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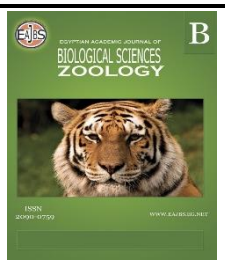

Therapeutic Role of Low Doses of Gamma Irradiation on Ehrlich Carcinoma Bearing Mice

Rahma S. Abd Allah [1] , Dina M.I. Heibashy [1] ,Walaa A.M.El-Nahrawy[1] and Neamat H. Ahmmed[2]

[1]Zoology department, Faculty of Women for Arts, Science and Education, Ain Shams University.
[2]National Center for Radiation Biology – Egyptian Atomic Authority, Cairo, Egypt.
*** E-mail** : Rahma.Sayed@women.asu.edu.eg - Dina.Heibashy@women.asu.edu.eg - Walaa_yao@women.asu.edu.eg - Neamathanafi@ymail.com

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ABSTRACT

Cancer is a significant reason for death globally, emerging as the second most common cause of mortality worldwide. Ehrlich ascites carcinoma (EAC) cells are investigational tumor models used globally in cancer research. Radiation therapy is commonly applied to cancerous tumors because of its ability to control cell growth. This study aims to explore the potential therapeutic effects of Low Doses of Gamma Irradiation (γ-radiation) on Ehrlich carcinoma-bearing mice. Forty adult female Swiss albino mice were divided into four groups: Normal control group (NC) of 10 mice were given saline; Ehrlich carcinoma group (EC) of 10 mice were intramuscularly inoculated with 0.2ml of EAC containing $2.5x10^6$ in the right thigh of the lower limb of female mice; Tumor-bearing EC-Irradiated group (EC-IR) of 10 mice were exposed to 0.5Gy of gamma radiation two times weekly for 2 weeks; Radiation group (IR) of 10 mice were exposed to 0.5 Gy of gamma radiation two times weekly for 2 weeks. The current result showed a significant increment in muscle size of the right thigh, MDA, H_2O_2, TNF-α, IL-6, VEGF, WBC, and Platelets (PLT). Also, EC causes a reduction of antioxidant enzymes (GSH), RBCs and Heamoglobin (Hb). However, the therapeutic group (EC-IR) showed an improvement in biochemical and hematological parameters.

INTRODUCTION

Cancer is one of the leading causes of death and a significant public health issue (Zheng *et al*., 2022). Cancer mortality is still high and there is currently no effective medication to stop tumor growth despite advances in the molecular basis, detection, and treatment of the disease (Jafari *et al*., 2021). Over six million people die from cancer each year, making it one of the worst risks to human existence (Abdullaev *et al*., 2000).

Ehrlich ascites carcinoma (EAC) is a fast-growing, extremely aggressive type of cancer. It can grow in nearly all mouse strains (Bhattacharya *et al*., 2011 and Hemdan, 2022). Radulski *et al*. (2023) reported that when an Ehrlich ascitic tumor is implanted, a local inflammatory response and increased vascular permeability are automatically induced.

These results in the formation of a substantial amount of edoema, cellular migration, and a slow accumulation of ascitic fluid. Researchers have effectively used Ehrlich cancer, especially in its solid form (EST) as a model for *in vivo* research because of its rapid development and spread (Ali *et al*., 2015). EAC cells are 100% malignant, have a short life span, exhibit no regression, multiply quickly, are highly transplantable, and lack the tumor-specific transplantation antigen (TSTA) (Das *et al.*, 2011).

Chemotherapy, radiation, and surgery are the typical procedures utilized in modern medicine for cancer treatment (Debela *et al*., 2021). According to Cremonesi *et al.* (2014), radiation was the second clinical medical treatment that was utilized to treat a variety of malignancies. It is a therapy using ionizing radiation, generally provided as part of cancer treatment to control or destroy malignant cells.

Radiation therapy is commonly applied to cancerous tumors because of its ability to control cell growth. Ionizing radiation works by damaging the DNA of cancerous tissue leading to cellular death. Radiotherapy may be used in combination with surgery and/or chemotherapy as in breast cancer (Bollet *et al*., 2007) or rectal cancer (Vini, 2007).

Recent years have seen remarkable improvements in this discipline. Ionizing radiation (X-rays, γ-rays) kills most organisms by way of the free radicals produced by the radiolytic breakdown of cellular water. When this species of free radical interacts with vital targets like DNA and membranes, it causes irreparable harm that eventually results in cell death (Baskar *et al*., 2012 and Christensen *et al*., 2014).

