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Radioprotective efficacy of ginger (*Zingiber officinale*) extract against gamma-ray radiation-induced genotoxicity in rats

D.D. Abd El-Monem and S.H.B. Elwakeel*

Department of Zoology, Faculty of Women for Arts, Science and Education, Ain Shams University, Cairo, Egypt

► ***Original article***

Corresponding authors:
Dr. Shereen H.B. Elwakeel,
Fax: *+ 02 2290 9186*
E-mail:
sherien.elwakeel@women.asu.edu.eg

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ABSTRACT

Background: Ginger *(Zingiber officinale)*, a member of the Zingiberaceae family that contains phenolic compounds such as gingerol, paradol, zingerone, zingiberol and shogaols, has antioxidant, anti-inflammatory, antimicrobial, antifungal and antitumour activity. ***Materials:*** The present investigation was intended to evaluate the radioprotective effects of ginger extract in Wistar albino rats against whole-body gamma-ray irradiation. Rats were orally administered 250 mg/kg b.w. of ginger extract by gavage for 14 consecutive days. On the 14th day, 2 hr after the last ginger administration, the animals were exposed to whole-body gamma-rays of 6 Gy. The radioprotective potential of ginger was assessed through measurement of the DNA oxidative stress marker 8-hydroxy-2'-deoxyguanosine in serum, analysis of chromosomal abnormalities and micronucleus formation in bone marrow cells and estimation of DNA impairment in both bone marrow cells and epidydimal sperm using comet assay. Sperm DNA integrity and sperm shape abnormalities were also studied. ***Results:*** The results revealed that ginger extract reduced DNA oxidation by restoring the levels of 8-hydroxy-2'-deoxyguanosine in serum. Ginger also significantly reduced radiation-induced chromosomal abnormality and micronucleus formation. Additionally, pretreatment with ginger extract significantly decreased DNA damage in both bone marrow cells and epididymal sperm, maintained sperm DNA integrity and reduced the occurrence of sperm anomalies after irradiation. ***Conclusion:*** Our results confirmed that ginger extract offers rats significant protection against whole-body gamma-rays and helps to alleviate the effects of radiation. Our findings suggest a new strategy to combat the effects of acute radiation doses that impair biological systems.

Keywords: *Ginger, gamma-radiation, DNA damage, genotoxicity.*

INTRODUCTION

Ionizing radiation (IR) produces free radicals known as reactive oxygen species (ROS) that damage cellular components in healthy cells, leading to DNA injury in the form of single- or double-strand breaks (DSBs) and base changes and resulting in carcinogenesis, mutagenesis and even cell death [1]. The oxidative stress induced by radiation exposure can damage critical cellular macromolecules [2], alter genomic expression [3] and induce protein modification and genomic instability [4, 5]. Additionally, ROS generated after radiation exposure can overwhelm antioxidant defence mechanisms, leading to reductions in endogenous antioxidants and ultimately to the development of systemic diseases [6]. Direct contact of mammals with IR such as gamma radiation can induce a series of potentially lethal physiological and morphological changes [7, 8]. The harmful biological effects of IR can be induced directly via the ionization of biological molecules or the formation of free radicals, such as superoxide

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anions, hydrogen peroxide (H_2O_2) and hydroxyl radicals, after exposure to radiation or indirectly through the absorption of radiation by water in cells, which causes excitation and ionization and ultimately results in the production of highly reactive radiolytic products and free radicals that injure biomolecules [9, 10]. Therefore, it is necessary to find an appropriate antioxidant with which to prevent or reduce ROS toxicity and protect humans against the destructive outcomes of IR.

Recently, increasing attention has been paid to the potential therapeutic use of medicinal plants as antioxidants to reduce free radi cal-induced tissue injury [11]. Several studies have indicated that the antioxidant activity of medicinal plants might be due to their content of phenolic compounds, thus suggesting that higher levels of phenolic compounds confer plants with greater antioxidant activity [12]. Ginger *(Zingiber officinale)*, a member of the Zingiberaceae family, contains active phenolic compounds such as gingerol, paradol, zingerone, zingiberol and shogaols. Ginger has been used worldwide as a spice and in traditional medicine as a cure for many diseases involving inflammation due to oxidative stress [13]. Ginger extract has been used to treat ulcers [14], diabetes [15], cardiovascular disease [16], obesity [17], depression [18], Alzheimer's disease [19] and even cancer [20] due to its antioxidant, anti-inflammatory, antimicrobial and antitumour properties [21, 22]. Therefore, the current study was performed to evaluate the radioprotective efficacy of ginger *(Zingiber officinale)* extract, a natural product, against gamma radiation toxicity in Wistar albino rats through assessment of DNA oxidative stress, bone marrow genotoxicity, DNA damage in both bone marrow cells and epididymal sperm, sperm DNA chromatin integrity and sperm shape anomalies.

MATERIALS AND METHODS

Animals

Twenty-four male adult Wistar albino rats weighing approximately 140±20 g were used throughout the study. The rats were obtained from the animal house of El-Salam farm, Giza, Egypt, housed in plastic cages covered with metal wire covers and kept under standard laboratory conditions with a 12-hr light-dark cycle. The rats had free access to standard commercial laboratory food and tap water and were allowed to adapt to the laboratory conditions for two weeks before the beginning of the experiment. The rat was chosen as the experimental animal in this study because of its genetic stability and its very low rate of spontaneous mutation.

