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Radioprotective Effects of *Vitis vinifera* L. Seed against Radiation-Induced Short-Term Memory Loss in Young Adult Wistar Rats

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ABSTRACT

Introduction: Brain radiation therapy often results in short-term memory loss that progresses to cognitive impairment. This issue primarily arises from ionizing radiation generating reactive oxygen species, contributing to chronic oxidative stress that can damage brain cells. While dose fractionation, intensity-modulated radiotherapy, and neural stem cell transplantation have demonstrated limited effectiveness, natural plant antioxidants offer a promising alternative. To investigate the potential of these antioxidants in preventing radiation-induced short-term memory loss, this study examined the radioprotective effects of *Vitis vinifera* L. seeds in Wistar rats.

Material and Methods: Seventy-two young adult male Wistar rats were randomly divided into three equal groups. Group A was the control group, while Groups B and C were subjected to 40 Gy of fractionated whole-brain gamma irradiation. Additionally, the rats in Group C received an oral dose of 100 mg/kg/day of *Vitis vinifera* L. seeds before, during, and after the radiation treatment. Short-term memory and anxiety levels were assessed at weeks 1, 2, 3, and 4 post-irradiation, followed by routine histological analysis. Statistical significance between the groups was evaluated using a T-test and one-way analysis of variance.

Results: The study found that group B rats experienced a significant increase in anxiety states, neurodegeneration, and short-term memory loss compared to groups A and C rats ($P < 0.005$). The comparison between Groups A and C revealed a significant increase in anxiety levels in Group A ($P < 0.005$). However, there was no significant difference in neurodegeneration, except at week 3 ($P < 0.005$). Additionally, the results of the memory assessment became significant at the end of weeks two, three, and four ($P < 0.005$).

Conclusion: Exposure to 40 Gy of fractionated whole-brain gamma irradiation-induced short-term memory loss in rats. However, *Vitis vinifera* L. seed attenuated the radiation-induced short-term memory loss.

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Introduction

Radiation therapy uses ionizing radiation to destroy cancerous cells [1]. It is a common treatment for malignant diseases of the central nervous system [2]. However, this treatment can cause damage to the brain as a result of the radiation [3]. Several techniques and interventions have been employed to reduce the damage experienced by patients undergoing radiation therapy. These include dose fractionation [4], intensity-modulated radiotherapy [5], neural stem cell transplantation [6], and the use of anti-inflammatory agents [7]. However, none of these methods have fully eliminated the harmful effects of ionizing radiation on patients. Anxiety, attention deficit, and short-term memory loss are primary effects of radiation-induced brain injury [9, 10]. These effects are categorized as early-delayed effects of the radiation-induced brain injury [8], and may be reversible [11]. However, if left untreated, they can worsen and lead to progressive cognitive impairment which can be life-threatening [12, 13]. Statistics indicate that nearly half of all brain tumor patients who undergo radiation therapy and survive for more than six months experience cognitive impairment [8, 14]. This impairment significantly impacts patients' quality of life and can ultimately affect their survival [15, 16].

The onset of radiation-induced cognitive impairment can be identified through two main processes: a decrease in the formation of new neurons (neurogenesis) and the death of existing brain neurons (neuronal apoptosis) [17-19]. These effects result from chronic oxidative stress and inflammation in the brain, which are both triggered by ionizing radiation [20-22]. When ionizing radiation interacts with brain cells, it produces reactive oxygen species (ROS) [23]. The presence of ROS can inhibit

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neurogenesis and lead to cell death, primarily by activating transcription factors such as Nuclear factor-kappaB (NF-κB), Signal transducer and activator of transcription 3 (STAT-3), and Hypoxia-inducible factor 1 (HIF-1) [17-19, 24, 25]. To limit radiation-induced memory loss, researchers have suggested the use of antioxidants [8]. These antioxidants work by neutralizing the reactive oxygen species (ROS) produced during brain radiation therapy [8]. A study by El-Missiry et al. found that Melatonin protected irradiated rat brains against gamma-radiation-induced neuronal apoptosis [7]. Additionally, administering melatonin before acute radiation exposure was shown to reduce radiation-induced protein oxidation and lipid peroxidation in mice brain tissue, as well as inhibit radiation-induced decline in learning ability [26]. Another study by Monje at al. found that Indomethacin restores neurogenesis following endotoxin-induced inflammation and ameliorate neurogenesis inhibition after cranial irradiation in rats [27]. Zhao et al. showed that the administration of pioglitazone to rats before, during, and after exposure to 40 Gy of fractionated whole-brain irradiation (fWBI) prevented radiation-induced cognitive impairments in the rats [28].

