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# *Cynodon dactylon* extract ameliorates cognitive functions and cerebellar oxidative stress in whole body irradiated mice

Roopesh Poojary[1], Nayanatara Arun Kumar[1]✉, Reshma Kumarchandra[2], Vinodini NA[1], Bhagyalakshmi K[1], Ganesh Sanjeev[3]

[1]*Department of Physiology, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India*

[2]*Department of Biochemistry, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India*

[3]*Microtron Centre, Department of Studies in Physics, Mangalore University, Mangalagangotri, Karnataka, India*

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ABSTRACT

**Objective:** To explore the effect of hydroalcoholic extract of *Cynodon dactylon* on the whole body radiation-induced oxidative status of the cerebellum and cognitive impairments in mice.

**Methods:** Swiss albino mice were randomly divided into the control group, radiation control group, low dose and high dose *Cynodon dactylon* extract treated groups and pre-treated with *Cynodon dactylon* extract before irradiation. *Cynodon dactylon* extract was administered for 7 d daily in low dose (0.25 g/kg) and high dose (1 g/kg). On day 7, mice were irradiated with a sublethal dose of 5 Gy gamma rays. Motor coordination was assessed by elevated rotarod test and spatial memory was studied by water maze test. Subsequently, biochemical markers (glutathione, lipid peroxidation and nitric oxide levels) in the cerebellum were evaluated.

**Results:** The gamma irradiated group showed significant impairment in motor coordination and spatial memory compared to normal mice. Mice treated by *Cynodon dactylon* extract prior to gamma radiation showed good improvement in both paradigms compared to the radiation control group. Moreover, glutathione level was increased, while lipid peroxidation and nitric oxide levels were significantly reduced in mice receiving low dose and high dose of *Cynodon dactylon* extract compared to the radiation control group.

**Conclusions:** The present study suggests the neuroprotective role of *Cynodon dactylon* against radiation-induced cognitive impairment and oxidative stress on the cerebellum of mice.

## 1. Introduction

Human beings are often exposed to radiation in natural and man-made condition, such as radiotherapy, work in nuclear stations, nuclear battlefields, *etc*. Ionizing radiation exposure results in an array of biological consequences. Ionizing radiation absorption of living cells can produce chemical and biological changes by directly disrupting the atomic structures. Oxidative stress induced by ionizing radiation generates the increased production of free radicals that attack various components in the cell, leading to biochemical variations, changes of macromolecules, and damage to nucleic

✉Corresponding author: Dr. Nayanatara Arun Kumar, M.Sc, PhD, Associate Professor in Physiology, Department of Physiology, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India.
E-mail:nayanatara.arun@manipal.edu
Tel: +919845551070
Fax: +91 824 2428 183.

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acids, proteins and lipids[1]. Brain tissue is rich in polyunsaturated fatty acids, metal ions and has a low level of antioxidant enzymes[2]. The increased susceptibility of the brain tissue to oxidative stress leads to various neurodegenerative disorders, which have been a major issue of concern[3]. Previously, early biochemical alterations that take place in a short time after irradiation were thought to be liable for most of the effects of ionizing radiation. However, this oxidative alteration might continue to remain for days and months after the first exposure probably because of continuous generation of reactive oxygen and reactive nitrogen species[4]. Total body irradiation is known to cause a pronounced decrease in antioxidant capacity and an excessive increase in oxidant stress[5]. Antioxidant defense systems in the body decrease toxic effects associated with radiation damage by scavenging free radicals and minimizing the formation of reactive oxygen species. However, these systems are not always fully operative and have some limits. In recent years, radioprotective agents with novel modes of action have been under investigation. The aim of this strategy is to protect and increase the survival rate of the radiation-induced damaged cell population.