Chemicals

Preparation of ginger aqueous extract

Ginger rhizomes were purchased from the local market, and the aqueous extract of *Zingiber officinale* was prepared as described by [23]. Fresh ginger rhizomes (1 kg) were washed, peeled, cut into pieces and dried in a hot air oven at 40±2°C. The ginger was then ground using an electric blender, soaked in 2 litres of sterile water for 3 hr, heated at 60-65°C for 30 min, and then filtered to obtain the crude extract. The process was repeated four times, and all the filtrates were collected, concentrated by evaporation in a rotary vacuum evaporator at 55°C and then dried at room temperature. The powdered extract of ginger was stored at -20°C for future use. The final solution of ginger extract was made by dissolving ginger powder in saline solution.

Irradiation procedure

Whole-body gamma-irradiation was performed at the Atomic Energy Authority, Cairo, Egypt, using a Gammacell-40 Carloirradiator caesium-137 source. Animals were acutely irradiated with a single dose of 6 Gy delivered at a rate of 0.713 rad/sec. All animal procedures in the present study were performed in accordance with the guidelines of the Committee on the Care and Use of Experimental Animal Resources, Medical Research Centre, Ain Shams University.

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Experimental design

Twenty-four male albino rats were randomly distributed into four groups of six rats each. Group I served as a healthy control and was orally given normal saline by gavage every day for 14 days. The animals in Group II (the IR group) were exposed to whole-body gamma radiation (6 Gy) [24]. In Group III, the rats orally received freshly prepared ginger extract (250 mg/kg b.w.) for 14 consecutive days. The protective dose was chosen based on the findings of [23]. In Group IV, the rats were orally given freshly prepared ginger extract (250 mg/kg b.w.) every day for 14 consecutive days and then exposed to whole-body gamma radiation (6 Gy) 2 hr after the last administration of ginger. Twenty-four hours after the last treatment, all animals were anaesthetized with ether, and blood samples were collected from the retro-orbital sinus with non-heparinized haematocrit tubes into clean, dry centrifuge tubes. The centrifuge tubes were allowed to sit at room temperature for at least one hour so the blood would coagulate and were then centrifuged at approximately 2500-3000 rpm for 10 min. The supernatant (serum) was transferred into clean Eppendorf tubes and stored in a deep freezer at -20°C. The animals were euthanized by cervical dislocation after blood withdrawal.

DNA oxidative stress

Serum 8 - hydroxy - 2′ - deoxyguanosine (8-OHdG) levels were measured using the enzyme-linked immunosorbent assay (ELISA) method with a DRG 8-OHdGELISA kit (www.MyBioSource.com, USA, catalogue number MBS269902) according to the kit manufacturer's instructions (version: 09.3.1).

Chromosomal aberration assay

Metaphase chromosomes were prepared from bone marrow cells of control and treated rats according to the method proposed by [25]. A total of 1000 cells/animal were examined to determine the mitotic index, and 50 metaphases/animal were analysed for chromosomal aberrations with a light microscope at 1000x magnification. Any deviation from normality was documented.

Micronucleus assay

A micronucleus assay was performed on polychromatic erythrocytes (PCEs) from bone marrow as described by [26]. A total of 1000 PCEs were inspected per animal under 1000x magnification using light microscopy to assess the rate of occurrence of micronucleated polychromatic erythrocytes (MNPCEs). Additionally, the PCE/normochromatic erythrocyte (NCE) ratio was calculated for a total of 500 erythrocytes to indicate the degree of erythropoiesis.

Comet assay (single-cell gel electrophoresis)

DNA damage in bone marrow cells and epididymal sperm was determined using an alkaline comet assay as described by [27]. The cells were adjusted to concentrations of 2-3 × 10^5 cells/ml and 6 × 10^6 sperm/ml, respectively. A total of 10 µl of each sample was mixed with 90 µl of low melting point agarose (0.7% in PBS) at 37°C, and the mixtures were placed on fully frosted microscope slides precoated with 110 µl of normal melting point agarose (1% in PBS). Cover slips were immediately placed on top of the agarose layers, and the agarose was allowed to solidify on a cold plate for 10 min at 4°C. After gel solidification, the cover slips were gently removed, and a second layer of low melting point agarose was added and allowed to solidify at 4°C. Next, the slides were submerged for at least 2 hr at 4°C in lysis buffer (2.5 mol/L sodium chloride, 10 mmol/L Tris (pH 10) and 100 mmol/L EDTA) with freshly added 10% DMSO and 1% Triton X-100. 100 µg/ml proteinase K was added to the sperm lysis buffer. After lysis, all liquid was drained from the cells, which were then incubated in chilled alkaline electrophoresis buffer (pH > 13) (300 mmol/L NaOH and 1 mmol/L Na_2EDTA) for 20 min at 4°C and electrophoresed for 30 min at 300 mA and 25 V. After electrophoresis, the slides were washed thrice with neutralizing buffer [0.4 mol/L Tris (pH 7.5)] for 5 min each. Finally, the slides were stained with50 µl of ethidium bromide (2 mg/ml), covered with cover slips and observed at 400x magnification

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under an Optika Axioscope fluorescence microscope.

