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The Radioprotective and Anticancer Effects of Banana Peels Extract on Male Mice

Amaal M. Kamal, Mervat S. Taha, Amr M. Mousa*

Department of biological Applications, Nuclear Research Center, Atomic Energy Authority, Egypt
*Corresponding author: amr_halim72@yahoo.com

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Abstract This study was performed to evaluate the radioprotective and anticancer effect of banana peels extract on male mice. Sixty male mice weighted 18-25 gm were used, the animals divided equally into six groups as follow first group act as normal , second group (Tumor control) implanted with Ehrlich tumor, third group ,irradiated group exposed to single dose of 3.0 GY of gamma rays, fourth group (banana peels extract 300 mg/kg/day orally for 3weeks, fifth group (tumor implanted + banana peels extract 300 mg/kg/day orally for 3weeks, sixth group (irradiated with dose 3.0 GY gamma+ 300 mg/kg/day for 3 weeks). At the end of experiment mice were sacrificed by anesthesia and the blood were collected to evaluate biochemical parameters (Complete Blood Count (CBC), Carcino embryonic antigen,(CEA), Malonaldehyde (MDA), Molecular study, electrophoretic assayed. The results showed that banana peels extract ameliorate the alteration in CBC in irradiated and tumor group, and significantly decrease $p \leq 0.05$ the elevation of Carcino embryonic antigen in tumor implanted group, significantly decrease the elevation of Malonaldehyde in tumor implanted group and irradiated group. According to protein fractions and western blotting data it could be concluded that, addition banana peels extract consider a crucial impact for Irradiation dose which cleared through huge increase of Polymorphism % for addition banana peels extract (20%) comparing with to Irradiation treatment which didn't reflect polymorphism. Furthermore, noticeable stimulation for P53 expression level was detected for applying banana peels extract and Irradiation as Compound dosage.

Keywords: *banana peels extract, antitumor, irradiation protective and mice*

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1. Introduction

Cancer is a multi-factorial disease in the world and economic burden. At all ages, cancer may be affect adults and even fetuses, and the hazard for most varieties increases with age [1]. Cancer causes about 13% of human deaths [2]. Every year about 7.6 million people die from cancer, according to the American Cancer Society [3]. According to World Health Organization, every year more than 10 million new cases of cancer are diagnosed, and in 2020 the statistical tendencies indicate that this number would double [4]. Though there are many therapeutic tactics to treating cancer depend on the toxic compounds. Regrettably, the cytotoxicity properties of most chemotherapy drug is nonspecific and thus don't differentiate between tumor cells and normal healthy cells [5]. In previous years, phenolic compounds derived from natural sources have been found that it possesses antioxidant, anti-inflammatory and has anti-proliferative effects [6]. Banana (Musa species), is one of the important valued plant species which having a number of pharmacological activities [7]. Banana has been considered as one of the antioxidative foods [8]. Ascorbic acid, tocopherol, beta-carotene, phenolic groups, dopamine and gallocatechin had been included in Musa acuminate as antioxidant compounds [9,10]. The banana peels is rich in phytochemical compounds than its pulp [11,12]. Flavonoids and phenols in medicinal plants have a positively role in cancer prevenation through the regulation of genetic pathways without any side effects [13,14]. The mechanistic sides of fruits bioactive constituents may be prevent cancer through various type of action including antioxidant activity. Inhibition of cell proliferation, stimulate of apoptosis, Inhibition of cell invasion and subcellular signaling pathways [15,16].

Protection systems from ionizing radiation are utmost importance in planned and accidental exposures to radiation [17,18]. Improvement of new and effective agents to less radiation hazard using nontoxic radio protectors is considerable interest in defense particularly in radio diagnostics and therapy. Many synthetic and natural compounds have been explored in the recent years for their ability to protect the biological systems against radiations.

The aim of the current investigation aimed to study the protective effect of banana peels extracts against gamma radiation and Ehrlich tumor in male mice.