In recent years, substantial consideration has been focused on the identification of plants with antioxidant ability. The herbs have been commonly used to treat various disorders since the advent of human history. Phytochemical constituents have remarkable combined effects on numerous complications. Numerous plants have been reported to be advantageous for treating radiation-induced complications[6]. It is implied that plants contain a group of compounds and can protect against radiation-induced reactive oxygen species as anti-inflammatory agents[7,8]. Either non-toxic or less toxic herbal drugs have been found to offer an alternative to synthetic compounds and could be a better choice. *Cynodon dactylon* (*C. dactylon*) (Family: Poaceae) commonly known as Durva grass in India, has been reported to possess various medicinal properties. The plant possesses the antimicrobial and anti-hypertensive activity, and has also been used to treat urinary tract infection, calculi and prostatitis[9]. In folk medicine, the roots and rhizomes of the plant have been used for the treatment of depression, epilepsy, and hemorrhage[10-12]. Literature survey also showed the role of this plant extract as a potential therapeutic antioxidant in treating Parkinson's disease and other movement disorders[13]. It is rich in phytochemical compounds which have been proven as well known natural antioxidant agent[14,15]. Our previous studies also reported the presence of flavonoids, tannins, steroids, saponins, and glycosides alkaloid. Moreover, HPLC analysis showed the presence of bioactive polyphenolic flavonoids such as gallic acid, orientin, rutin, morin. Moreover, *in-vitro* study of *C. dactylon* extract showed increased level of free radical scavenging at a dose-dependent manner[16,17].

Cerebellum, a fist-sized, transversely fissured mass of central nervous system tissue, is attached to the dorsum of the brain stem by three peduncles. Increasing evidences suggest that the cerebellum plays an important role in motor coordination and cognitive functions like spatial learning and memory[18,19]. Studies have shown that cerebellar mutant and experimental lesion in rodents affects spatial learning[20]. The present study was therefore designed, to evaluate the neuroprotective effect of *C. dactylon* extract on whole body radiation-induced cognitive disorder and cerebellar oxidative status in mice.

## 2. Materials and methods

### 2.1. Animals

Adult Swiss albino male mice, weighing (25±2) g were used for all *in vivo* studies. The experimental animals were obtained from Central animal house, Kasturba Medical College, Mangalore (Reg.No.213/CPCSEA). The experimental mice were placed in polypropylene cages with paddy husk beddings. Throughout the research period, animals were maintained at (25 ± 2)℃ temperature and (50±5)% humidity with 12 hours of dark-light cycles. Mice were provided with *ad libtum* access to laboratory food (commercial mice pellets from VRK nutritional solutions, India) and water. All investigations were performed in accordance with guideline of Committee for the Purpose of Control and Supervision of Experiments on Animals. All experimental procedures were approved by Institutional Animal Ethical (IAEC), Kasturba Medical College, Mangalore (F No.25/439/2009; approved date: 31 March 2016).

### 2.2. Irradiation

The albino mice were placed in well-ventilated circular perspex box restrainers. Six mice were placed in single restrainers and exposed to whole-body radiation of gamma - rays. The source of radiation was low dose gamma irradiation (11 Gy/min) from Centre for Application of Radioisotopes and Radiation Technology, Mangalore University, Mangalagangotri, Karnataka, India.

### 2.3. Determination of $LD_{50/30}$ in mice exposed to gamma radiation

The lethal dose causing 50% death in animals exposed to radiation was determined by separate groups. A total of 70 mice were divided into 7 groups with 10 mice in each group. Whole body gamma irradiation was administered to the experimental animals by $^{60}Co$ with a dose rate of 11 Gy/min and a distance from the source to the subject of 61 centimeters. Each group of experimental animals was administered with 4 Gy, 6 Gy, 8 Gy, 10 Gy, 12 Gy or 14 Gy of radiation. The group that was not irradiated served as control. Animals were observed for 30 days post-irradiation. The number of animals survived in each group post radiation for a period of 30 days was recorded. The median lethal dose was calculated by probit analysis.

### 2.4. Preparation of plant extract

The whole plant along with the roots of *C. dactylon* was collected from the campus of Kasturba Medical College, Manipal Academy of Higher Education. The authentication of the plant was done by Mrs. Suvarna, Department of Botany from Mahatma Gandhi Memorial College, Udupi Karnataka, India. The collected *C. dactylon* was

washed thoroughly in tap water and dried in room temperature for 15 d. The dried plant was powdered and the hydroalcoholic extract was prepared following the procedure[21]. In this procedure, ground plant powder (100 g) and 50% of methanol in water (Total volume of 500 mL) were refluxed at 50-60 ℃ in a Soxhlet apparatus for 72 h. The liquid extract was cooled and concentrated by using rotary vacuum flash evaporator. The extract was kept in a sterile bottle for further use.