Comet scoring and analysis

A total of 100 randomly selected cells/ sample were photographed, scanned and analysed with TriTek CometScore freeware v1.5. The length of DNA migration (tail length) was measured in px. The tail moment was calculated as the tail length X the percentage of migrated DNA / 100 and is expressed in arbitrary units.

Sperm morphology assay

A sperm morphology assay was performed as described by [28]. The epididymis was dissected out and trimmed of fat. Then, the distal end of the cauda epididymis was removed and placed in a petri dish containing 2 ml of Ham's F10 medium (Bio Sense, El Haram, Giza, Egypt). Several deep cuts were made in the epididymal tissue, and the sperm were allowed to swim out into the petri dish. Then, the sperm were gently aspirated, and one drop of the mixture was smeared on each microscopic slide. The sperm smears were fixed with methyl alcohol, stained with haematoxylin and eosin and analysed under a research microscope at 1000x magnification. A total of 1000 sperm from each rat were scored to calculate the percentage of abnormal sperm.

Sperm DNA integrity analysis

Acridine orange (AO) staining was performed to assess sperm DNA integrity as described by [29]. Briefly, sperm smears were fixed with Carnoy's fixative (3:1 methanol: acetic acid) at 4°C for 14 hr, and then the slides were stained with AO (0.19% in phosphate citrate buffer, pH=2.5) for 10 min. After staining, the excess AO stain was gently removed by washing the slides for 5 min with distilled water, after which the slides were air dried and observed under a fluorescence microscope at 400x magnification. The types of staining patterns observed in the sperm head included green staining, which indicated the presence of normal double-stranded DNA, and orange or yellow staining, which indicated the presence of abnormal single-stranded DNA. At least 100 sperm/slide were examined to calculate the percentage of sperm with double-stranded DNA.

Statistical analysis

The obtained data were subjected to one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. Differences with p values ≤ 0.05 were regarded as statistically significant. The data are expressed as the mean ± S.E.

RESULTS

DNA oxidative stress

The data showed that the 8-OHdG level was five-fold higher (13.5±0.13) in the irradiated group than in the control group (2.67 ± 0.69) and the ginger group (2.45±0.14). Pretreatment with ginger significantly (P<0.01) reduced the 8-OHdG level (4.25±0.44) compared to irradiation alone (figure 1).

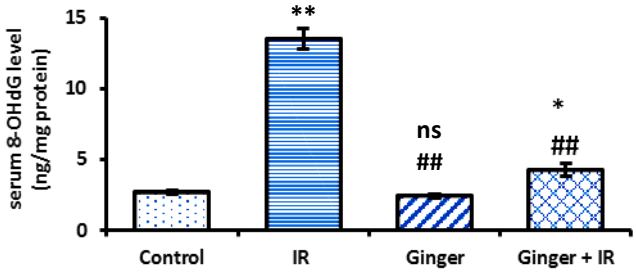

Figure 1. The mean levels of 8-OHdG in the control, irradiated and/or ginger-treated groups.

^{ns}P>0.05 compared with the control group. *P<0.05 compared with the control group.
**P<0.01 compared with the control and ginger groups.
$^{\#\#}$P<0.01 compared with the IR group.

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Chromosomal aberrations

The group of rats exposed to gamma radiation exhibited a highly significant (P<0.01) increase in the mean frequency of aberrant cells along with a significant decrease in the mitotic index compared to the control and ginger groups (table 1 and figure 4). The types of structural chromosomal aberrations most frequently observed in the IR group were breaks, dicentric chromosomes, acentric fragments and ring chromosomes (figure 2). Numerical aberrations were also recorded in all experimental groups, as depicted in figure 3. Pretreatment with ginger extract significantly (P<0.01) increased the mitotic index (figure 4) and significantly reduced the number of aberrant cells (table 1) compared to irradiation alone.

Table 1. Structural chromosomal anomalies induced after exposure to 6 Gy of whole-body gamma-radiation and/or ginger.

Treatment group	Aberrant cells	Types of structural chromosomal aberrations							
		Br.	Gap	A.F.	Dic.	Ring	C.F.	Ch.Ex.	Del.
Control	5.33±0.98	1.67±0.33	0.33±0.2	0.67±0.21	0.83±0.3	1.67±0.167	0.33±0.2	0.16±0.16	0.66±0.21
IR	$38.83\pm1.4^{**}$	$29.3\pm2.3^{**}$	1 ± 0.51^{ns}	$24.5\pm2.0^{**}$	$25.8\pm4.9^{**}$	$14.1\pm1.4^{**}$	3.8 ± 1.5^{ns}	1.8 ± 0.8^{ns}	$11.17\pm2.8^{**}$
Ginger	$5.83\pm0.83^{ns\#\#}$	1.67 ± 0.33^{ns}	0.5 ± 0.2^{ns}	1.17 ± 0.16^{ns}	1 ± 0.25^{ns}	0.83 ± 0.3^{ns}	0.33 ± 0.2^{ns}	0.5 ± 0.2^{ns}	0.66 ± 0.21^{ns}
Ginger + IR	$17.17\pm1.5^{**\#\#}$	$14\pm1.15^{**\#\#}$	0.8 ± 0.3^{nsa}	$10\pm1.39^{**\#\#}$	$13.5\pm0.9^{**\#}$	$7.1\pm1.5^{**\#\#}$	2.8 ± 0.8^{nsa}	1.6 ± 0.3^{nsa}	$3\pm0.57^{ns\#\#}$

Br.: Break. A.F.: Acentric fragment. Dic.: Dicentric chromosome. C.F.: Centric fusion
Ch.Ex.: Chromatid exchange. Del.: Deletion. C.S.: Centric separation. N.B. gaps were excluded from calculation.
All the values are presented as the mean ±SEM (n=6). ^{ns}P>0.05 compared with the control group.
**P<0.01 compared with the control group. ^{a}P>0.05 compared with the IR group.
$^{\#}$P<0.05 compared with the IR group. $^{\#\#}$P<0.01 compared with the IR group.