2. Material and Methods

2.1. Sample Collection and Preparation

The banana peels used for the investigation were bought from Local market, Zagazig City, Egypt. Banana peels were air-dried for two weeks, ground into powder with a mechanical blender, and sieved with a mesh of size 0.5mm. The powdered samples obtained were stored in clean brown bottles at room temperature (30±2°C) until needed for use.

2.2. Preparation of Ethanolic Banana Peels Extract

Twenty five (25) grams of the powdered peels was dispensed in 100ml of 95% ethanol in conical flask. The mixture was standed for 3 days, and filtered through Whitman No 1 filter paper. The filtrate was then concentrated to dryness at 40°C in a rotary evaporator. The crude extracts were stored in a refrigerator until further analysis.

2.3. Acute Toxicity Studies (Ld50)

According to OECD 2001, acute toxicity studies were performed in Swiss albino mice [19]. Mice received ethanolic extract at dose (300 mg/Kg) by stomach tube. Clinical signs, symptoms and mortality were recorded for the first 4 h after dosing. Finally, the number of survivors was observed after 24 h. In this study, no mortality occurred within 24 h under the tested doses of ethanolic banana peels extract.

2.4. Animals

Sixty (60) male Swiss mice weighted 18-25 gm were purchased from experimental animal unit, National Cancer Institute, Cairo University, Cairo, Egypt. Mice were feed 2weeks on commercial diet and tap water for adaptation before the beginning of the experiment under optimum conditions of light and humidity. The animals were exposed to a single dose of 3 Gy whole body weight using an indoor shielded cesium (Cs-137) Canadian Gamma Cell-40, located at National Centre for Radiation Research and Technology. The dose rate of cell = 0.664 rad/Sec (3, Gray/7.5 minutes). The experimental protocol was approved by the Research Ethics Committee, serial number (18A/19) of the National Center for Radiation Research and Technology, Egypt.

2.5. Experimental Design.

The sixty adult male mice were categorized into 6 groups, (10 mice / each group) as shown in the following:

a) First group (N) served as (normal).

b) Second group (T.C) Tumor control, implanted with Ehrlich tumor. The mice were infected subcutaneously (at right thigh region) with 1X10 single cell/ml submission isolated from Ehrlich ascites carcinomas. The injections of 0.2 ml were made into the right leg.

c) Third group (IR) exposed to single dose of 3.0 Gy of γ-rays.

d) Fourth group (BPEx), banana peels extract (300 mg/Kg/day) intake orally by oral tube for three weeks.

e) Fifth group (T+BPEx) implanted with Ehrlich tumor and treated with ethanolic banana peels extract (300 mg/Kg/day) for three weeks.

f) Sixth group (IR+BPEx) treated with ethanolic banana peels extract (300 mg/Kg/day) for three week and exposed to single dose of 3.0 Gy of γ-rays.

Table 1. The tumor size during 3, Weeks of different groups

Groups / weeks	T.C Mean of Tumor Size cm^2	T+EX Mean of Tumor Size cm^2	% of change
1st. Week	1.043	0.472	54.74
2nd. Week	1.16	0.663	42.84
3rd. Week	1.63	0.673	58.71

Tumor size was determined by caliper measurements at least twice a week. According to Carla *et al*., [20] using this formula $T_{vol.} = \frac{l.w.h}{2}$.

Where: l, length; w, width and h, height of the tumor.

2.6. Biochemical Studies

2.6.1. Blood Samples

After decapitation of the mice blood samples were collected in a clean test tube with anticoagulant (EDTA), blood CBC was evaluated immediately close in automated hematology analyzer; after that the blood was centrifuged to separate plasma for CEA assessment.

2.6.2. Tissue Samples

Tissue samples from right thigh region were collected from the right thigh of the mice about (20-30 mg.) of tissue in a clean tube and stored at (-80°C).

A) - Complete Blood Count (CBC): The (CBC) was determined by using Sysmex XN-350™ Automated Hematology Analyzer.

B) - Carcino-Embryonic Antigen (CEA): Enzyme Immunoassay Test Kit (genway bio.com) GWB-FB64BF, assayed by using (Elisa – Spectra MAX ABX PLUS 384).

