AMELIORATIVE EFFECT OF BLUE BERRY AGAINST MULTIPLE ORGAN DAMAGE BY γ-IRRADIATION IN ADULT MALE ALBINO RATS

By

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ABSTRACT

Background: Blue berry fruit are rich in bioactive constituents, including flavonoids, anthocyanins, phenolic acids, stilbenes, and tannins, as well as nutritive compounds such as sugars, essential oils, carotenoids, vitamins and minerals. Numerous scientific studies provide ample evidence that bioactive compounds have the potential to decrease the risk of cardiovascular and degenerative diseases. Whole body exposure to ionizing radiation induces oxidative stress through generation of free radicals which often trigger chain reactions mediated tissue damage.

Objective: This work was done to study the potential protective effect of blue berry against injury of heart, liver and kidney caused by exposure to gamma irradiation .

Material and Methods: Forty adult male albino rats were used and divided into four equal groups: **Group 1** served as control group, **group 2** received blue berry juice (BBJ) 1ml/100g body wt. by oral intubation gavage for 14 consecutive days , **group 3** was exposed to single dose of 7Gy whole body gamma-irradiation, and **group 4** received BBJ (1ml/100g body wt.) by oral gavage for 14 consecutive days before irradiation.

All groups of rats were anesthetized and sacrificed on the last day after treatment and/or irradiation. Blood samples were taken from all groups to estimate lactate dehydrogenase (LDH), creatine phosphokinase (CPK), interleukin-6 (IL-6), total cholesterol (TC), triacylglycerol (TAG), high density lipoprotein cholesterol (HDL-C), malondialdehyde (MDA), alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), urea, creatinine, cystatin and lipocalin.

Results: BBJ administration before exposure to γ-irradiation significantly reduced serum LDH, CPK, IL-6, TC, TAG, and MDA versus a significant increase of serum HDL-C. Moreover, amelioration of liver and kidney function test was observed by significant decrease in ALT, AST, ALP, serum urea, creatinine, cyctatin-C and lipocalin-2 in comparison with irradiated group.

Conclusion: The study pointed out to the promising positive role of blue berry supplementation as a natural product to reduce oxidative stress and protect body organs from gamma irradiation.

Key words: Oxidative stress, blue berry, γ- radiation, lipid profile, liver enzymes.

INTRODUCTION

Radiation has been used increasingly in medicine and industry to help with diagnosis, treatment and technology.

Radiations have tremendous therapeutic benefits for human. However, it is also associated with the risk of serious adverse effects **(Saada *et al.,* 2009).**

The absorption of ionizing radiation by living cells can directly disrupt atomic structures, producing chemical and biological changes. It can also act indirectly through radiolysis of water, thereby generating reactive chemical species known as free radicals. Together, the direct and indirect effects of radiation initiate a series of biochemical and molecular signaling events that may repair the damage or culminate in permanent physiological changes or cell death due to oxidative stress (**Azzam** *et al.,* **2012).**

Oxidative stress is caused by an imbalance between the production of reactive oxygen species (ROS) and theability of a biological system to eliminate ROS or repair the resulting damage(**Abd el-Aal, 2012**). Once this imbalance takes place, cellular molecules such as nucleic acids, proteins, structural carbohydrates, and lipids may be damaged by oxidative modifications. Also, ROS play a causative role in numerous disease pathologies such as cancer, ischemia, and degenerative diseases such as aging, atherosclerosis, arthritis and neurodege-neration (**Farag and Darwish , 2016**):

Evidence of oxidative injury is proved from measurements of biochemical markers of lipid peroxidation and protein oxidation. Lipid peroxidation is believed to be an important cause of destruction and damage to cell membranes and has been shown to be a contributing factor to the development of oxygen radicals-mediated tissue damage. However, cells are equipped with several natural enzymatic and non-enzymatic antioxidant defenses (**Azab** *et al.,* **2011**). The exposure of the human body to ionizing radiation leads to depletion of these endogenous antioxidants and ultimately to the development of systemic diseases (**El-Missiry** *et al.***, 2007**).

Antioxidants can prevent or inhibit the oxidation of a target biomolecules. Dieticians actually prescribe diets containing antioxidants for conditions resistant to conventional pharmacological treatments (**John** *et al.,* **2011**)**.**

Keeping a close watch on the amount of antioxidants consumed and their action against free radicals is ,therefore, of the essence in maintaining a condition of health. Numerous epidemiological studies have revealed the existence of a positive correlation between eating fruit and the reduction of heart disorders, cancer and other degenerative pathologies (**Basu** *et al.,* **2010-b**). The various kinds of fruit investigated and described in the literature notably include blue berries, which have a strong antioxidant capacity (**El-Nekeety** *et al.***, 2007**).