Numerous authors have demonstrated that low-dose radiation (LDR) has the potential to increase the response to anticancer medications and decrease side effects by enhancing various phenomena, such as adaptive response and cell-cell communication (Chandna *et al.,* 2002; Liu *et al*., 2004 and Paithankar *et al*., 2023). Additionally, response of the immune system (Hosoi & Sakamoto, 1993) and inhibition of metastasis subsequently have been observed with LDR (Liu, 2007).

Exposure to low doses of ionized radiation (LDIR) has a positive effect on biological systems so that repair mechanisms in the body are stimulated and activated (Baldwin & Grantham, 2015). Interestingly, several studies using both animal and human models showed that LDIR can promote normal cell proliferation, enzymatic repair, and tissue repair, increase immune response, slow down ageing, and even prevent or delay carcinogenesis/cancer progression (Luckey, 2006 and Doss, 2016).

Additionally, LDIR stimulates DNA repair pathways and affects cells involved in the inflammatory response, leading to anti-inflammatory effects (Lau *et al*., 2021). Also, LDIR has been demonstrated to activate each antioxidant defense mechanism, reducing genomic instability, and preventing harm to healthy cells from free radicals and/or reactive oxygen species (Kim *et al.*, 2020). The current study was designated to explore the potential therapeutic effects of low doses of γ-radiation on Ehrlich carcinoma-bearing mice. The current study was designated to explore the potential therapeutic effects of low doses of γ-radiation on Ehrlich carcinoma-bearing mice.

MATERIAS AND METHODS

Forty female Swiss albino mice were purchased from the Egyptian Organization for Biological Products and Vaccines, Cairo, Egypt. They weighed between 22 and 25 g, and their average age was 8–10 weeks. To prevent any issues during the experiment, the animals were allowed 14-day pre-experimentation periods to adapt to laboratory conditions. The animals were housed in metabolic cages with enough ventilation, regular temperature and humidity ranges, and a daily fresh supply of food and drink.

Ehrlich Ascites Carcinoma Cell Line:

The study utilized Ehrlich ascites carcinoma (EAC) cells, which were sourced from the Egyptian National Cancer Institute (NCI) at Cairo University, Egypt. EAC cells were regularly transplanted into female Swiss albino mice through intraperitoneal injection of 2.5 x 10^6 cells per mouse weekly throughout the duration of the experiment (Salem *et al*., 2011).

Radiation Facility:

Mice were subjected to whole-body gamma irradiation at the National Center for Radiation Research and Technology (NCRRT), which is located at the Egyptian Atomic Energy Authority in Nasr City, Cairo, Egypt. The radiation used for the experiment was generated by an indoor-shielded Canadian Gamma Cell-40 (137Cs). This source ensured a uniform distribution of the radiation dose across the entire irradiation tray. The experimental animals were housed in a specially designed acrylic container that provided adequate ventilation. They were exposed to whole-body γ-radiation at a dose of 0.5 Gy of gamma radiation twice a week for two weeks. This radiation treatment began eight days after the tumor transplantation. According to the following procedure, mice received 1Gy/week for two weeks (1Gy/ week X 2), resulting in a total cumulative radiation dose of 2Gy over the two-week period. Each individual dose of γ-radiation lasted for 1.5 minutes.

Experimental Design:

Experimental animals were separated into four groups each containing 10 mice. The first group (Normal Control group) remained as normal control was given saline. The second group (EC group) was intramuscularly inoculated with 0.2ml of EAC containing $2.5x10^6$ in the right thigh of the lower limb of female mice. The third group (EC-IR group) was subjected to 0.5Gy of gamma radiation two times weekly for 2 weeks after eight days of tumor inoculation. The fourth group (IR group) was exposed to 0.5Gy of gamma radiation two times weekly for 2 weeks.

Measurement of Tumor Size:

A Vernier caliper was used to measure the size of the solid one week after implantation. The tumor's size was calculated using the formula below Schirner *et al.* (1998).

$$\text{Tumor size } (mm^3) = (\text{width})^2 \times \text{length} \times 0.52.$$

Assessment of Oxidative Stress and Antioxidant Enzymes Activities:

The colorimetric kit was purchased from Bio Diagnostic Company and used for the determination of Malondialdehyde (MDA), Hydrogen peroxide (H_2O_2) levels and GSH activity in tissue.