C) - Malondialdehyde (MDA): Plasma MDA was estimated spectrophotometrically as thiobarbituric acid reactive substances (TBARS) according to Sangeetha et al., 1990, [21].

2.7. Electrophoretic Study

SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis) was performed to evaluate of banana peels extract as cancer resistant factor. Total soluble proteins for Mus musculus liver which treated with Irradiation , Banana peels Extract , Tumor + Banana peels Extract and Irradiation + Banana peels Extract compared with Normal and tumor control were purified via TriFast (Peqlab, VWR company). Then, total purified were fractionated through SDS-PAGE (sodium dodecyl sulfate–polyacrylamide gel electrophoresis) according to Laemmli [22] on a 12% (W/V) polyacrylamide gel.

2.8. Blotting Technique

P53 expression level was evaluated for different six treatments via western blotting method. After SDS-PAGE fractionation, total fractions were transfer to a Hybond™ nylon membrane (GE Healthcare) via TE62 Standard Transfer Tank with Cooling Chamber (Hoefer Inc. and incubate for 1 hour at room temperature in Blocking Solution. Additionally, β-actin was applied as housekeeping protein. Then, Anti- P53 primary antibody (abcam, ab131442) was applied (Vedpal et al., 1994) [23]. Finally, data was visualized and analyzed via Gel documentation system (Geldoc-it, UVP, England), was applied for data analysis using Totallab analysis software, ww.totallab.com, (Ver.1.0.1).

3. Results

3.1. Hematological Studies

As shown in Table 2, there was a significantly decrease ($p<0.05$) in hematological parameters (WBC, RBC, Hb, HCT and MCV) and there was a significantly increase ($p< 0.05$) in platelet count in tumor group compared to control group on the other hand the irradiated group showing significant decline in (WBC, Hb, HCT and MCV) and significant elevation in platelet count compared to control group, administration of banana peels extract reversed the alteration in those parameters.

As shown in Table 3 there was a significant increase $p<0.05$ in Carcino Embryonic Antigen (CEA) in tumor group comparing to normal group, and non-significant change in in Carcino Embryonic Antigen (CEA) in irradiated group compared to normal group, administration of banana peels extract significantly reduced the elevation level of (CEA) in tumor group and cause slight increase in the level of (CEA) in irradiated group respectively.

As shown in Table 4 there was a significant increase ($P<0.05$) in malonaldehyde (MDA) in tumor and irradiated group compared to control group respectively, administration of banana peels diminished the elevation in MDA in tumor and irradiated group.

Table 2. Effect of ionizing gamma radiation and/or tumor which treated with (300 mg/Kg/day) of banana peels extract on some hematological parameters in male mice

GROUPS parameters	N	T.C	IR	BPEx	T+BPEx	IR+BPEx	p-value
WBC	7.50±0.11a	3.75±0.11^{e}	5.64±0.11^{c}	4.77±0.11^{d}	4.87±0.14^{d}	6.84±0.11^{b}	0.000
RBC (106/mm3)	4.76±0.11a	4.19±0.11^{c}	4.77±0.11^{a}	4.20±0.11b^{c}	4.28±0.11^{bc}	4.58±0.11^{ab}	0.007
Hbg (g/100ml)	14.27±0.11a	11.98±0.11^{e}	13.52±0.11^{b}	12.41±0.11^{d}	12.76±0.11^{c}	13.71±0.06^{b}	0.000
Hct %	42.100±1.1a	35.36±1.4^{c}	36.43±1.1b^{c}	36.95±1.1b^{c}	37.54±1.1b^{c}	39.84±0.68^{ab}	0.019
Platelet count (/mm3)	266.15±1.15f	325.88±0.05^{a}	301.94±0.09^{c}	311.52±0.11^{b}	298.54±1.45^{d}	289.65±0.11^{e}	0.001
MCV	95.00±0.05a	79.00±0.57^{e}	83.00±0.57^{d}	82.00±0.57^{d}	85.00±0.57^{c}	88.00±0.05^{b}	0.000

Values are expressed as means ± SEM (n= 10). Values (for the same parameter) with different superscript are significantly different (P<0.05 or less).