Antioxidants are known for their potential benefits, which include disease prevention, enhanced organ function, and improved overall health and well-being. [7, 29]. Plants are a source of natural antioxidants and contain various compounds that can protect against radiation damage. They do this by reducing inflammation and oxidative stress, repairing deoxyribonucleic acid (DNA), and inhibiting DNA damage [26 – 30]. One such plant is *Vitis vinifera* L., commonly known as grape seed. It is recognized for its anti-inflammatory, antioxidant, and neuroprotective properties, which stem from its active components, including flavonoids, polyphenols, anthocyanins, proanthocyanidins, and procyanidins [32 - 34]. Due to these properties, *Vitis vinifera* L. seed may be a viable candidate for protecting against radiation-induced damage to the brain. This study aims to investigate the radioprotective effects of *Vitis vinifera* L. seed on short-term memory loss in Wistar rats exposed to 40 Gy of fractionated whole-body irradiation (fWBI).

Materials and Methods

Wistar Rat Breeding

Adult female and male Wistar rats were obtained from the animal holding facility of Obafemi Awolowo University, Ile-Ife, Nigeria. Breeder Wistar rats were mated and allowed to give birth to litters. After four weeks, 72 male litter rats were weaned and nurtured until they reached weights between 100-150g. These rats were then randomly selected and equally divided into three different groups, namely groups A, B, and C. The rats were housed inside clean, well-ventilated plastic cages and were exposed to natural light and dark cycles. They were also provided with pelletized rat chow and water ad libitum. Ethical approval with registration number SCP14/15/H/0661 was obtained from the health research and ethical committee of the Obafemi Awolowo University, Ile-Ife, Nigeria.

Study Design

Seventy-two young adult male Wistar rats, weighing between 100 and 150 grams, were randomly divided into three groups: A, B, and C. Rats in groups B and C were exposed to a total dose of 40 Gy of gamma radiation targeted at their heads, while the rats in group A served as the control group and were exposed to natural light. The radiation dose was administered at 5 Gy per exposure twice a week and over 4 weeks, using a ^{60}Co radiation source delivered posterior-anterior. In addition, group C rats were administered 100 mg/kg/day of *Vitis vinifera* L. seed, while groups A and B rats received distilled water. The powdered *Vitis vinifera* L. seed was purchased from Swanson Health Products in Fargo, United States of America (USA) and encapsulated in gelatin, containing 380 mg of *Vitis vinifera* L. seed per capsule. The *Vitis vinifera* L. seed was dissolved in distilled water and administered to rats through an oral cannula. The administration of the *Vitis vinifera* L. seed was started a week before irradiation and continued until the time of sacrifice.

A ^{60}Co source from a GAMMA BEAMX200 research irradiator and manufactured by Best Theratronics Ltd. in Ontario, Canada was used for the study. The irradiator is located at the National Institute of Radiation Protection and Research, University of Ibadan, Nigeria. The irradiator had a source-to-surface distance of 80 cm and a field size of 10 × 10 cm^2. The dose rates for the respective treatment days were measured as 15.11 mGy/s, 15.101 mGy/s, 15.090 mGy/s, 15.063 mGy/s, 15.041 mGy/s, 15.025 mGy/s, 14.993 mGy/s, 14.972 mGy/s. The time for each radiation exposure was calculated using Eq. 1. The source activity at the time of irradiation was 292.3 TBq. The radiation dose was administered without causing any pain to the rats or the need for anesthesia. To minimize stress on the animals, comfortable treatment positions and improvised cushy immobilizers were used. In addition, lead blocks were used to shield the rat's body, which lowered the absorbed dose to 263 mSv.

$$\text{Irradiation time} = \frac{\text{radiation dose}}{\textit{dose rate}} \quad (1)$$

At weeks 1, 2, 3, and 4 post-irradiation, we recorded physical observations and weight gain in rats. We assessed short-term memory using a radial arm maze and anxiety states using an open field maze. At the end of each timeline, six rats were selected randomly from each group and humanely sacrificed through cervical dislocation. Following rat sacrifice, the brains were harvested and one-millimeter thick slice of the cerebral cortex was obtained at the level of the optic chiasma. The slice was then fixed in 10% formal saline and processed for routine histology.