### 2.5. Acute drug toxicity of hydroalcoholic extract of C. dactylon

Hydro-alcoholic extract of *C. dactylon* (CDE) was dissolved in double distilled water. Swiss albino mice were divided into 6 groups. Each group consisted of 10 mice (total of 60 mice). Mice in group Ⅰ as normal control received double distilled water. Mice in groups Ⅱ to Ⅵ received a single dose of 1, 2, 3, 4 and 5 g/kg bodyweight of CDE orally. All mice were provided with food and water *ad libitum* and the mortality was recorded for 14 d.

### 2.6. Experimental design

Mice were randomly divided into 6 groups with 12 mice in each group (total 72 mice) as follows: Control group (G-1): Normal healthy mice receiving distilled water *via* oral gavages for 7 d; Radiation control group (G-2): Mice exposed to 5 Gy of gamma radiation; Low dose CDE group (G-3): Mice received a low dose of CDE at 0.25 g/kg body weight for 7 d; High dose CDE group (G-4): Mice received a high dose of CDE at 1 g/kg body weight for 7 d; Low dose CDE+ IR group (G-5): Mice received 0.25 g/kg body weight of CDE for 7 d prior to exposure of radiation; High dose CDE+ IR Group (G-6): Mice received 1 g/kg body weight of CDE for 7 d prior to exposure of radiation. Spatial learning and memory study was assessed by water maze test[22,23]. Motor coordination and motor balance in the cognitive test was assessed by Rotarod test[24].

After 7 d, the animals were sacrificed by cervical dislocation and the whole brain was removed quickly, washed with chilled saline to remove blood and other debris. For biochemical estimations, brain was perfused with chilled 0.9% saline. Cerebellum was separated and 10% of homogenates were prepared with ice-cold phosphate buffer saline at pH 7.4 using a homogenizer (RO-1727A Remi Motors, India). The total glutathione content was measured by the Ellman's method[25]. Lipid peroxidation assay was estimated by the method of Ohkawa *et al*[26]. Nitric oxide was analyzed by the method of Green *et al*[27].

### 2.7. Statistical analysis

$LD_{50/30}$ was calculated by probit analysis. Data of water maze training sessions were analyzed individually by two-way repeated measures analysis of variance (ANOVA). Probe trials and other results were expressed as Mean ± SEM. Data were analyzed by one-way analysis of variance (ANOVA) following *post hoc* test Tukey using IBM SPSS statistics 20, $P<0.05$ was considered significant.

## 3. Results

### 3.1. Acute toxicity studies

Acute toxicity studies showed that CDE was nontoxic up to 5 g/kg body weight. It did not display any behavioral changes and mortality up during observation period. Therefore, 1/20th and 1/5th of this dose *i.e.*, 0.25 g/kg and 1 g/kg body weight were used as a low dose and high dose, respectively in the subsequent study.

### 3.2. Radiation dose selection

In this experiment, it was found that at 4 Gy of radiation dose, the mortality was 0%, whereas at 6 Gy, it increased to 33.3% and at 8 -14 Gy it was 100%. Animals exposed to 8 Gy died 25 days after irradiation, while mice exposed to 10 Gy and above died within 10 days with severe radiation sickness such as diarrhea, loss of appetite and loss of body hairs. The probit values were plotted against the log dose of radiation and dose corresponding could be found out. In this experiment, it was Log 0.86 (Figure 1), and the $LD_{50/30}$ was found to be 6.9 Gy.

### 3.3. Water maze test

In the first session, all mice failed to find out the platform and spent more time swimming around the water. In the second session, all mice except Group-2 learned to reach the platform and the escape latency was reduced gradually from session to session. Mice in Group-2 spent significantly more time reaching platform ($P<0.001$) than control mice, which indicated that the whole body irradiation may induce memory impairment in adult mice. Significant improvement in escape latency during training sessions was observed in Group-5 ($P<0.001$) and Group-6 ($P<0.001$) compared to Group-2 (Table 1).

In probe trials, mice of Group-2 spent significantly less time ($P<0.001$) in the target quadrant and more time around the tank compared to Group-1; while after CDE treatment, mice in Group-5 ($P<0.05$) and Group-6 ($P<0.05$) spent more time in target quadrant compared to Group-2 (Figure 2).