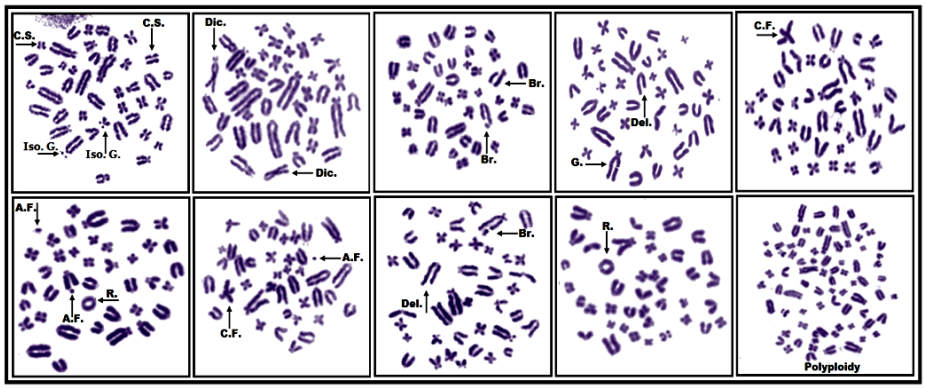
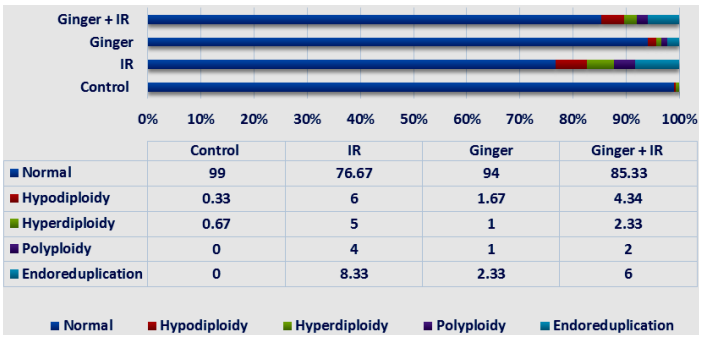


Figure 2. Metaphase plates from bone marrow cells of rats exposed to 6 Gy of whole-body radiation showing various types of structural chromosomal aberrations.

C.S.: Centric separation. Iso.G.: Isochromatid gap. Dic.: Dicentric chromosome. Br.: Break. Del.: Deletion. G. Gap. C.F.: Centric fusion. A.F.: Acentric fragment. R.: ring.



	Control	IR	Ginger	Ginger + IR
Normal	99	76.67	94	85.33
Hypodiploidy	0.33	6	1.67	4.34
Hyperdiploidy	0.67	5	1	2.33
Polyploidy	0	4	1	2
Endoreduplication	0	8.33	2.33	6

Figure 3. Mean percentages of different types of numerical chromosomal aberrations recorded in the control, irradiated and/or ginger-treated groups.

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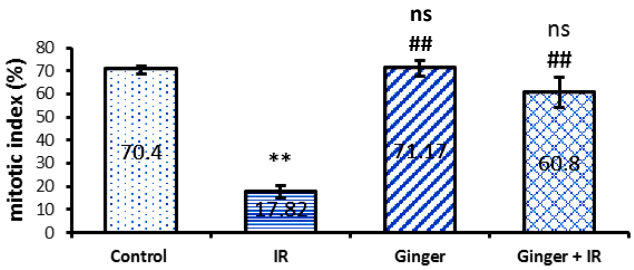

Figure 4. The mitotic index percentages of the control, irradiated and/or ginger-treated groups.

^{ns}P>0.05 compared with the control group. $^{\#\#}$P<0.01 compared with the IR group. **P<0.01 compared with the control and ginger groups.

Micronucleus formation and DNA damage in bone marrow cells

The results revealed statistically nonsignificant differences (P>0.05) in the mean percentage of micronucleated PCEs and in the PCE/NCE ratios between the control and ginger groups. The group exposed to gamma radiation alone revealed a highly significant (P<0.01) increase in the mean percentage of MNPCEs and a significant decrease (P<0.01) in the PCE/NCE ratio compared to the control and ginger groups (figure 5 & table 2). Pretreatment of rats with ginger extract (250 mg/kg) significantly (P<0.01) reduced the mean percentage of MNPCEs and significantly increased the PCE/NCE ratio.