Anxiety and Motor Activities

To assess anxiety states in rat models, an open-field test was conducted. A box was constructed based on the specifications provided by Hall *et al.* [35]. The rats' behavioral patterns, specifically their line-crossing frequency with all four paws, were noted and recorded. Each rat was introduced to the box without any aversive or appetitive stimuli and observed for three minutes. The rats' free exploratory behavior was recorded during this time. To prevent odor cues between successive rat trials, the box was wiped clean with cotton wool and ethanol.

Spatial Learning and Memory Assessment

A radial arm maze [36] was employed to perform the memory test. The maze consisted of eight arms of equal distance that extended from a central platform. The maze test was conducted in a new environment without any aversive or appetitive stimuli. One arm of the maze was loaded with standard chow, which was hidden from view in a recess at the end of the arm. Each rat was placed in the center of the maze and observed for the sequence of arm entries and consumption of the chow. Criterion performance was defined as the identification of the baited arm of the maze within the test period [37]. Rats were removed from the maze after failing to identify the baited arm within three minutes. The sequence of entries into baited and unbaited arms of the radial maze was recorded during behavioral trials. The maze was wiped clean with cotton and ethanol to prevent odor cues between successive rat trials.

Histological Evaluation of the Rat Brain and Photomicrographs

A one-millimeter-thick coronal brain slice was obtained at the level of the optic chiasma, and the tissue was cut into 5 µm sections. The Haematoxylin and Eosin method was used to reveal the histology and morphology of the rat brain neurons [38]. The stained sections were viewed under a LEICA research microscope (LEICA DM 750, Switzerland), which was interfaced with a digital camera (LEICA ICC 50 Leica Microsystems Inc., U.S.A). Digital photomicrographs of the stained sections were taken at X400 magnification. Micrographs were imported onto the GraphPad Prism (Version 5.03, GraphPad Inc, USA), and a grid of uniform dimension having 16 compartments of equal area was superimposed on the micrograph. Neurons within alternate grid compartment were counted. Only neurons with more than 50% of its size within the grid compartment were counted. The counts for normal and degenerating neurons were kept separate. Total grid compartment area was calculated and the subsequent neuronal density was calculated.

Statistical Analysis

The data was presented as the mean and standard error of the mean (SEM). To evaluate statistical significance, T-Test using Stata (Version 12, USA) and one-way analysis of variance (ANOVA) were used. A p-value of less than 0.05 was considered as an indication of a significant difference between any two groups.

Results

Physical Observation

The rats were healthy and showed a normal pattern of weight gain from birth to adulthood. After receiving the initial radiation dose of 5 Gy, noticeable physical changes occured, including frequent scratching, drowsiness, and fatigue. A decrease in appetite was observed in Groups B and C starting in the third week of radiation exposure. However, by three weeks after irradiation, the feeding habits of the rat groups began to improve. Group B experienced three deaths before completing the total radiation dose of 40 Gy, and one rat from this group was found to be blind after three weeks of exposure. Hair loss occurred in all irradiated rat groups, with the most pronounced loss observed in Group B. Additionally, abdominal swelling was noted in the rats from Group B.

Body Weights

The study results indicated a significant weight gain in Group A rats compared to both Group B ($p = 0.0021$) and Group C ($p = 0.036$) over the duration of the study. In the first three weeks of observation, there was no statistically significant difference ($p = 0.345$) in weight gain between Groups B and C. However, by the fourth week, a significant difference was noted ($p = 0.042$). Group A rats exhibited the highest weight gain, while Group B rats experienced the most significant weight loss throughout the study period. Notable differences in weight loss were observed in Groups B ($p = 0.017$) and C ($p = 0.028$) between weeks 2 and 3. Both Groups B and C recorded significant weight gain between weeks 3 and 4 ($p = 0.011$ and $p = 0.0038$, respectively). Figure 1 illustrates the average weight gain for all rat groups.

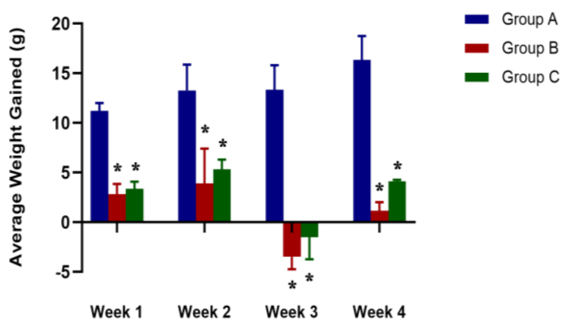

Figure 1. Average body weight gained in rat models in the presence (Group C) or absence (Groups A and B) of Vitis vinifera L. seed and exposure (Groups B and C) to 40 Gy gamma radiation from ^{60}Co radiation source from one to four weeks post-irradiation (*P < 0.05 between groups)