Table 3. Effect of banana peels extract, ionizing gamma radiation and/or tumor on Carcino Embryonic Antigen (C.E.A.) as tumor marker on mice

Groups	CEA	p-value
N	16.10^{f}±0.27	0.000
T.C	52.11^{a}±0.29	
IR	16.45^{f}±0.28	
BPEx	11.46^{g}±0.27	
T+BPEx	18.31^{e}±0.29	
IR+BPEx	22.27^{c}±0.27	

Values are expressed as means ± SEM (n= 10). Values (for the same parameter) with different superscript are significantly different (P<0.05 or less).

Table 4. Effect of banana peels extract, on ionizing gamma radiation and/or tumor on Malonaldehyde (MDA) on mice

Groups	MDA	p-value
N	0.84±0.01e	0.000
T.C	2.71±0.11a	
IR	1.76±0.11c	
BPEx	2.38±0.05b	
T+BPEx	1.44±0.11d	
IR+BPEx	1.28±0.08d	

Values are expressed as means ± SEM (n= 10). Values (for the same parameter) with different superscript are significantly different (P<0.05 or less).

3.2. Molecular Studies

This investigation was carried out to evaluate influence of banana peels extract (BPEx) as cancer resistant factor. Direct influence of BPEx was reflected by suppressed seven protein fractions with 205, 120, 66, 39, 34, 27 and 19.5 KDa and expressed new nine protein fractions with 167, 92, 54, 43, 29, 20.5, 20, 18 and 14 KDa were expressed which may be play a key role in BPEx anticancer mechanism.

Highly significant response between BPEx and tumor as simulation agent was cleared via comparing protein profile of treated with BPEx and combination between tumors (T) and BPEx. Tumor implanted stimulates expression of new ten protein fractions with 167, 92, 58, 45, 43, 36, 29, 20, 18 and 14 KDa. Previous findings indicate BPEx influence as anticancer.

Combination of irradiation (IR) and BPEx influence as radioprotective agent was studied. Treated with IR+ BPEx stimulate new twelve expressed fractions with 150, 130, 100, 82, 43, 37, 36, 23, 20, 19.5, 12 and 11.5 KDa which indicate significant influence of banana peels extract for increasing irradiation effectively.

There are seven proteins generated in tumor-infected mice that disappear after being treated with banana peel extract (205, 120, 66, 39, 34, 27 and 19.5 KDa). In the same context, three proteins disappeared in tumor-infected mice and reappeared when treated with banana peel extract (54, 43 and 29 KDa).

There are also six new proteins (92, 50, 34, 29, 18 and 16.5 KDa) when mice are exposed to radiation that did not exist in mice that were given banana peel extract as protection before exposure to radiation. Three proteins disappeared in IR group and reappeared in IR+BPEx group (54, 43 and 29 KDa). Table 4 & Figure 1 – Figure 2.

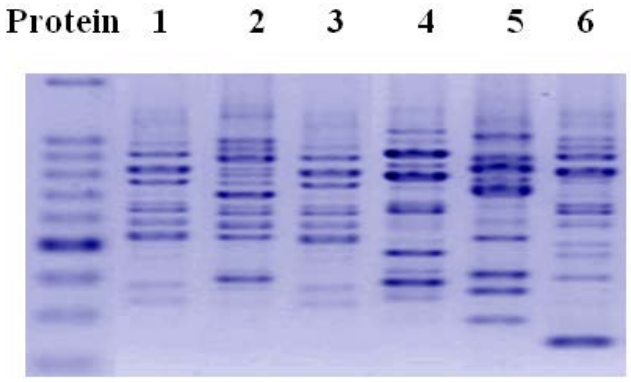

Figure 1. Electrophoretic fractions for different treatments patterns (1. Normal (N) group; 2. Tumor control (TC) group; 3. Irradiated (IR) group; 4. Banana peels extract (BPEx)group; 5. Tumor + Banana peels extract (T+BPEx) group; 6. Irradiation + Banana peels extract (IR+BPEx) group)

The phylogenetic tree of protein fraction patterns differentiated the six groups to three clusters, the first cluster was T+BPEx considered as the root of the bootstrapping tree. The second group was composed of two groups; Normal and IR groups which highly closed similar. Finally, the third group was composed of three groups BPEx, T.C and IR+EX which highly closed similar too Figure 3.