The berry fruits, including blueberry, cranberry, raspberry and strawberry, are known to be good sources of a number of bioactive compounds such as vitamins and phenolics having an antioxidant activity (**Paredes-Lopez** *et al.,* **2010**)

The blue berry (Wild blueberry, Vaccinium angustifolium) contain higher level of polyphenols such as anthocyanins, flavonols, tannins and phenolic acids which show the potentiality to decrease the risk of cardiovascular and degenera-tive diseases, and to prevent cancer through their biological activities (**Yi** *et al.,* **2005**). However, there is a limited number of studies on the effect of blueberry in irradiation induced multiple organ damage.

The aim of the present study was to investigate the radio-modifying effect of a blueberry juice against possible hazards of irradiation on heart, liver and kidney in adult male albino rats.

MATERIAL AND METHODS

(I) Experimental animal and design: The present study was carried out on forty adult male albino rats weighing 130–160 g . Rats were acclimatized for 14 days in the animal house of Egyptian Atomic Energy Authority, under normal conditions, temperature range of $25 \pm 5°C$, and regular light/dark cycle in cages (150x60x50 cm- 5rats/cage). Animals were allowed free access of water and fed on a diet of normal rats chow.

Animals were divided randomly into fourequal groups**:**

Group 1: Untreated control group.

Group 2: Rats received blue berry juice (BBJ) 1ml/kg body wt. by oral intubation gavage for 14 consecutive days (**Zhong *et al.,* 2015**).

Group 3: Rats were exposed to whole body gamma irradiation at 7 Gy applied as single sublethal dose (**Abd El-Azime and Ossman, 2012**).

Group 4: Rats received BBJ 1ml/100g body wt. by oral gavage for 14 consecutive days before irradiation. This group was exposed to whole body γ-irradiation in the 14th day of experiment as a single dose of 7Gy.

(II) Preparation of blue berry juice (BBJ): Blue berry fruit was purchased from local marked and prepared according to the method described by **Wang *et al.* (2013)**. Fresh BBJ was prepared by homogenization of the fresh fruit right before the start of experiments (1 ml of BBJ contained about 2 g of dried blueberry).

(III) Irradiation Source and Technique: Irradiation was performed using a Canadian gamma cell-40 (^{137}Cs), at the Egyptian Atomic Energy Authority, Nasr City, Cairo, Egypt. Rats were placed individually into cages, each cage is 40×60×40 cm in size. Animals were whole body exposed to 7 Gy delivered as a single sublethal dose at dose rate of 0.45 Gy/minute (**Abd El-Azime and Ossman, 2012**).

(IV) Blood Sampling: All groups of rats were anesthetized on the next day after treatment and/or irradiation. Blood samples were obtained from the retro-orbital plexus veins from the individual rat (**Simmons and Brick, 1970**) by fine capillary heparinized tubes. Blood was collected into a plain centrifuge tube for serum preparation to assay the biochemical parameters of blood including some cardiac enzymes, liver function tests, kidney function tests and the rest of biochemical parameters of inflammation and oxidative stress. Serum was separated in individual ependorf tubes and stored at -40°C until biochemical measurements.

(V) Serum Assay: The separated sera were analyzed for estimation of:

Lipid profile and lipid peroxide byproduct:

- Serum total cholesterol (TC) and triacyl-glycerol (TAG) were estimated as described in the method of **Sharma *et al.* (1987).**

- Serum HDL was measured according to the method described by **Grillo *et al.* (1981).**

- Serum MDA was measured according to the method described by **Liu** *et al.* **(2000)**.

   Biomarkers of cardiac injury and inflammation:

- Serum creatine phosphokinase kinase (CPK) was estimated according to **Tietz (1995)**
- Serum LDH was determined according to **Guder** *et al.* **(2009).**
- Serum IL-6 was determined by solid phase sandwich Enzyme-Linked Immuno-sorbent Assay (ELISA) kit (supplied by Gamma trade) using an ELISA reader (Triturus, Grifols Diagnotistic, Barcelona, Spain) according to the manufacturer's instructions **(Kaminska** *et al.,* **2000).**

Biomarkers of liver function: Serum Liver transaminases (AST, ALT) and alkaline phosphatase (ALP) were determined as described by **Ochei and Kolhackar (2008).**

Biomarkers of kidney function:

- Serum urea and creatinine were determined according to the methods described by **Henry** *et al.* **(1974**) **and Tabacco** *et al.* **(1979)** respectively.