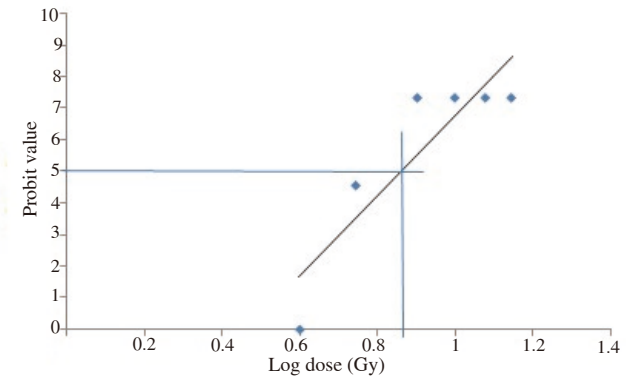


**Figure 1.** Plot of log dose of radiation *versus* probit values and calculation of $LD_{50/30}$.

**Table 1.** Latency to escape on to the platform during learning sessions in water maze test (s) (mean± SEM, $n$=12).

| Session | G-1 | G-2 | G-3 | G-4 | G-5 | G-6 |
|---|---|---|---|---|---|---|
| 1 | 60.00±0.00 | 60.00±0.00 | 59.81±0.12 | 60.00±0.00 | 60.00±0.00 | 60.00±0.00 |
| 2 | 45.04±0.92 | 53.22±0.45 | 45.16±0.82 | 45.08±0.85 | 52.70±0.64 | 47.16±0.57 |
| 3 | 30.04±0.74 | 43.56±0.39 | 29.41±0.43 | 29.27±0.39 | 37.41±0.75 | 33.58±0.65 |
| 4 | 24.20±0.34 | 36.64±0.36 | 23.35±0.31 | 22.79±0.40 | 24.33±0.35 | 21.18±0.33 |
| 5 | 50.47±0.68 | 56.77±0.31 | 49.89±0.71 | 49.66±0.79 | 55.00±0.34 | 52.83±0.62 |
| 6 | 32.31±0.66 | 46.08±0.52 | 32.31±0.59 | 31.82±0.77 | 41.72±0.68 | 36.43±0.40 |
| 7 | 28.00±0.58 | 41.20±0.53 | 27.53±0.51 | 27.15±0.52 | 33.89±0.59 | 26.85±0.40 |
| 8 | 20.97±0.53 | 36.85±0.45 | 20.74±0.4 | 21.29±0.33 | 29.25±0.46 | 27.81±0.44 |
| 9 | 11.85±0.57 | 31.60±0.51 | 12.25±0.63 | 12.20±0.67 | 26.12±0.29 | 22.81±0.58 |
| 10 | 7.25±0.17 | 25.31±0.33$^{***}$ | 8.51±0.36 | 7.59±0.17 | 21.45±0.40$^{\$\$\$}$ | 20.18±0.40$^{\#\#\#}$ |

Visible: 1-4 sessions, hidden: 5-10 sessions. For comparison with Group-1 and Group-2, $^{***}P$<0.001; for comparison with Group-2 and Group-5, $^{\$\$\$}P$<0.001; for comparison with Group-2 and Group-6, $^{\#\#\#}P$<0.001.

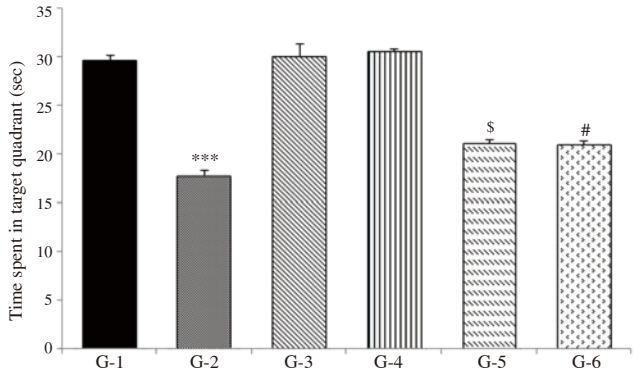


**Figure 2.** Time spent in the target quadrant by mice in different groups during water maze retention test. This figure is a representative of the results obtained from three probe trials. Each bar represents mean of time in seconds ± SEM, $n$ = 12. For comparison with Group-1 and Group-2, $^{***}P$<0.001, for comparison with Group-2 and Group-5, $^{\$}P$< 0.05, for comparison with Group-2 and Group-6, $^{\#}P$<0.05.