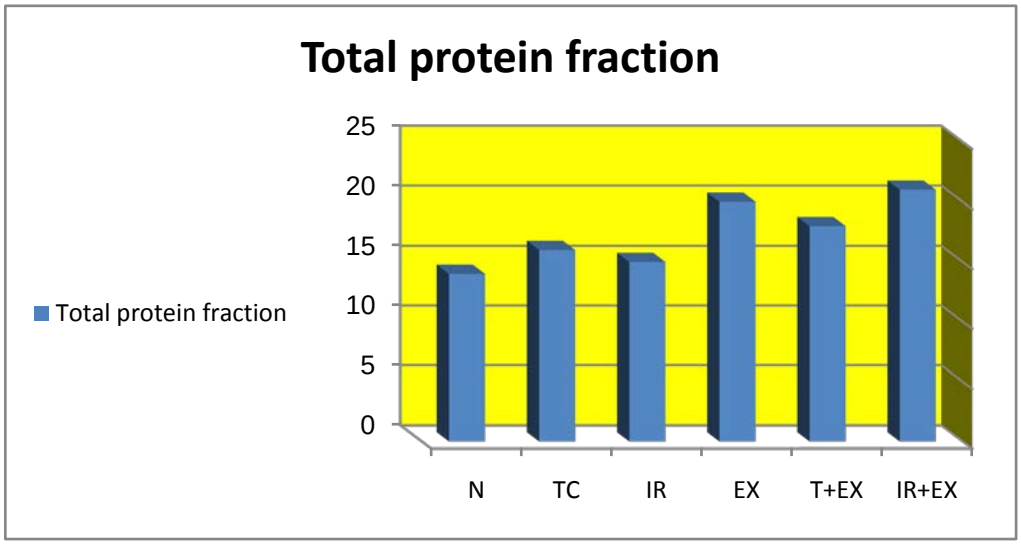

Figure 2. Total protein fractions for different treatments based on protein fraction patterns

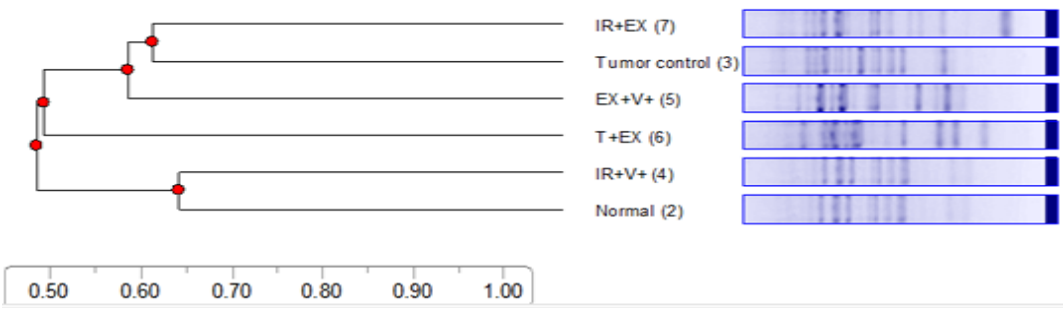

Figure 3. Phylogenetic tree for different treatments based on protein fraction pattern

Table 5. Protein fractions for different treatments based on protein fraction patterns