- Serum cystatin-C was determined by Enzo Cystatin-C ELISA kits **(Haves-Zburof, 2011**).

- Serum lipocalin-2 was determined by ELISA kit which allows for the in vitro quantitative determination of lipocalin-2 concentrations in serum from Sigma **(Bolignano** *et al.,* **2008)**.

Statistical Analysis: was done using statistic package for social science version 16 (SPSS, 16) for windows. A One-way analysis of variance (ANOVA) for a completely randomized design and Duncan's multiple range tests were used to analyze experimental data. Results were expressed as Mean ± Standard error of mean (S.E.M) and statistically analyzed using Tukey multiple comparison tests. Results were considered significant at $P < 0.05$.

RESULTS

Whole body γ-irradiation of rats at a single dose of 7Gy induced significant increase in the serum levels of lipid profile; serum total cholesterol (TC) and triacylglycerol (TAG) and lipid peroxide byproduct malondialdehyde (MDA) versus a significant decrease in serum high density lipoprotein cholesterol (HDL-C) in comparison to control group. On the other hand, blue berry supplemented rats showed insignificant change in all the tested parameters, if compared to control group. Blue berry administration before irradiation of rats resulted in improvement of lipid profile state as there was a significant decrease in serum TC, TAG and MDA while HDL-C was increased significantly in comparison with γ-irradiated rats. Moreover, blue berry administration before irradiation could return serum TAG to normal levels as there was insignificant difference (p>0.05) in TAG when compared to blue berry only administered group. But, serum TC and MDA still showing a significant increase and serum HDL-C still showing significant decrease relative to the corresponding control group (Table 1).

Table (1): Effect of Blue berry administration on serum lipid profile [total cholesterol (mg/dl), triacylglycerol (mg/dl) and high density lipoprotein (mg/dl)] and malondialdehyde (nmol/ml) of irradiated rats.

Groups \ Parameters	Control (I) Mean± S.E.M	Blue berry Group (II) Mean± S.E.M	Irradiated Group (III) Mean± S.E.M	Irradiated Group treated with Blue berry (IV) Mean± S.E.M	ANOVA F	ANOVA P- value
Serum TC (mg/dl)	134.8± 3.06	143.06 ± 2.7	210.6 ^{a} ± 5.4	162.8 ^{b,c}± 3.9	8.2	0.002
Serum TAG (mg/dl)	92.9 ± 4.7	86.9± 4.3	132.9 ^{a} ± 2.6	89.8 ^{b} ± 4.6	9.7	0.001
Serum HDL-C (mmol/l)	59.2 ± 1.07	56.1 ± 1.07	30.7 ^{a} ± 1.3	51.8 ^{b,c}± 1.3	6.9	0.004
Serum MDA (nmol/ml)	10.05 ± 0.7	11.2 ± 0.46	101.02^a± 6.2	57.8^{b,c} ± 4.5	7.09	0.003

a: significant values compared to control.   b: significant values compared to irradiated group.
c: significant values compared to blue berry group.

Gamma-irradiated rats exhibited a significant elevation in serum biomarkers of cardiac injury and inflammation [creatine phosphokinase (CPK), lactate dehydrogenase (LDH) and interleukin- 6 (IL-6)] compared to control group. On the other hand, blue berry supplemented rats showed insignificant change in all the tested parameters, if compared to control group, blue berry treated rats before being γ-irradiated demonstrated an obvious decrease in serum levels of CPK, LDH and IL-6 in comparison to untreated γ-irradiated group. Moreover, Blue berry pretreated γ-irradiated rats could return all the measured cardiac parameters to the normal levels as there were insignificant differences, if compared to their respective control group (Table 2).

Table (2): Effect of Blue berry administration on serum biomarkers of cardiac injury and inflammation and malondialdehyde of irradiated rats.

Groups \ Parameters	Control (I) Mean± S.E.M	Blue berry Group (II) Mean± S.E.M	Irradiated Group (III) Mean± S.E.M	Irradiated Group treated with Blue berry (IV) Mean± S.E.M	ANOVA F	ANOVA P- value
Serum CPK (mmol/l)	118.04± 2.3	122.01± 5.6	177.8 ^{a} ± 9.3	124.4 ^{b}± 4.8	9.7	0.001
Serum LDH (mmol/l)	182.5 ± 7.9	188.7± 6.2	258.4^a± 12.4	179.6 ^{b} ± 6.4	6.9	0.004
Serum IL-6 (pg/dl)	32.25±1.27	38.45 ± 1.1	146.73^a± 9.8	42.92^b± 2.01	7.09	0.003

a: significant values compared to control.   b: significant values compared to irradiated group.
c: significant values compared to Blue berry group.