## 3.4. Rotarod test

Latency fall indicated considerable decline in motor coordination. Irradiated mice in Group-2 showed significantly reduced time of latency fall ($P$<0.001) in comparison to normal control (Group-1). After CDE treatment, the time of latency fall was significantly increased in mice of Group-5 ($P$=0.035) and Group-6 ($P$=0.011) compared to Group-2 (Figure 3).

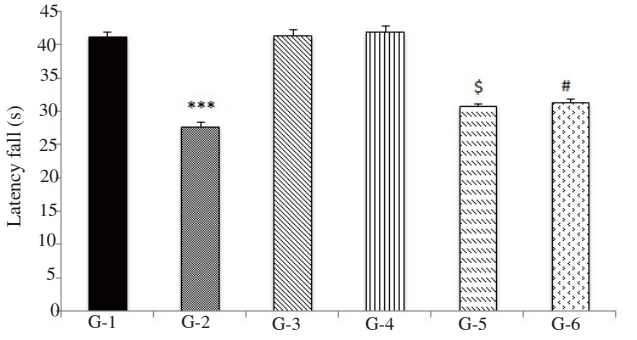


**Figure 3.** Latency falls of mice of different groups in rotarod test. Each bar represents mean ± SEM, $n$ = 12. For comparison with Group-1 and Group-2, $^{***}P$<0.001; for comparison with Group-2 and Group-5, $^{\$}P$<0.05; for comparison with Group-2 and Group-6, $^{\#}P$<0.05.

## 3.5. Biochemical estimation of the cerebellum

The level of reduced glutathione was significantly declined ($P$<0.001) in the cerebellum of Group-2 mice compared to Group-1, while the level was significantly increased in mice of Group-5 ($P$=0.019) and Group-6 ($P$=0.012) compared to Group-2 (Figure 4). The levels of lipid peroxidation and nitric oxide were significantly increased ($P$<0.001) in mice of Group-2 compared to Group-1; while they were significantly decreased in Group-5 ($P$=0.031 for lipid peroxidation, and $P$=0.024 for nitric oxide) and Group-6 ($P$=0.003 for lipid peroxidation, and $P$=0.012 for nitric oxide) compared to Group-2 (Figure 5&6).

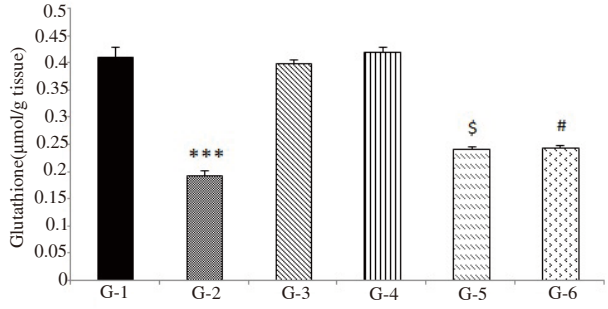


**Figure 4.** Changes in reduced glutathione level in the cerebellum of mice of different groups. Each bar represents mean ± SEM, $n$ = 12. For comparison with Group-1 and Group-2, $^{***}P$<0.001; for comparison with Group-2 and Group-5, $^{\$}P$<0.05; for comparison with Group-2 and Group-6, $^{\#}P$<0.05.

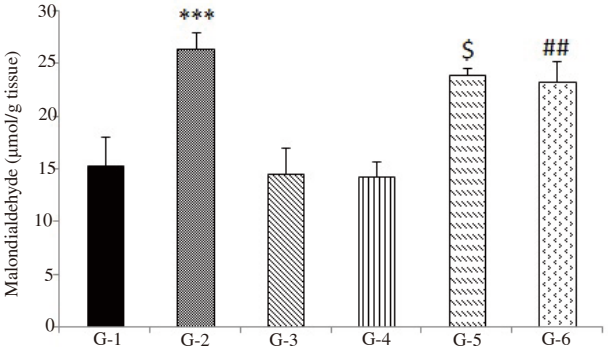


**Figure 5.** Changes in lipid peroxidation level in the cerebellum of mice of different groups. Each bar represents mean ± SEM, $n$ = 12. For comparison with Group-1 and Group-2, $^{***}P$<0.001; for comparison with Group-2 and Group-5, $^{\$}P$<0.05; for comparison with Group-2 and Group-6, $^{\#\#}P$<0.01.

