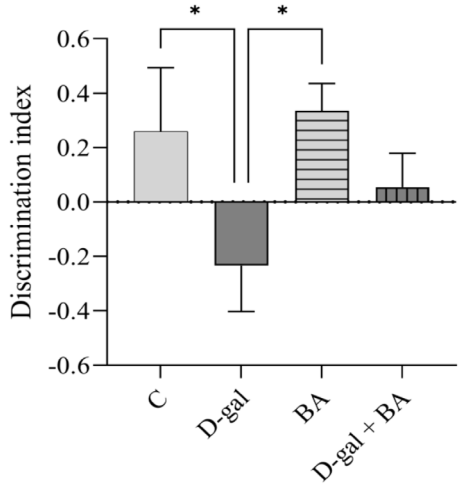

Figure 4. Short-term discrimination index in the novel object recognition test.

*p<0.05, C: Control, D-gal: D-galactose, BA: Boric acid

In the MWM, the D-gal+BA group spent more time in the target quadrant than the D-gal (p=0.017) and BA (p=0.0183) groups (Figure 6).

There was a reduction in the time required to locate the platform in the MWM test the BA and D-gal+BA groups showed shorter platform-finding times than the D-gal group (p=0.0253), while the control group (p=0.0475) experienced longer platform-finding times (Figure 7).

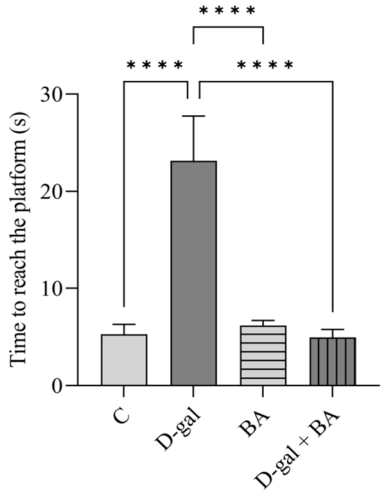

Figure 5. Time to reach the platform in Morris water maze.

****p<0.0001, C: Control, D-gal: D-galactose, BA: Boric acid

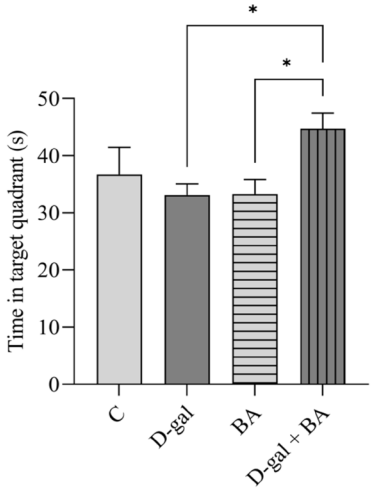

Figure 6. Time spent in the platform quadrant in Morris water maze.

*p<0.05, C: Control, D-gal: D-galactose, BA: Boric acid

DISCUSSION

Neurodegenerative diseases may be caused by the brain aging rapidly. Because of its high lipid content, high metabolic activity, and weak antioxidant defense mechanisms, the brain is an organ that is particularly vulnerable to oxidative damage. Free radical generation and antioxidants are in balance in healthy people and other organisms under typical physiological conditions. However, as we age, this balance is disturbed, which increases the generation of free radicals and gradually reduces the effectiveness of the antioxidant defense system[20]. In some studies, LT D-gal administration led to cognitive and motor deficits, which provided an animal model of aging similar to that of humans[21].

Studies conducted by administering D-gal have shown that brain LPO levels increase, and this leads to DNA damage and a decrease in antioxidant systems. Studies have shown that an aging model can be induced by administering D-gal (100-500 mg/kg/day)[16,22]. Hence, we have chosen rats as the experimental animals, determine the dosage, and set up the experimental groups. D-gal treatment in rodents was shown in some investigations to raise MDA levels in brain tissue samples and reduce GSH levels in serum. Furthermore, histological alterations were also observed, along with disturbances in memory and learning[7,12]. According to a recent study, various boron compounds raised antioxidant enzyme activity at modest supplement levels without putting blood cells under oxidative stress. Conversely, exposure to D-gal was found to significantly reduce the antioxidant enzyme activities of the rat brain's neurons and glial cells. Additionally, the direct impact of D-gal on enzyme

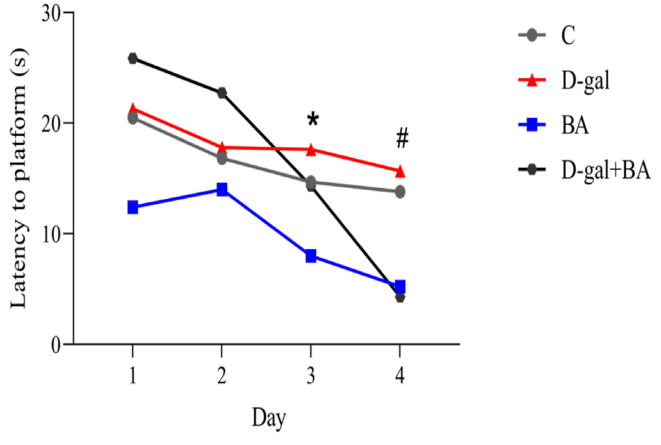

Figure 7. Four-day platform reach time in Morris water maze.