Gamma-irradiated rats exhibited a significant increase in serum biomarkers of liver function tests (ALT, AST and ALP) in comparison with control group. On the other hand, Blue berry supplemented rats showed insignificant change in all the tested parameters, if compared to control group. Meanwhile, blue berry pretreated γ-irradiated rats could improve liver functions as there was a significant decrease in serum levels of ALT, AST and ALP in comparison with untreated γ-irradiated animal group. However, their levels still higher than normal as they were significantly higher than their corresponding control group (Table 3).

Table (3): Effect of Blue berry administration on serum biomarkers of liver function [alanine transaminase (U/L), aspartate transaminase (U/L) and alkaline phosphatase (U/L)] of irradiated rats..

Groups / Parameters	Control (I)	Blue berry Group (II)	Irradiated Group (III)	Irradiated Group treated with Blue berry (IV)	ANOVA	
	Mean± S.E.M	Mean± S.E.M	Mean± S.E.M	Mean± S.E.M	F	P- value
Serum ALT (U/L)	16.78 ± 0.2	17.03 ± 0.2	$76.07^{a} \pm 1.4$	$30.8^{b,c} \pm 1.6$	6.2	0.009
Serum AST (U/L)	12.5 ± 0.2	12.9 ± 0.3	$52.8^{a} \pm 1.05$	$21.9^{b,c} \pm 1.1$	17.06	0.000
Serum ALP (U/L)	118.6 ± 0.3	118.8 ± 3.06	$216.3^{a} \pm 0.8$	$128.1^{b,c} \pm 1.2$	8.8	0.001

a: significant values compared to control.   b: significant values compared to irradiated group.
c: significant values compared to Blue berry group.

Gamma-irradiation of rats produced a significant increase in serum biomarkers of kidney function tests (urea, creatinine, cystatin-C and lipocalin-2) relative to control group. On contrary, blue berry supplemented rats showed insignificant change in all the tested parameters, if compared to control group. Blue berry pretreated γ-irradiated rats exhibited a significant decrease in serum levels of urea, creatinine, cystatin-C and lipocalin-2 compared with γ-irradiated rats. Moreover, it could return all of them, except cystatin-C, to normal levels as there were insignificant change as regard serum levels of urea, creatinine and lipocalin-2 but serum level of cystatin-C still significantly higher as compared to their respective control group (Table 4).

Table (4): Effect of Blue berry administration on serum biomarkers of kidney function [urea (mg/dl), creatinine (mg/dl), cystatin-C (ng/ml) and lipocalin-2 (pg/dl)] of irradiated rats.

Groups \\ Parameters	Control (I) Mean± S.E.M	Blue berry Group (II) Mean± S.E.M	Irradiated Group (III) Mean± S.E.M	Irradiated Group treated with Blue berry (IV) Mean± S.E.M	ANOVA F	ANOVA P- value
Serum Urea (mg/dl)	42.2 ± 0.9	43.4 ± 2.2	102.3 ^{a} ± 0.8	40.8 ^{b} ± 1.8	8.2	0.002
Serum Creatinine (mg/dl)	0.43 ±0.04	0.44 ±0.03	2.97 ^{a} ± 0.06	0.38 ^{b} ± 0.04	9.7	0.001
Serum cystatin-C (ng/ml)	0.3 ±0.005	0.33 ±0.01	1.07 ^{a} ± 0.03	0.38^{b,c} ±0.02	6.9	0.004
Serum lipocalin-2 (pg/dl)	0.3 ± 0.009	0.37 ± 0.04	0.86 ^{a} ± 0.03	0.3 ^{b} ± 0.03	7.09	0.003

a: significant values compared to control.   b: significant values compared to irradiated group.
c: significant values compared to Blue berry group.