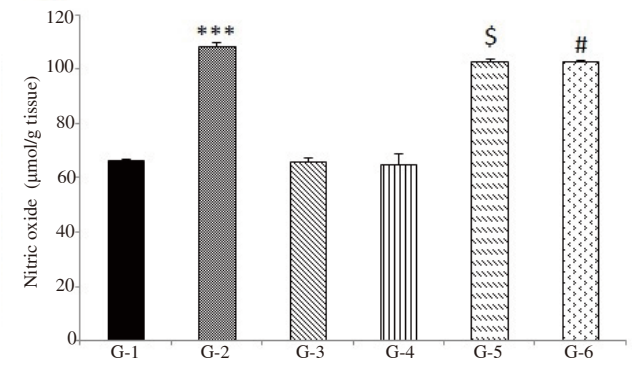


**Figure 6.** Changes in nitric oxide level in the cerebellum of mice of different groups. Each bar represents mean ± SEM, $n$ = 12. For comparison with Group-1 and Group-2, $^{***}P<0.001$, for comparison with Group-2 and Group-5, $^{\$}P<0.05$; for comparison with Group-2 and Group-6 , $^{\#}P<0.05$.

## 4. Discussion

Diminished memory and impaired learning ability are the most common symptoms of cognitive function loss. In the present study, the mice exposed to radiation showed a decrease in the cognitive functions compared to the non-irradiated mice. Exposure to ionizing radiation causes the depletion of antioxidant enzymes and might probably lead to cognitive dysfunctions. Our study showed that whole body irradiation increased oxidative stress in the cerebellum. This might be mainly due to the generation of oxidative stress posed on the other organs indirectly disrupting homeostasis. The water maze test mainly works on spatial localization and is extensively used to study neurological mechanisms. Our study revealed that gamma-irradiated mice showed reduced potential for learning to reach the platform and increased escape latency in all the session of water maze test. Lack of memory was observed in irradiated mice in all probe trails by spending less time in the target quadrant. Our results are in accordance with the previous reports which also showed the radiation-induced cognitive dysfunction[28]. Administration of *C. dactylon* could decrease escape latency and increase time spent in the target quadrant. These results support the potent role of this herbal extract in treating radiation-induced cognitive dysfunction.

Performance in a rotarod has been widely used in rodents for assessing balance and coordination aspects of motor function. Intact cerebellar function and motor coordination play a very important role in this performance. Whenever there are severe motor coordination problems, the mice will have difficulties in staying on the rotating rod. Mice exposed to the sublethal dose displayed dreadful performance in rotarod test compared with normal mice. The results are inconsistent with the previous studies which showed the early postnatal irradiation of the cerebellum resulted in tremor, ataxia, hypoactivity, and cognitive deficits[29]. Oxidative stress also plays a very important role[30]. Mice with treatment of antioxidant-rich extract of *C. dactylon* prior to radiation showed better performance in the rotarod test with the increased time of latency fall, which suggested the improvement in the impaired motor function and sensorimotor coordination.

Radiation produces reactive oxygen species and reactive nitrogen species, which adversely react with cell molecules lipids proteins and nucleic acids[31–33]. Radiation exposure also activates various signaling pathways enhancing the activation and expression of inflammatory, cytokines, and apoptosis[34]. The brain contains a high concentration of lipids and fatty acids which are highly vulnerable to radiation-induced oxidative damage[35]. The dendritic tree of a Purkinje cell in the cerebellum receives up to 100 000 inputs and has a major role in signaling[36,37]. Phytochemicals of the herbal extracts can reduce the intensity of free radicals generated by oxidative stress[38]. We found that in cerebellum of mice exposed to sublethal gamma rays, the level of glutathione content was decreased, while malondialdehyde and nitric oxide were elevated. Endogenous enzyme like glutathione can protect biomolecules from oxidative damage[39]. Malondialdehyde is a potent biomarker for lipid peroxidation. Reactive nitrogen species such as nitric oxide are involved in various pathological conditions such as neurodegeneration and neuroinflammation[40]. Pretreatment of *C. dactylon* prior to radiation can keep the balance between the oxidant and antioxidant by increasing glutathione and decreasing malondialdehyde and nitric oxide levels.

The present study showed the neuroprotective role of *C. dactylon* extract by reducing the radiation-induced oxidative stress and cognitive dysfunction. The possible underlying mechanisms should be explored to better understand their novel benefits.

## Conflict of interest statement

Authors declare that there are no competing interests.

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