Anxiety and Motor Activities

The results from the open field test indicate that rats in group B had significantly fewer line crossings compared to those in group A ($p = 0.025$) and group C ($p = 0.037$). In addition, group C rats also exhibited significantly fewer line crossings than the rats in group A ($p = 0.029$). When comparing anxiety and motor activities on a weekly basis among the rat groups, there were no significant differences in groups A and B. However, group C rats demonstrated a significant increase in line crossings during week 4 compared to week 1 ($p = 0.033$). Figure 2 illustrates a graph depicting the assessment of anxiety and motor activities in the rat models.

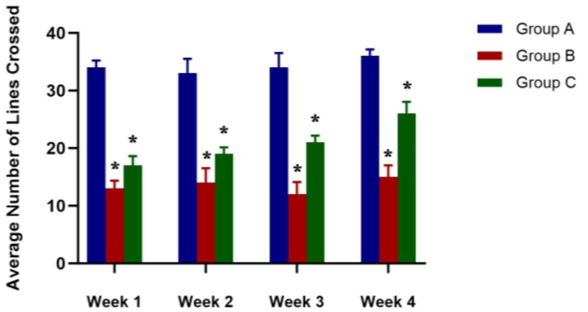

Figure 2. Anxiety and motor activities assessment in rat models in the presence (Group C) or absence (groups A and B) of Vitis vinifera L. seed and exposure (Groups B and C) to 40 Gy gamma radiation from ^{60}Co radiation source from one to four weeks post-irradiation (*P < 0.05 between groups)

Spatial Learning and Memory Assessment

The results of the memory assessment demonstrated significant differences between groups A and B ($p = 0.035$) and groups B and C ($p < 0.026$). Notably, there was no significant difference between the rats in groups A and C during the first two weeks ($p = 0.73$). However, significant differences were observed in weeks 3 ($p = 0.041$) and 4 ($p = 0.035$). Additionally, rats in group B showed a significant increase in the average time taken to identify the baited arm over the weeks ($p < 0.05$). Figure 3 provides a visual representation of the spatial learning and memory assessment among the rat groups.

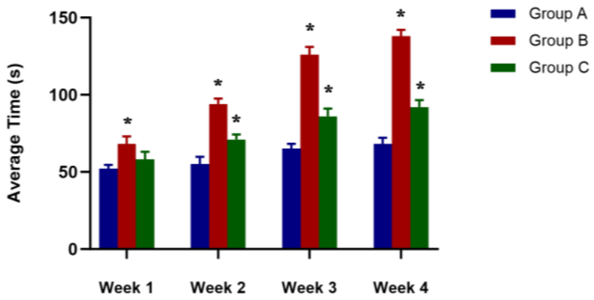

Figure 3. Spatial learning and memory assessment in rat models in the presence (Group C) or absence (groups A and B) of Vitis vinifera L. seed and exposure (Groups B and C) to 40 Gy gamma radiation from ^{60}Co radiation source from one to four weeks post-irradiation (*P < 0.05 between groups)

Histological Staining and Photomicrograph

Figure. 4 shows the histological staining of the mid-cortical region of rat brains for groups A, B, and C, at weeks 1, 2, 3, and 4 after irradiation.