	N	T.C	IR	BPEx	T+BPEx	IR+BPEx
Fractions	-	205	-	-	-	-
	-	-	-	176	-	-
	-	-	-	-	167	-
	-	-	-	-		-
	-	150	-	150	150	150
	130	-	-	-	-	130
	-	120	-	-	-	-
	111	-	111	111	-	111
	-	100	-	100	100	100
	-	-	92		92	-
	82	82	-	82	82	82
	72	72	72	72	72	72
	-	66	66	66	-	66
	58	58	58	-	58	58
	54		54	54	54	54
	-	50	50	50	50	-
	-	45	-	-	45	-
	43	-	-	-	43	43
	-	-	42	42	-	42
	40	40	40	40	40	40
	39	39	39	39	-	39
	-	-	-	-	-	37
	-	36	-	-	36	36
	-	34	34	34	-	-
	29		29	-	29	-
	27	27	27	-	-	27
	-	-	-	25	-	-
	-	-	-	23	-	23
	-	-	-	22	-	-
	-	-	-	20.5	20.5	-
	-	-	-	-	20	20
	-	19.5		19.5	-	19.5
	19	-	-	19	-	-
	-	-	18	-	18	-
	-	-	-	17	-	-
	16.5	-	16.5	-	-	-
	16	-	-	-	-	-
	-	-	-	-	14	-
	-	-	-	-	-	12
	-	-	-	-	-	11.5

The protein expression levels of p53 in mice thigh tissues were determined using western blot assays Figure 4 - Figure 6. Comparing highest P53 expression level which detected for Irradiation + Banana peels extract with 11.29 %, with lower expression value of separate Irradiation (4.80 %) indicated stimulation and over expression influence of addition banana peels extract to Irradiation as a combined dose. Interestingly, clear positive correlation between banana peels extract and tumor existence was detected based on P53 over expression for tumor + Banana peels extract (8.51 %) comparing with Banana peels extract treatment (5.91 %) which indicate stimulation effect of tumor on Banana peels extract Table 6.

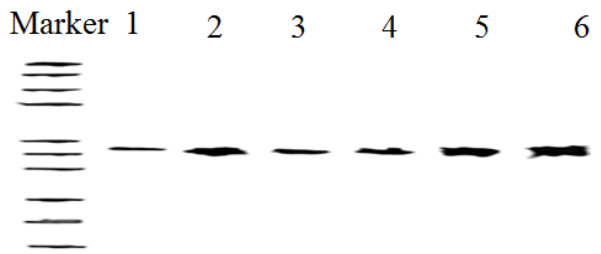

Figure 4. P53 protein expression level for different treatments patterns (1- Normal (N) group; 2- Tumor control (TC) group; 3- Irradiated (IR) group; 4- Banana peels extract (EX) group; 5- Tumor + Banana peels extract (T+EX) group; 6. Irradiation + Banana peels extract (IR+EX) group)

According to protein fractions and western blotting data it could be concluded that, addition banana peels extract consider a crucial impact for Irradiation dose which cleared through huge increase of Polymorphism % for addition banana peels extract (20%) comparing with to Irradiation treatment which didn't reflect polymorphism Table 7. Furthermore, noticeable stimulation for P53 expression level was detected for applying banana peels extract and Irradiation as compound dosage.

Table 6. P53 expression level with control and treated groups

Samples	P53 expression level (Lane %)
N	3.91
T.C	9.43
IR	4.80
BPEx	5.91
T+BPEx	8.51
IR+BPEx	11.29