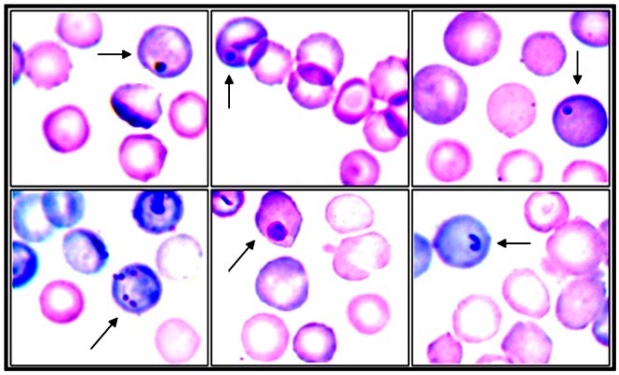

Figure 5. Different types of micronuclei observed after exposing rats to 6 Gy of whole-body gamma-radiation.

Table 2. Incidences of MNPCEs and DNA fragmentation in bone marrow cells of rats exposed to 6 Gy of whole-body gamma-radiation and/or ginger.

Treatment group	Mean % of MNPCEs	PCEs/NCEs	DNA damage in bone marrow cells			
			Tail length (px)	DNA in tail %	Tail moment	Olive tail moment
Control	0.217± 0.65	1.08± 0.07	4.32±0.79	4.04 ± 0.82	0.19 ± 0.06	0.386±0.13
IR	2.11± 1.6**	0.45± 0.03**	10.99 ± 1.5**	8.2 ± 0.31**	0.9 ± 0.14**	1.76±0.34**
Ginger	0.20± 0.68$^{ns\#\#}$	1.08± 0.08$^{ns\#\#}$	4.42±0.75$^{ns\#\#}$	3.51± 0.65$^{ns\#\#}$	0.15 ±0.05$^{ns\#\#}$	0.31±0.12$^{ns\#\#}$
Ginger + IR	0.433± 1.1$^{ns\#\#}$	0.99± 0.13$^{ns\#\#}$	5.73±0.93$^{ns\#\#}$	4.52 ±0.66$^{ns\#\#}$	0.28 ±0.08$^{ns\#\#}$	0.56±0.11$^{ns\#\#}$

All the values are presented as the mean ±SEM (n=6). ^{ns}P>0.05 compared with the control group.
$^{\#}$P<0.05 compared with the IR group. **P<0.01 compared with the control group. $^{\#\#}$P<0.01 compared with the IR group.

In addition, the IR group revealed a highly significant increase (P<0.01) in cellular DNA damage of bone marrow cells, as demonstrated by increased comet tail length, percent of DNA in the tail, tail moment, and Olive tail moment values, compared to the control and ginger groups (table 2). Pretreatment of rats with ginger extract significantly reduced DNA damage compared with irradiation alone (figures 6 & 7).

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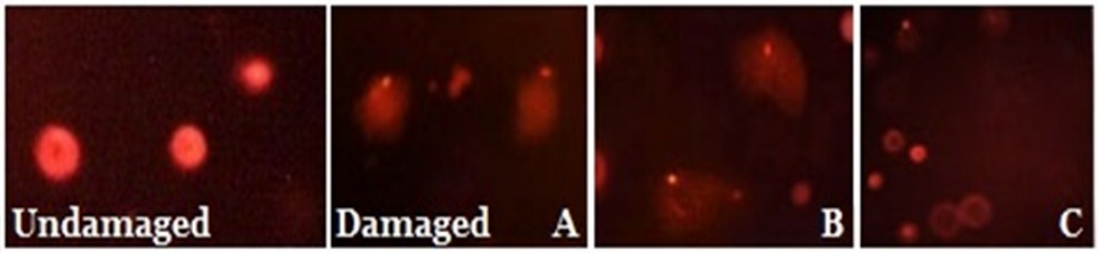

Figure 6. DNA in undamaged bone marrow cells from control rats and damaged cells from irradiated rats **(A&B)** and ginger extract-pretreated irradiated rats **(C)**.