Assessment of Inflammatory Response Markers (TNF-α, IL-6) and Angiogenesis (VEGF) Markers:

ELISA Kit obtained from CUSABIO Company was used to determine the quantitative level of serum TNF-α. IL-6 was determined by PCR technique using a high-capacity cDNA reverse transcription kit (#K4374966, Thermo Fisher Scientific, USA) which was used to convert the extracted RNA into cDNA. Software version 3.1 was used to perform real-time qPCR amplification and analysis. The primer sets are listed in table (1). ELISA Kit obtained from CUSABIO company was used to determine the quantitative level of serum VEGF.

Table 1: Primers Sequence of IL-6.

Gene	Primer sequence
Interleukin-6 (IL-6)	ıer 5'- GCCCTTCAGGAACAGCTATGA-3',
	ΓGTCAACAACATCAGTCCCAAGA-3',

Determination of Hematological Parameters:

All mice were anesthetized by using urethane before being sacrificed and the blood was collected via heart piercing by using disposable plastic syringes. Part of the whole blood was collected in EDTA (ethylene diamine tetra acetic acid) tubes for hematological parameters such as complete blood count (CBC). The CELL-DYN 1700, an automated hematology analyzer system (Abbott Diagnostics, Abbott Park, IL, USA), was utilized for the CBC analysis.

Statistical Analysis:

SPSS was used for statistical analysis, version 20.0. The data obtained in the present work were represented in tables as mean ± standard error. Statistical analysis was carried out using one-way analysis of variance (ANOVA) for testing the significance between various treated groups.

RESULTS

The size of the Ehrlich Carcinoma Tumors Monitoring:

As illustrated in Table (2), it was obvious that injection of $2.5x10^6$ EAC cells in 0.2 ml physiological saline resulted in the formation of a solid tumor in the right thigh of the mice on the 15^{th} day after tumor inoculation (ATI)), a solid tumor with a mean size of 638.17±66mm3. Ehrlich tumor size develops over days, reaching 1406.3±123mm^3 on the 21 th days ATI. A group of experimental animals was exposed to 0.5 Gy of γ-radiation twice weekly for two weeks, which led to a significant delay in the progression of EC. The tumor size was recorded 171±28mm^3 on the 15^{th} day ATI and 215±17 mm^3 on the 21^{st} day ATI.

Table 2: The therapeutic effect of a low dose of γ-radiation on Ehrlich carcinoma (EC) tumor size

Days ATI	EC	EC+IR
15^{th}day ATI	638.17±66	171±28‡
21^{th}day ATI	1406.3±123	215±17‡

All data are the means (mm3) ±SE where n=6. EC: Ehrlich group, EC+IR: Tumor-bearing EC Irradiated group. ‡: Values are statistically significant than their corresponding tumor size of EC group ($P \leq 0.001$).

Oxidative Stress Markers and Antioxidant Enzymes:

Malondialdehyde (MDA), and H_2O_2 levels in muscle tissue were revealed in Table (3). In EC group a notable elevation was observed in tissue MDA and H_2O_2 levels. However, the group treated with a low dose of γ-irradiation (IR) produced a remarkable reduction in the level of MDA and H_2O_2 in comparison to the EC group. Also, GSH activity in tissue declined remarkably in the EC group. While low-dose radiation treatment caused a significant rise in GSH activity.

Table 3: The therapeutic effect of a low dose of γ-radiation on tissue MDA, H_2O_2 levels and GSH activity in control and EC groups.

Groups \ Parameters		MDA (nmol/g tissue)	H_2O_2 (nmol/g tissue)	GSH (mmol/g tissue)
NC	**Mean ±S.E**	37.52±0.32^{b‡}	85.42±0.84^{b‡}	128.22±0.32^{b‡}
	% Change from NC	0	0	0
	EC	-77	-63	108
EC	**Mean ±S.E**	163.44±0.56^{a‡}	232.74±1.29^{a‡}	61.66±0.35^{a‡}
	% Change from NC	335	172	-51
	EC	0	0	0
EC+IR	**Mean ±S.E**	118.72±0.32^{a‡b‡}	152.49±0.22^{a‡b‡}	92.14±0.50^{a‡b‡}
	% Change from NC	216	79	-28
	EC	-27	-34	49
IR	**Mean ±S.E**	99.3±0.53^{a‡b‡}	113±1^{a‡b‡}	111.80±0.80^{a‡b‡}
	% Change from NC	164	32	-12
	EC	-39	-51	81

Values are expressed as Means ± Standard Error (M±SE) where n=6. **NC**: Normal control group, **EC**: Ehrlich group, **EC+IR**: Tumor-bearing EC-irradiated group; and **IR**: radiated group. **a‡**: Values are statistically significant against NC at ($P \leq 0.001$). **b‡**: significant against EC at ($P \leq 0.001$).