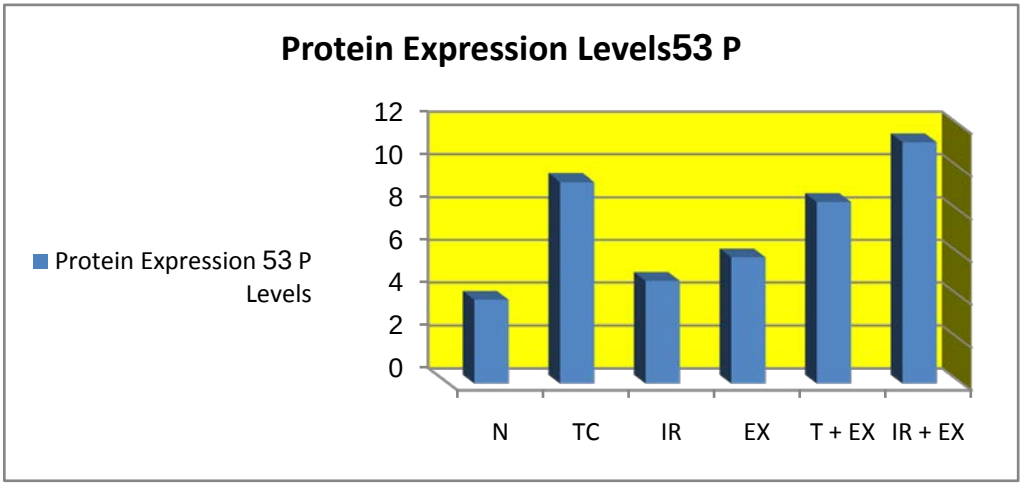

Figure 5. P53 expression level

Table 7. Total fractions, Polymorphic fractions and Polymorphism % for different treatments based on protein fraction patterns.

Treatments	Total fractions	Polymorphic fractions	Monomorphic fractions	Polymorphism %
Normal	14	1	13	7.1
Tumor control	16	2	14	12.5
Irradiation	15	0	15	0
Banana peels Extract	20	4	16	20.0
Tumor + Banana peels Extract	18	2	16	11.1
Irradiation + Banana peels Extract	21	3	18	14.2

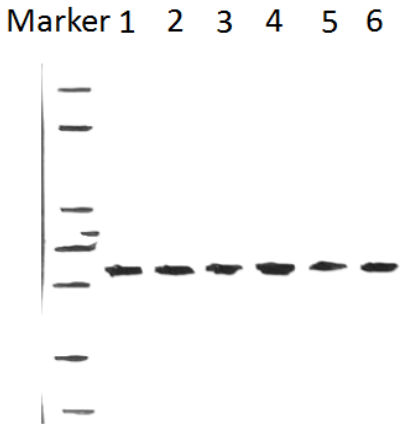

Figure 6. β-actin protein expression level.

4. Discussion

Cancer is an abnormal growth of cells caused by multiple changes in gene expression leading to deregulate balance of cell proliferation and cell death causing significant morbidity [24]. It is known that oxidative stress in erythrocytes play a role in hematological disorders and progression of many diseases like carcinogenesis (Childress, [25]) with ascites carcinoma disease, myelosuppression and anemia have been seen [26]. Iron deficiency is the main reason for anemia either by hemolytic or myelopthic conditions, which finally reduced RBCS [27].

In the present study as shown in Table 2, reduction in WBCs' count, hemoglobin and RBCs' count, HT,MCV

were observed in EAC control mice, while administrated banana peels extract exhibited improvement in hematological parameters of mice as seen by a significant increase in RBCs, WBCs, Hb, HCT and MCV this improvement due to the protective action of banana peels on hemopoetic system. In the present study there was marked elevation of platelets count in tumor this finding is line with Buergy et al., [28] who reported increased platelet counts simply an epiphenomenon of tumor growth with greater tumors resulting in higher platelet counts. Thrombocytosis is therefore considered an adverse prognostic factor in tumor entities responsible for at least 50% of all cancer-related deaths [29],