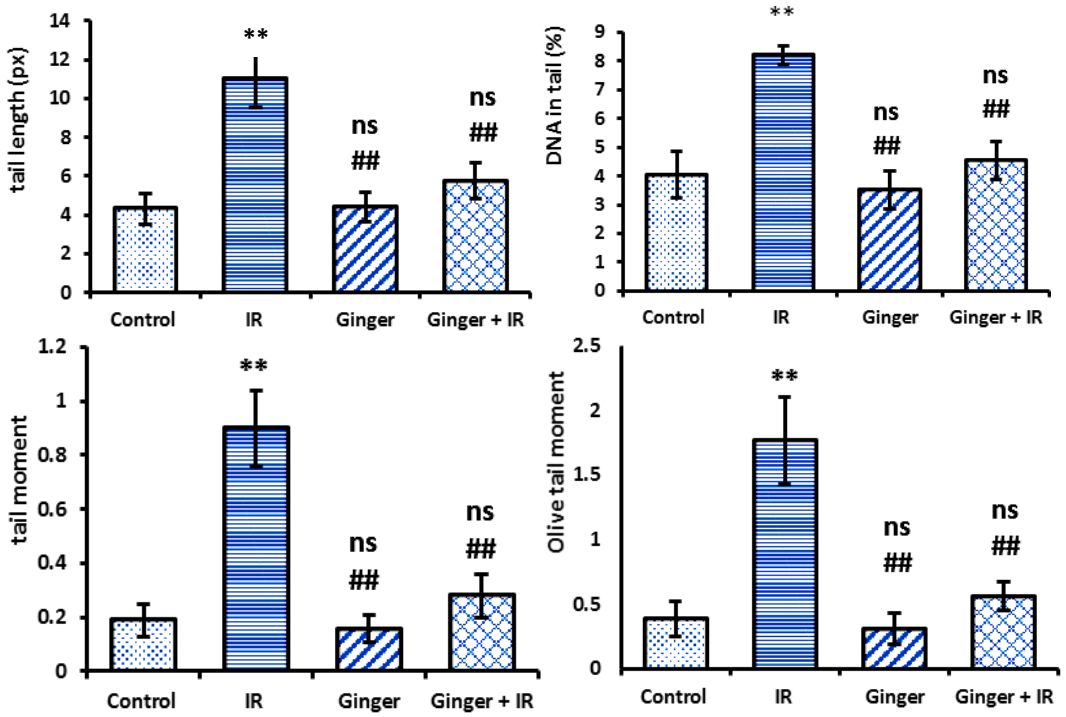

Figure 7. The tail length, percent of DNA in the tail, tail moment and Olive tail moment recorded in bone marrow cells of the control, irradiated and/or ginger-treated groups.

^{ns}P>0.05 compared with the control group. **P<0.01 compared with the control group. $^{\#\#}$P<0.01 compared with the IR group.

Epididymal sperm DNA damage

The gamma-irradiated group showed significantly higher comet tail length, percent of DNA in the tail, tail moment and Olive tail moment values than the control and ginger groups (table 3). These values were significantly lower in the group pretreated with ginger extract (figures 8 & 9).

Table 3. Sperm abnormalities, DNA integrity and DNA damage in the control, irradiated and/or ginger-treated groups.

Treatment group	Sperm abnormalities %	Sperm DNA integrity%	Epididymal sperm DNA damage			
			Tail length (px)	DNA in tail %	Tail moment	Olive tail moment
Control	2.88 ± 1.5	5.67±0.8	9.65 ± 0.64	4.19 ± 0.19	0.39 ± 0.04	0.67 ± 0.07
IR group	8.21± 3.86**	42.33±2.1**	16.18 ±1.35**	7.37 ± 1.06*	1.27 ± 0.25**	1.52 ± 0.22**
Ginger	2.85 ± 1.05^{ns}	6.67±0.8$^{ns\#\#}$	11.62 ± 0.85$^{ns\#}$	3.78 ± 0.28$^{ns\#\#}$	0.41 ± 0.03$^{ns\#\#}$	0.65 ± 0.06$^{ns\#\#}$
Ginger + IR	3.85 ± 1.74$^{*\#\#}$	35.3±1.5$^{**\#}$	11.83 ± 1.09$^{ns\#}$	4.5 ±0.61$^{ns\#}$	0.55 ± 0.11$^{ns\#\#}$	0.83 ± 0.08$^{ns\#\#}$

All the values are presented as the mean ±SEM (n=6). ^{ns}P>0.05 compared with the control group.
*P<0.05 compared with the control group. $^{\#}$P<0.05 compared with the IR group.
**P<0.01 compared with the control group. $^{\#\#}$P<0.01 compared with the IR group.

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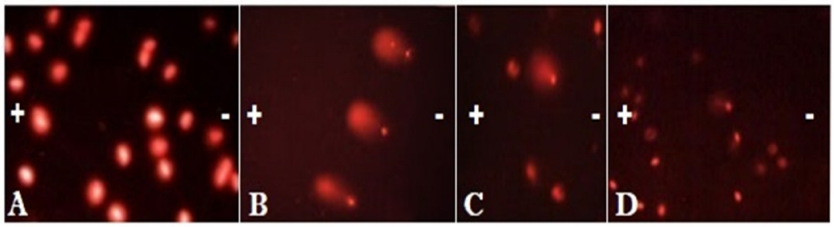

Figure 8. Epididymal sperm showing undamaged DNA in the control group **(A)** and damaged DNA in the irradiated group **(B&C)** and ginger extract-pretreated irradiated group **(D)**.