Inflammatory Response Markers (TNF-α, IL-6) and Angiogenesis (VEGF) Markers:

Table (4) provides information on evaluating the serum levels of TNF-α, IL-6, and VEGF. According to the control mice, a remarkable elevation in TNF-α, IL-6 as well as VEGF levels were observed in mice inoculated with EC. Moreover, experimental animals treated with low doses of gamma radiation revealed a huge reduction in TNF-α, IL-6 and VEGF levels.

Table 4: The therapeutic impact of a low dose of γ-radiation on serum TNF-α, IL-6, and VEGF levels in control and EC groups.

Groups \ Parameters		TNF-α (pg/ml)	IL-6	VEGF (pg/ml)
NC	**Mean ±S.E**	17.34±0.25^{b‡}	1.05±0.01^{b‡}	113.52±0.47^{b‡}
	% Change from NC	0	0	0
	EC	-82	-86	-59
EC	**Mean ±S.E**	96.64±0.33^{a‡}	7.36±0.23^{a‡}	282.60±0.30^{a‡}
	% Change from NC	457	601	149
	EC	0	0	0
EC+IR	**Mean ±S.E**	61.1±0.40$^{a‡ b‡}$	4.21±0.10$^{a‡ b‡}$	191.12±0.30$^{a‡ b‡}$
	% Change from NC	252	301	68
	EC	-37	-43	-32
IR	**Mean ±S.E**	24.40±0.33$^{a‡ b‡}$	1.65±0.02$^{a‡ b‡}$	120.04±0.44$^{a‡ b‡}$
	% Change from NC	41	57	6
	EC	-75	-78	-58

Values are expressed as Means ± Standard Error (M±SE) where n=6. **NC**: Normal control group, EC: Ehrlich group, EC+IR: Tumor-bearing EC-irradiated group, and IR: radiated group. a‡: Values are statistically significant against NC at ($P \leq 0.001$). b‡: significant against EC at ($P \leq 0.001$).

Hematological parameters (WBCs, PLT, RBCs and Hb):

a.White blood cells count (WBCs) and Platelets (PLT):WBCs and PLT counts are illustrated in **Table (5).** There was a notable increment in the count of WBCs and PLT in EC group when compared to NC group. However, these parameters notably declined after treatment with a low dose of gamma radiation as shown in EC-IR group.

Table 5: The therapeutic role of low dose of γ-radiation on WBCs and PLT counts in control and EC groups.

Parameters / Groups		**WBCs (10^3/ul)**	**PLT (10^3/ul)**
NC	**Mean ±S.E**	$7.58\pm0.1^{b‡}$	$640.40\pm1.63^{b‡}$
	% Change from NC	0	0
	EC	-44	-48
EC	**Mean ±S.E**	$13.62\pm0.1^{a‡}$	$947.80\pm2.41^{a‡}$
	% Change from NC	80	48
	EC	0	0
EC+IR	**Mean ±S.E**	$10.22\pm0.1^{a‡\ b‡}$	$821.40\pm0.51^{a‡b‡}$
	% Change from NC	35	28
	EC	-25	-13
IR	**Mean ±S.E**	$6.12\pm0.05^{a‡\ b‡}$	$602\pm1^{a‡b‡}$
	% Change from NC	-19	-6
	EC	-55	-36

Values are expressed as Means ± Standard Error (M±SE) where n=6. NC: Normal control group, EC: Ehrlich group, EC+IR: Tumor-bearing EC-irradiated group, and IR: radiated group. a‡: Values are statistically significant against NC at ($P \leq 0.001$). b‡: significant against EC at ($P \leq 0.001$).

b- Red blood cell count (RBCs) and Haemoglobin (Hb):

RBC count and Hb concentration are shown in Table (6). Mice that were intramuscularly injected with EC showed a huge decline in RBC count and Hb concentration when compared to the control group. On the other hand, treatment with radiation caused amelioration in these hematological parameters.

Table 6: The curative role of the low dose of γ-radiation on RBC count and Hb concentration in control and EC groups.