*p<0.05, #p<0.05, C: Control, D-gal: D-galactose, BA: Boric acid

molecules or their formation was accompanied by an increase in oxidative stress. Therefore, a decline in antioxidant activity may lead to the development of certain neurodegenerative diseases. In many studies conducted on various boron compounds[12]. Boron can behave as an indirect proton donor and has a special effect on the structure and function of cell membranes. Accordingly, it has been claimed that cyclic adenosine monophosphate, whose concentration increases when boron is present, can disrupt mitochondrial oxidative phosphorylation metabolism and suppress the activity of hydrolytic enzymes[9,10,13]. Herein, the antioxidant properties of boron compounds, like BA, that have been studied in neural cells may be related to their important functions in mitochondrial dynamics.

Kar et al.[14] assessed the effects of various BA dosages on kidney tissue using an ischemia-reperfusion model. Following three distinct intraperitoneal doses of 50, 100, and 200 mg/kg BA, they found that the administration of 200 mg/kg BA reduced MDA levels in the kidney tissue while elevating GSH, superoxide dismutase, and Catalase levels[14]. It was reported that administering 50 mg/kg of BA for 35 days decreased oxidative stress in a study utilizing a Parkinson's model[13]. Conivaptan and BA combined treatment was found to raise GSH levels and lower MDA levels in comparison to the control group in a study on acute renal damage[23]. In comparison to the control group, the D-gal treated group had higher MDA and lower GSH levels in both serum and brain homogenates. However, we found that the dosage applied in the BA group did not significantly increase GSH levels compared to antioxidants such as quercetin and vitamin C in both serum and brain homogenates compared to the control. Moreover, BA might modulate the cell's own antioxidant defense mechanisms, causing a pro-oxidant effect. When we compared the data between D-gal and D-gal+BA, we observed that while the GSH level raised in both groups, MDA levels dropped in the D-gal+BA group. All the results obtained were statistically significant, as seen in Figures 1 and 2.

In the current investigation, we used a NORT and a MWM to evaluate non-aversive learning and spatial memory in rats administered BA and D-gal. Özdemir et al.[15] evaluated the effects of BA on brain tissue in an experimental Alzheimer's model. The results of the radial arm maze test indicated that BA (200 mg/kg) reduced the damage to learning and memory functions in this model. In addition, it was reported that BA dramatically lowered oxidative stress markers and that total antioxidant capacity levels rose in the BA group and declined in the Alzheimer group[15]. Furthermore, Cui et al.[24] reported that D-gal can cause behavioral impairment in C57BL/6J mice, and Reitz et al.[25] reported that D-gal can reduce spatial preference for the target quadrant in the MWM test.

Similar to the studies of Khan et al.[18] and Kaviani et al.[26] in our study, we found that the ST recognition and DI in the NORT was significantly reduced in the D-gal applied group compared to the control. However, BA reversed the working memory and desire for novelty deficits caused by D-gal. As a result, both RI and DI were found to be higher in the D-gal+BA group compared to the D-gal group (Figures 3 and 4).

Changes in redox state play a critical role in aging and the resulting decrease in memory[27,28]. D-gal treatment resulted in memory impairment, and the MWM test showed longer escape latency. According to the MWM test results in the aging model created by Samad et al.[29] by administering D-gal, the number of rats reaching the platform increased in the D-gal group compared to the control. We also obtained similar results in our study (Figure 5). Zhang et al.[21] showed, that the time spent in the target quadrant in the MWM test decreased in the Alzheimer's model induced by D-gal and aluminum chloride. Similarly, in our study, we found that the time spent in the target quadrant decreased in the D-gal group compared to the control group, although this time was not statistically significant. There was, however, a statistically significant increase in the D-gal+BA groups compared to the BA and D-gal groups (Figure 6). Consistent with the study of Zhang et al.[21], an increase in the latency period was observed in our study in the D-gal group compared to the control group[21]. MWM testing illustrated the increased latency of rats, consistent with previous research by Wang et al.[30], indicating successful aging modeling. In contrast, we detected an increase in the latency period in the D-gal+BA group compared to the D-gal group. According to this finding, BA may help the cognitive deficits seen in the mimetic aging model[30].

Study Limitation

In light of this, individuals with underlying medical conditions that mimic normal aging, as well as the elderly, should consume fewer foods high in D-gal. The current investigation additionally revealed that D-gal-induced brain aging and cognitive impairment in young rats were prevented by administering BA. According to these findings, a diet high in D-gal may cause or hasten the aging process, but regular lifestyle changes can stop this from happening. Hence, further clinical studies are needed to understand how D-gal and BA affect brain aging, neurotoxicity, and cognitive functions. In the current study, different doses of BA should be tried

and examined in detail with molecular and histological studies. This is the limitation of our study.

CONCLUSION

Our study revealed that BA reduces oxidative damage by lowering LPO levels in the mimetic aging model. BA improved the ST DI in the NORT and had positive effects on memory by reducing the time to reach the platform and the time spent on the platform in the MWM. However, further studies are needed on the effects of BA on aging-related neurodegenerative disorders, involving different doses. At the same time, we foresee benefiting from its anti-aging properties by consuming foods containing BA.

Ethics

Ethics Committee Approval: This study was approved by the Üsküdar University Animal Experiments Ethics Committee (approval no: 2021-10, date: 24.12.2021).

Informed Consent: Since this study is on animals, patient consent is not required.

Foonotes

Authorship Contributions

Surgical and Medical Practices: E.S.K., B.Ç., F.N.S., Concept: E.S.K., B.Ç., F.N.S., Z.G., A.S., Design: E.S.K., B.Ç., Data Collection or Processing: E.S.K., B.Ç., Z.G., A.S., R.S., Analysis or Interpretation: E.S.K., B.Ç., F.N.S., Z.G., A.S., R.S., Literature Search: E.S.K., B.Ç., A.S., R.S., Writing: E.S.K., B.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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