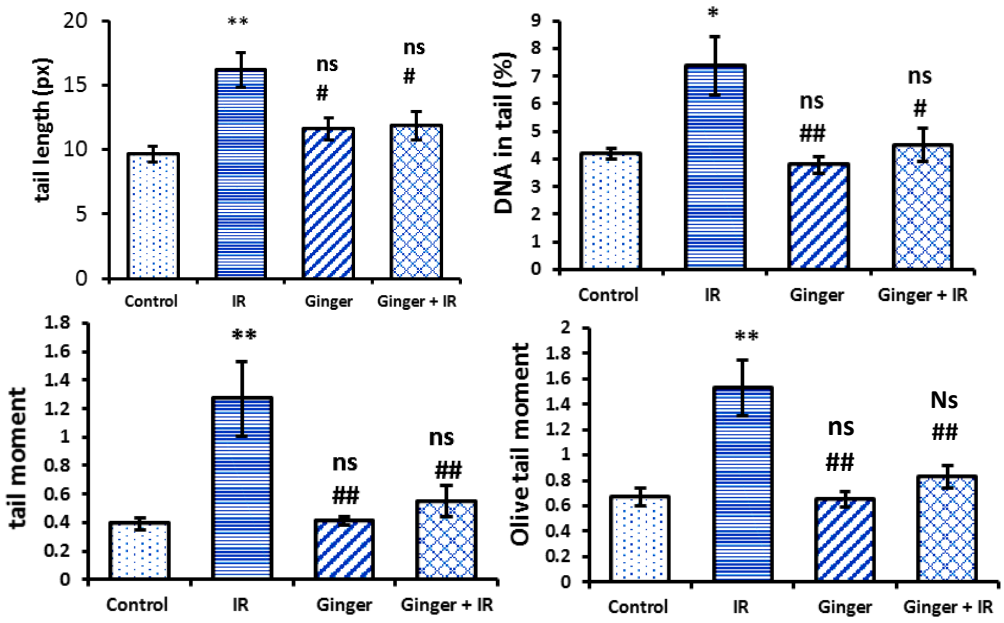

Figure 9. The tail length, percent of DNA in the tail, tail moment and Olive tail moment recorded in epididymal sperm of the control, irradiated and/or ginger-treated groups.

^{ns}P>0.05 compared with the control group. $^{\#}$P<0.05 compared with the IR group. *P<0.05 compared with the control group. $^{\#\#}$P<0.01 compared with the IR group. **P<0.01 compared with the control group.

Sperm DNA integrity and sperm shape abnormalities

AO staining showed that gamma radiation had a clear effect on sperm DNA integrity (figure 10). This effect was significantly (P< 0.05) diminished in the group pretreated with ginger. Moreover, H&E staining revealed that gamma-radiation significantly (P<0.01) increased the percentage of abnormal sperm. Ginger pretreatment significantly attenuated the sperm abnormalities caused by irradiation, as demonstrated by the lower percentage of abnormal sperm in the group receiving ginger and radiation than in the radiation-only group (P<0.01). Figure 11 illustrates the types of sperm shape abnormalities induced by irradiation. Ginger alone did not significantly affect this parameter, as there was no difference between the ginger-only group and the control group (table 3 & figure 12).

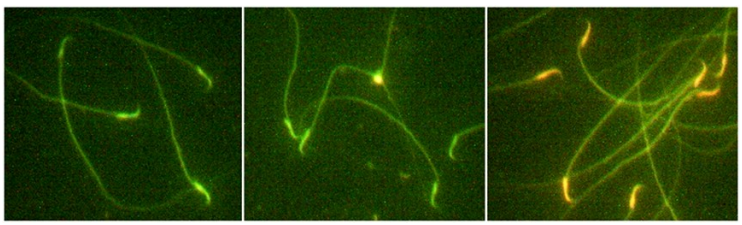

Figure 10. Sperm smears stained with AO showing normal sperm (with green heads) and abnormal sperm (with orange or yellow heads).

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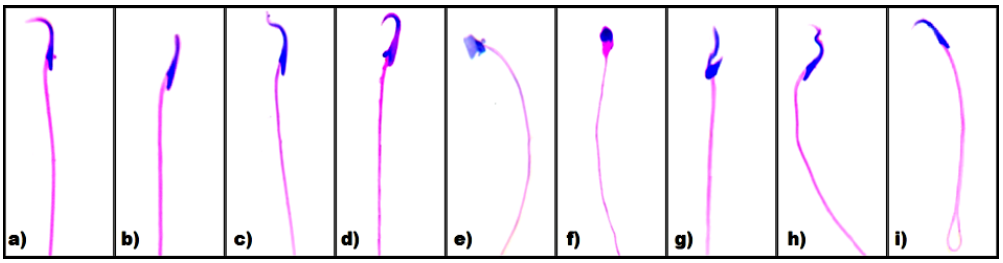

Figure 11. The different types of sperm anomalies recorded after exposing rats to 6 Gy of gamma-radiation.

include the following:
a): No anomaly (normal). b): Lack of hook. c): Deformed hook. d):Acute curvature. e): Triangular head. f &g): Amorphous. h):Zigzag-shaped curvature. i):Coiled tail.

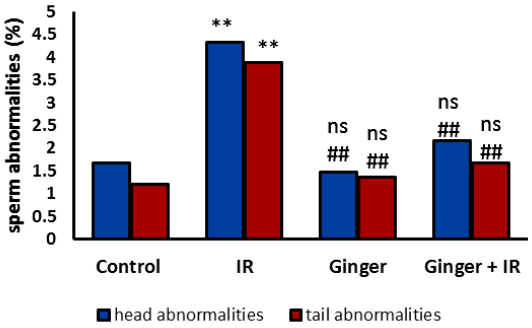

Figure 12. Mean percentages of head and tail abnormalities detected in the control, irradiated and/or ginger-treated groups.

^{ns}P>0.05 compared with the control group. **P<0.01 compared with the control group. $^{\#\#}$P<0.01 compared with the IR group.