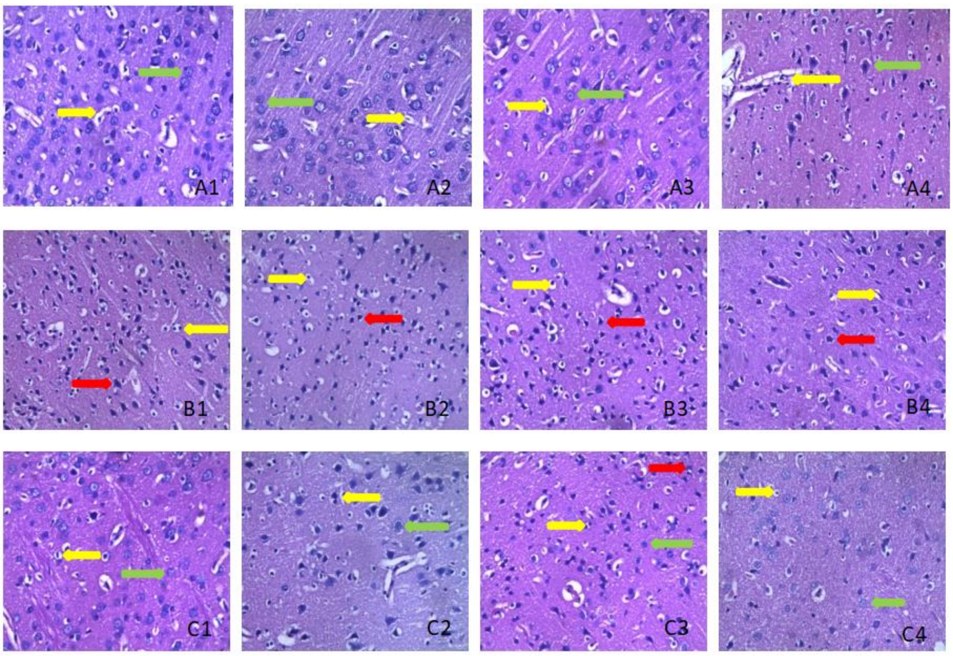

Figure 4. Photomicrograph of the mid-cortical region of rat brains with Hematoxylin and Eosin (H&E) stain in the presence (Group C) or absence (Groups A and B) of Vitis vinifera L. seed and exposure (Groups B and C) to 40 Gy gamma radiation from ^{60}Co radiation source from one to four weeks post-irradiation. Normal neuron (green arrow), Glial cell (yellow arrow), and degenerating neuron (red arrow). Group A is shown in row 1, group B is in row 2 and group C is in row 3. Columns a, b, c and d indicate weeks 1, 2, 3 and 4

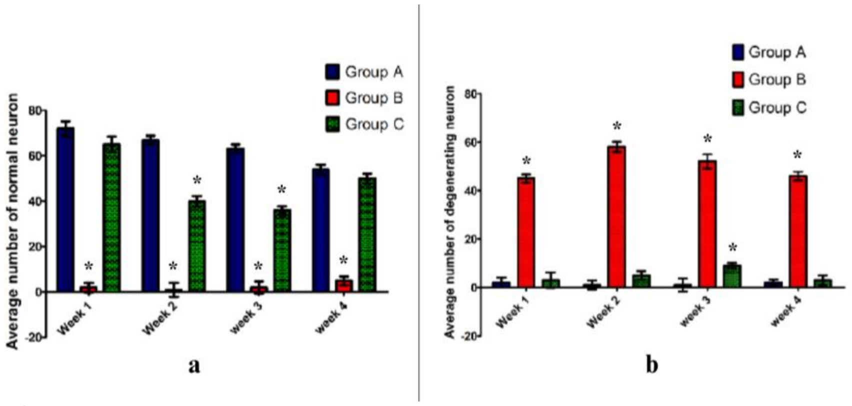

Figure 5. Average number of normal (a) and degenerating (b) neurons in rat models in the presence (group C) or absence (groups A and B) of Vitis vinifera L. seed and exposure (groups B and C) to 40 Gy gamma radiation from ^{60}Co radiation source from one to four weeks post-irradiation (*P < 0.05 between groups)

Average Number of apparent Normal and Degenerating Neuron

The analysis of the photomicrographs showed a significant decrease in the average number of normal neurons in Group B rats when compared to Groups A (p = 0.013) and C (p = 0.002). Furthermore, Group C exhibited a significant reduction in the average number of normal neurons at weeks 2 (p = 0.025) and 3 (p = 0.030) in comparison to Group A. There were no significant differences in the average number of degenerating neurons between Groups A and C, except at week 3 (p = 0.43). However, significant differences were observed in the average number of degenerating neurons between Groups A and B (p = 0.013) and between Groups B and C (p = 0.002) throughout the study period. Figure 5 illustrates the average number of normal and degenerating neurons for all rat groups.

Discussion

Brain radiation therapy often leads to short-term memory loss in patients [3]. This memory loss can progress to cognitive impairment, potentially affecting the patient’s survival and quality of life [13 - 16]. The short-term memory loss occurs primarily because ionizing radiation produces reactive oxygen species, which can damage vital organelles within brain cells [21, 22]. This suggests that using antioxidants, which can effectively neutralize these free radicals, may help prevent short-term memory loss in patients [8]. This study investigates the radioprotective effects of *Vitis vinifera* L. seeds, a plant known for its natural antioxidant properties, against short-term memory loss in Wistar rats. The study involved three groups of rats: A, B, and C. Group A were the control group, while Groups B and C were were exposed to 40 Gy gamma radiation that was delivered in fractions of 5 Gy per exposure over four weeks. To assess the radioprotective effects of *Vitis vinifera* L. seeds against radiation-induced short-term memory loss, Group C rats received an oral dosage of 100 mg/kg per day of *Vitis vinifera* L. seeds, starting before the radiation exposure and continuing until the study concluded. All groups of rats were observed for four weeks following the completion of the radiation treatment, during which their anxiety levels, short-term memory and neurodegeneration were assessed.