Parameters / Groups		**RBCs (10^6/ul)**	**Hb (g/dL)**
NC (G1)	**Mean ±S.E**	$8.34\pm0.08^{b‡}$	$13.08\pm0.44^{b‡}$
	% Change from NC	0	0
	EC	39	28
EC	**Mean ±S.E**	$5.98\pm0.36^{a‡}$	$10.18\pm0.18^{a‡}$
	% Change from NC	-28	-22
	EC	0	0
EC+IR	**Mean ±S.E**	$6.98\pm0.13^{a‡\ b‡}$	$11.24\pm0.18^{a‡b‡}$
	% Change from NC	-16	-14
	EC	14	10
IR	**Mean ±S.E**	$7.94\pm0.11^{a‡\ b‡}$	$12.15\pm0.18^{a‡b‡}$
	% Change from NC	-5	-7
	EC	33	19

DISCUSSION

Today, cancer is one of the major problems. Researchers are always looking for novel factors that contribute to the carcinogenesis process (Smolarz *et al*., 2022). Many therapy combinations have been proposed and are now being used to treat a variety of cancers throughout the last few decades (Anand *et al*., 2023). One of the deadliest diseases that affect women worldwide is breast cancer (Momenimovahed & Salehiniya, 2019). Salem *et al*. (2016) noted that Ehrlich Ascites Mammary Carcinoma is a well-known model in the field of cancer biology; it is a spontaneous mammary adenocarcinoma that occurs in mice stains.

Low doses of ionizing radiation have a stimulatory or positive impact; nevertheless, rising amounts of radiation are damaging (Lau *et al*., 2021). Low-dose irradiation has been found to have stimulatory and/or beneficial effects in a different range of organisms, including microbes, plants, invertebrates, and vertebrates (Muckerheide, 2001). The average lifespan of people and experimental animals was statistically significantly increased by low-dose irradiation (Luckey, 2006). Also, Ji *et al*. (2019) reported that numerous cancers have been effectively treated with low-dose irradiation without creating severe side effects or posing a serious risk.

In the current study, the muscle size of the right thigh of female mice changed as a result of an intramuscular inoculation of EAC cells. Our results are in line with Areida *et al*. (2015) who reported that the Ehrlich tumor is a fast-developing carcinoma in which cells constantly produce more nuclear material at the expense of their regular rate of apoptosis which leads to cell proliferation and development of a tumor mass. On the other hand, treatment with a low dose of γ-radiation produced a remarkable decline in tumor size. This result is consistent with Cuttler (2020), who noted that radiation exposure was used to treat cancer in order to remove cancer metastases, reduce the size of tumors, or stop their growth. The lipid peroxidation process yields many byproducts, including MDA, its plasma level serves as a marker for the total amount of lipid peroxidation (Ghazizadeh *et al*., 2019). Hydrogen peroxide is one important biological reactive oxygen species that can harm cells and tissues in excess amounts (Winterbourn, 2013). In the current work, EC increased levels of MDA and H_2O_2 and decreased antioxidant enzymes such as GSH. However, EC mice group exposed to the low dose of γ-radiation revealed a reduction in MDA and H_2O_2 levels and elevated GSH activity. This is due to EC causing the formation of excess ROS, which leads to lipid peroxidation and elevation of MDA (Said *et al*., 2014). Also, the decreased levels of GSH seen in tumor-bearing animals resulted from an increase in the conversion rate of GSH to oxidized GSH, which was an attempt to lower the intracellular concentration of hydrogen peroxide (Aldubayan *et al*., 2019). Furthermore, the exposure to γ-irradiation resulted in a decrease in free radicals, which in turn led to a decrease in MDA levels, H_2O_2 and oxidative stress, as well as an improvement in antioxidant enzymes like GSH (El Bakary *et al*., 2022).

A potent pro-inflammatory cytokine, tumor necrosis factor (TNF-α) is involved in inflammation, cell division, proliferation, apoptosis, and cancer (Zelová & Hošek, 2013). The inflammatory cytokine interleukin-6 (IL-6) has pleiotropic properties. High levels of circulating IL-6 have been linked to a number of illnesses, such as type 2 diabetes and cardiovascular disease. IL-6 might be involved in cancer as well (Heikkilä *et al*., 2008). According to Gowda *et al*. (2022), angiogenesis is a basic physiological and pathological mechanism that accelerates the development of tumors. VEGF (vascular endothelial growth factor) and its receptors play a crucial role in controlling the signaling tumor angiogenesis (Ranjbar *et al*., 2015).