DISCUSSION

It is well known that IR induces oxidative stress via excessive production of ROS, resulting in an imbalance in cell pro-oxidant/antioxidant status [30]. One of the well-established biomarkers of DNA oxidation and carcinogenesis is 8-OHdG or 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxodG), which is produced due to DNA oxidative damage by reactive oxygen and nitrogen species [31]. In the present study, exposing rats to whole-body gamma-radiation (6 Gy) significantly increased serum 8-OHdG to a level 5-fold greater than that in the control group, indicating that DNA oxidative damage was induced by radiation. This result is consistent with previous results obtained by Grygoryev [32]. On the other hand, pretreatment with ginger *(Zingiber officinale)* extract significantly reduced the 8-OHdG level until it was only 2-fold greater than that in the control group, consistent with the findings of Kota [33], who reported a protective effect of ginger extract mediated by regulation of glutathione (GSH) and antioxidant enzymes and reduction of lipid and protein oxidation. In addition, the genotoxic and cytotoxic effects of gamma radiation were revealed by the increased frequencies of chromosomal aberrations, micronucleus formation, and DNA damage and the reductions in both the mitotic index and PCE/NCE ratio in the IR group. These results are in accordance with those of prior studies affirming that IR induces a variety of types of DNA damage, such as DNA base and sugar changes, cross-links, and single-strand breaks and DSBs, resulting in the occurrence of chromatid and chromosomal aberrations [34, 35]. The most commonly recorded types of structural chromosomal aberrations in the current investigation were breaks, dicentric chromosomes, acentric fragments and ring chromosomes, consistent with the previous results of [36]. Radiation can generate ROS, which damage cell membranes and cause lipid peroxidation [37]. Moreover, malondialdehyde (MDA), the product of lipid peroxidation, is an endogenous genotoxic product that interacts with DNA, causing strand breaks that in turn

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develop into chromosomal breaks [38].

Micronuclei can be created either by acentric fragments or losses of whole chromosomes at anaphase and are associated with cell death [39]. In the current study, the group exposed to gamma-radiation exhibited significantly more MNPCEs and a significantly lower PCE/NCE ratio than the control group, consistent with the findings of [35, 40-42]. The reduction in the PCE/NCE ratio observed in the present study indicates the effect of radiation on the cell cycle, as radiation suppressed erythropoiesis [43].

The group treated only with *Zingiber officinale* extract for 58 consecutive days revealed statistically nonsignificant differences in all experimental parameters compared to the control group, in accordance with the findings of Bidinotto [44], who concluded that *Zingiber officinale* extract is not genotoxic. Additionally, pretreatment with *Zingiber officinale* extract significantly reduced structural chromosomal aberrations and micronucleus formation in PCEs and sustained both the mitotic index and PCE/NCE ratio after irradiation, consistent with the results of [36, 45].

Moreover, the present results showed that gamma irradiation increased cellular DNA damage in bone marrow cells and epididymal sperm of exposed rats, as indicated by the significant elevations in the percent of DNA in the tail, tail length and tail moment. Similar observations were reported by [46, 47]. However, treatment of rats with the ginger extract prior to radiation exposure prevented the effects of gamma-radiation on cellular DNA, in accordance with the results of Jeena [45], who reported that ginger essential oil revealed marked antioxidant activity and exhibited DNA-protective effects against the effects of gamma-radiation. The apparent protective effects of ginger extract in the current study could be due to its antioxidant potential, as antioxidation plays vital role in chelating metal ions and scavenging hydroxyl (OH) and hydrogen peroxide (H_2O_2) radicals [48, 49]. This antioxidant potential of ginger might be attributed to its constituents, such as 6-gingerol (the main bioactive compound in fresh ginger) and several antioxidant compounds such as vitamin C, vitamin E, beta-carotene, lutein, lycopene, quercetin, genistein, and tannin [20, 50]. The ascorbic acid in ginger suppresses peroxidation in both aqueous and lipid regions of cells [51], traps peroxyl radicals before they can provoke lipid peroxidation and aids in the regeneration of vitamin E [52]. In addition, earlier studies have confirmed that ginger extract protects against oxidative stress by enhancing superoxide dismutase (SOD) and catalase activity, increasing GSH content and decreasing MDA levels [53]. AO is a supravital stain that binds to genetic material (DNA and RNA) and provides a general picture of DNA denaturation status by indicating nuclear maturity and sperm DNA condensation; AO emits yellow, orange or red fluorescence when bound in immature sperm nuclei that contain mostly single-stranded, thiol-containing protamine nucleoproteins and emits green fluorescence when bound with double-stranded DNA [54]. In the present study, pretreatment with ginger extract significantly diminished the harmful effects of gamma-radiation on epididymal sperm morphology and DNA integrity. Previous investigations have revealed that ginger supplementation in oxidative stress conditions increases testicular and other sexual organ weight, enhances the activity of antioxidant enzymes, reduces testicular oxidative stress, increases testosterone production by enhancing luteinizing hormone (LH) production, increases testicular cholesterol levels, normalizes blood glucose, increases testicular blood flow and improves the fertility index by increasing sperm mobility, viability, count and morphology [55-58].

CONCLUSION

The need for natural radioprotective drugs to protect normal tissues in radiotherapy regimens is growing. The results of the present study indicate that ginger pretreatment provides protection against DNA oxidation induced by radiation by sustaining serum 8-OHdG levels. Additionally, ginger revealed antigenotoxic effects, reducing chromosomal abnormality incidence, micronucleus formation, and DNA

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damage in bone marrow and sperm as well as restoring DNA integrity and sperm morphology. All these findings suggest that ginger exhibits effective antioxidant activity and has a radioprotective effect against the effects of whole-body gamma-irradiation. This study suggests a new strategy to combat the effects of acute radiation and calls for the development of better ginger-based pharmaceutical drugs.

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