The study found that exposure to 40 Gy of gamma radiation led to several negative effects in rats. These included fatigue, weight loss, decreased appetite, abdominal swelling, blindness, hair loss, and an increased risk of mortality. Similar effects have also been observed in humans and other animals exposed to ionizing radiation [8, 39]. Rats in the experimental groups (B and C) showed significant weight reduction and progressive weight loss throughout the study, as illustrated in Figure 1. This weight loss may be attributed to radiation sickness or damage to the brain's feeding center, leading to a loss of appetite [40, 41]. However, the increased weight gain recorded in these groups by the end of the fourth week might be due to the natural repair mechanisms activated in the rats' bodies as they began to recover from radiation sickness [39, 42]. Additionally, rats in group B recorded mortalities compared to those in group C. This suggests that *Vitis vinifera* L. seeds may not only protect the central nervous system but also benefit other bodily systems, including the digestive, cardiovascular, lymphatic, endocrine, and respiratory systems. These findings support previous studies indicating that natural antioxidants derived from plants can enhance organ function, repair damaged tissues, and improve overall bodily functions [26 – 30].

Fatigue, increased anxiety, and reduced motor activity have been reported in patients undergoing radiation therapy for brain tumors [43]. These symptoms may arise from ionizing radiation damaging the cerebellum, which disrupts the transmission of impulses responsible for movement from the motor area of the cerebral cortex to the spinal cord [44, 45]. This disruption can lead to decreased communication with the relevant muscle groups, resulting in difficulties with bodily movement [46]. Consequently, these challenges can contribute to increased fatigue and heightened stress, ultimately exacerbating anxiety [43, 47]. The data presented in Figure. 2 indicate a significant decrease in the number of times rats in Group B crossed the line compared to those in Groups A and C. This finding suggests that ionizing radiation caused impairment in muscle function in the rats. In contrast, the improved line crossing observed in Group C rats compared to Group A rats suggests that *Vitis vinifera* L. seeds help protect the impulse transmission mechanisms responsible for movement. Furthermore, the weekly improvements in line crossing among the rats in Group C demonstrate that *Vitis vinifera* L. seeds may aid the body in repairing damage to the limbic system, as evidenced by the reduced anxiety levels in these rats. Furthermore, these results support previous studies that showed that *Vitis vinifera* L. seeds can improve hippocampal function [48, 49], reduce anxiety [50, 51] and improve muscular functions [52, 53].

Neurodegeneration and subsequent neuronal apoptosis are key indicators of short-term memory loss in brains exposed to radiation [17 - 19]. These effects results from chronic oxidative stress and neuroinflammation that occur following fWBI [20 - 23]. As shown in Figure 5, rats exposed to 40 Gy of gamma radiation without prior and continued administration of *Vitis vinifera* L. seeds experienced significant neurodegeneration in the mid-cortical region of their brains. In contrast, rats that were given *Vitis vinifera* L. seeds before irradiation and continued this treatment until the time of sacrifice showed preserved brain neurons and protection against neurodegeneration. The neurodegeneration observed in the first group of rats (Group B) may account for the increased short-term memory loss in the group. Additionally, the gradual short-term memory loss noted in the study reinforces previous findings indicating that such memory loss is progressive. However, the preservation of neurons in Group C and the corresponding reduction in short-term memory loss suggest that *Vitis vinifera* L. seeds may help limit radiation-induced short-term memory loss. Furthermore, the comparative results of the analysis of spatial learning and memory assessments between Groups A and C and neuronal preservation in Group C supports the hypothesis that radiation-induced short-term memory loss may be reversible [8, 11, 39]. These findings provide significant evidence that could influence clinical practices aimed at reducing cognitive impairment in brain tumor patients undergoing radiation therapy.

Conclusion

This study demonstrated that exposure to 40 Gy of fractionated whole-brain gamma irradiation induced short-term memory loss in rats. However, administering *Vitis vinifera* L. seeds helped protect the rats' brains from radiation-induced short-term memory loss. In the future, we plan to extend our research to investigate the long-term radioprotective effects of *Vitis vinifera* L. seeds on cognitive impairment in rats.

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