Our investigation revealed that TNF-α, IL-6, and VEGF levels elevated in the EC group. Moreover, levels of these parameters were remarkably decreased in the EC-IR group.

These findings align with the findings of Aldubayan *et al*. (2019), who noted that an increase in TNF-α gene expression was linked to disruptions in the systemic inflammatory response and an increase in the generation of free radicals. Furthermore, higher ROS production by macrophages, which promotes lipid peroxidation, may be the cause of elevated TNF-a expressions in tumor-bearing animals (El-Masry *et al*., 2020). EC-bearing mice exposed to low doses of gamma radiation had decreased TNF-α levels. This is due to the inhibition of STAT-3 caused by radiation leading to the suppression of cancer-related inflammation and a reduction in the immune suppressive tumor microenvironment. As a result, this reduction of TNF-α levels occurred (Hafez *et al*., 2020).

Our findings are consistent with Abd El-Salam *et al*. (2022), who reported that pro-inflammatory cytokines, including NF-κB and IL-6, increased in Ehrlich tumor, and had a significant impact on the development of growth and progression of Ehrlich carcinoma *in vitro*. Also, our work aligns with Moustafa *et al*. (2016), who demonstrated that EC mice exhibited a significant rise in IL-6 when compared to control mice. On the other hand, significant declines were observed in EC+IR when compared to EC mice. This is because doses of gamma radiation between 0.3 and 0.7Gy have been shown to have the potential to induce anti-inflammatory effects and stimulate the secretion of anti-inflammatory cytokines.

According to our research, the EC group had elevated VEGF. The present study is consistent with Dolcet *et al*. (2005), who observed that NF-κβ also stimulates a number of angiogenic factors, including VEGF, and matrix metalloproteinases linked to cell invasion. In addition, LDR significantly decreased VEGF expression. This might be caused by NF-κB inhibition. Furthermore, VEGF expression is regulated by NF-κB (Chen *et al*., 2012).
In the current study, there is a significant alternation in hematological parameters levels (increment in both WBCs and platelets and decrease in both RBcs and haemoglobin) in EC group as compared with the control group, but exposure to whole body γ-radiation caused remarkable amelioration in hematological parameters levels as compared with the EC group. These findings support those of Aldayel *et al*. (2023), who suggested that the higher WBC count could be due to carcinogenesis or tumour formation, which releases highly diffusible and damaging ROS, could be the reason for higher WBC count. An elevated blood platelet count is linked to cancer diagnosis and survival in a number of different types of cancer (Buergy *et al*., 2012). In the present investigation, tumor-bearing mice showed a decrease in HB level and RBC count. This decrease may be the result of hemolytic and myelopathic disorders linked to malignancy or iron deficiency (Rageh *et al*., 2022).

The current study showed a drop in the total WBC count (leucopenia) in the IR group following irradiation may be the result of mitotic suppression of bone marrow precursors, which lowers the bone marrow's capacity to create mature WBCs (Girish *et al*., 2011). Also, mice that were exposed to radiation for one or four weeks have thrombocytopenia. Megakaryocyte counts have significantly decreased, which is the cause of platelet count reduction (Ghoneum *et al.*, 2013). In addition, low doses of gamma radiation caused amoliration in RBC count and Hb concentration because IR reduces tumor volume which decreases RBC count and Hb concentration (Salama & Hassan, 2014).

Conclusion

Finally, our study discovered that the inoculation of Ehrlich carcinoma in adult female Swiss albino mice induced biochemical and hematological changes. Treatment with a low dose of gamma radiation relatively enhanced these changes. This could be attributed to the low dose of gamma radiation reducing tumor size, improving antioxidant activity, decreasing inflammation caused by the tumor, inhibiting metastasis, and ameliorating hematological parameters.

Declarations:

Ethical Approval: All animal procedures were accomplished in accordance with the

guidelines for the care and use of experimental animals established by Ain Shams University's Faculty of Women for Arts, Science and Education Committee which approved the experimental animal methods (Ref No.: SCI1312307002).

Conflicts of Interest: There is no conflict of interest.

Informed consent: All the authors of this manuscript accepted that the article is submitted for publication in the Egyptian Academic Journal of Biological Sciences, B. Zoology, and this article has not been published or accepted for publication in another journal, and it is not under consideration at another journal.

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