Ionizing radiation has lethal effects on blood cells and these effects contribute to the hematopoietic syndrome (HS) [30]. Our results coincidence with the previous study of Nunia and Goyal, [31] reported that radiation exposure significantly reduced the, hemoglobin (Hb), hematocrit (Hct), packed cell volume (PCV) another study of Billings et al., [30] reported that red blood cell (RBC) counts stopped stable after radiation exposure In the current study, there was a significant reduction in WBC counts in irradiated group at 24 h after radiation at dose levels of 3 GY compared to the control group This result was agreed with that of Thrall et al., [32] who showed a significant reduction in WBC counts at 24 h after radiation . this study showed that significant increase in platelets count ($p<0.05$) compared to control group may be related to iron deficiency anemia Nagai et al., [33] stated a case of severe iron deficiency anemia with marked thrombocytosis increase in platelet count also Alexander, [34] reported that bone marrow megakaryocyte counts were increased and the plausible explanation of the thrombocytosis might be an increased production of platelets The low red blood cell mean corpuscular (MCV) in the existence of an adequate hemoglobin (Hb; ≥12.5 g/dL) may be due to iron deficiency (Barbara et al., [35] in current study our result revealed that administration of banana peels extracts ameliorated the alteration in hematological parameters this effect may be due to that banana peels rich with phytoconstituent like flavonoids, tannins, phlobatannins, alkaloids, glycosides, anthocyanins, and terpenoids, also banana peels high in iron that can excite the production of hemoglobin in the blood and helps in cases of anemia [36].

Carcino embryonic antigen (CEA) is a tumor marker commonly measured in colorectal cancer, gastrointestinal, lung and breast carcinoma [37,38]. In the current investigation, there was a significant increase of CEA in tumor control group compared to normal group; the elevation of CEA levels confirmed the diagnosis of EAC implanted tumor in mice. the elevations of CEA may be associated with benign disease Regarding, CEA it showed marked decrease in BPEx and T+BPEx groups compared to normal and tumor control groups respectively, this attributed to the role of Banana peels which contain many antioxidants that destroy free radicals, the antioxidants in banana peels are able to minimise free radical damage in the body and fight cancer in its early stages [39]. The anticancer effect of banana may be due to presence of flavonoids (anthocyanin) [40,41], the finding of the present study is coincidence with Adinarayana et. Al., [40] who reported that the ethanolic extract of Musa acuminata exhibits significant antiproliferative and antioxidant activities, similarly, this results comparable with results of Abou-Elella and Mourad, [39], who reported that Anticancer activity against Ehrlich ascites carcinoma cells (EACC) by banana peel was (87% at 100µg/ml, IC50 =33.9 µg/ml). In the present study there was a significant increase in MDA $p < 0.05$ in tumor group compared to the control group this finding was coincidence with several investigation confirmed that Malondialdehyde (MDA) the end product of lipid peroxidation, are seen to be higher in cancer state than in normal [42]. Similarly, there was a significant increase in MDA in radiation group compared to the control group this increase may be due to exposure to ionizing radiation leading to radiolysis of water in tissues causes generation of ROS, and induce LPO resulting in increasing MDA levels Riley, 1994 [43], provision of banana peel extract reduces MDA levels in both banana peels treated group. Reduction in MDA levels in mice treated groups; confirm that antioxidants in banana act as anti-free radicals. The results of this research are in accordance with the recent study of Berawi and Bimandama, 2018 [44].

In this study as a response of a variety of cellular stresses such as (DNA damage, exposure to radiation, treated with nature compounds), we can trust that the increase in p53 expression may be due to encouraged accumulating of p53 in cell nucleus to employ its pro-apoptotic function. Activated p53 promotes cell cycle arrest to allow DNA repair and/or apoptosis to prevent the propagation of cells with serious DNA damage through the transactivation of its target genes implicated in the induction of cell cycle arrest and/or apoptosis. Thus, the DNA-binding activity of p53 is tightly linked to its tumor suppressive function [45]. This agrees with a previous study, which reported that the p53 protein was identified to be highly expressed in the esophageal squamous cell carcinoma (ESCC) tissue, with western blot analysis demonstrating that the expression level of p53 in the cancerous tissue was 1.89 times that of the tumor-adjacent normal tissue [46].

5. Conclusions

From the previous results of this study, it could be concluded that banana peels extract possess anti-cancer agents and great protective potential against radiation by improving hematological parameters, inhibiting Carcino Embryonic Antigen (C.E.A.) and attenuated lipid peroxidation. Stimulation for P53 expression level was detected for applying banana peels extract and Irradiation as Compound.

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Statement of Competing Interests

The authors declare no conflict of interest.

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