DISCUSSION

In the present work, the level of TC, TAG and MDA in serum was significantly higher in irradiated group than the control group. Remarkable decrease was observed in the concentration of HDL-C in the serum of γ-irradiated rats. These findings were in line with **Farag and Darwish (2016)** who attributed these findings to the generation of free radicals resulting to the peroxidation of membrane lipids which justifies a state of liver dysfunction. **Abou-Safi et al. (2005)** and **Adaramoye (2010)** observed that the elevation in serum lipid fractions might result from ionizing radiation ability to accelerate other pathways of cholesterol formation like increasing its rate of biosynthesis in the liver and other tissues, or destruction of cell membrane by radiation and also to disturbance of LDL cholesterol receptors,

leading to hypercholesterolemia. The recorded elevated level of triglycerides correlated with the previous findings of **Makhlouf and Makhlouf (2012)** who observed that, after irradiation, insulin level increases and synthesis of triglycerides increases in both adipose tissues and liver which are accompanied by an acceleration of fatty acids mobilization from fat depots to blood. Also, they suggested that oxidative stress might be an important determinant of altered lipid metabolism due to radiation exposure. Other possible mechanism of increased TAG levels might be related to the decrease in lipoprotein lipase activity in adipose tissue, leading to a reduction in the uptake of triglycerides (**Jedidi et al., 2003**).

The increase in MDA level might be attributed to the high level of oxidative

stress and the overproduction of ROS associated with irradiation which interact with the polyunsaturated fatty acids in the lipid portion of biological membranes, initiating the lipid peroxidation and finally damaging the cell membranes (**Mansour and Tawfik, 2012**). **Yilmaz and Yilmaz (2006)** reported that MDA is a major biomarker of oxidative damage to living cells is increased lipid peroxidation and commonly measured parameter of lipid damage after ionizing radiation exposure. Lipid peroxdation is believed to be an important cause of destruction and damage to cell membranes and has been suggested to be a contributing factor to the development of oxygen radicals-mediated tissue damage.

The present study showed that blueberry administration before irradiation of rats resulted in a significant decrease in serum level of TC, TAG and MDA with concomitant significant increment in the serum HDL-C compared to irradiated rats. The recorded data correlated with previous findings of **Jensen *et al.* (2008)** and **Baus *et al.* (2010-a)** who detected that berry anthocyanins may exert cardiopro-tective effects by reducing oxidative stress and inflammation through inhibitory effects of the anthocyanin fraction of berry extract on NO biosynthesis and inducible iNOS protein expression, thereby decreasing the inflammatory response in macrophages and inhibiting the formation of foam cells.

Another possible mechanism of the beneficial effect of BBJ pretreatment may be due to its high content of phytochemi-cals, mainly flavonols, phenolic acids and anthocyanins (**Brito *et al.,* 2014**). Also, **Qin *et al.* (2009)** proposed that the

elevated HDL-C may be partially mediated via the inhibition of cholesteryl ester transfer protein (CETP) by anthocyanins. CETP is a plasma protein that mediates the removal of cholesteryl esters from HDL in exchange for a triacylglycerol molecule derived primarily from either LDL, VLDL, or chylomicrons. Moreover, **Ikeda *et al.* (2005)** have indicated that polyphenols could exert their lipid lowering properties through various mechanisms, namely by slowing down triacylglycerol absorption through inhibition of pancreatic lipase, increasing cholesterol excretion in feces, attenuating hepatic lipid accumulation through activation of adenosine monophosphate (AMP)-activated protein kinase suppres-sing hepatic secretion of apo-lipoprotein B100 and increasing expression of LDL receptors in the liver**.**

Effects of whole body γ-irradiation of rats were accompanied by alteration of traditional serum biomarkers of cardiac injury, elevated activity of creatine phosphokinase (CPK) and lactate dehydrogenase (LDH) with concomitant increase in pro-inflammatory cytokine interleukein-6 (IL-6) compared with control group, indicating occurrence of cardiac injury. These results and conclusion were in accordance with **Guida *et al.* (2016)** who indicated that IR induces pro-inflammatory processes in which tumor necrosis factor (TNF-α), interferon (IFN-γ) and interleukin levels are altered, eventually leading to inflammatory disorders. Also, the current findings were consistent with several previous studies proved by **Mansour & Tawfik (2012), Freitas *et al.* (2013), and Elkady & Ibrahim (2014).**

γ-irradiation induced-cardiotoxicity might be produced by stress from acute radiation response. The cardiomyocyte plasma membrane loses its fluidity, causing extravasations of cytosolic enzymes (e.g. CPK and LDH) to circulating blood, indicating a pathological condition. In addition, the heart is in spite of being a vital organ, it generates intense oxidative imbalances because of its intense activity. Moreover, the heart presents a less potent antioxidant system when compared to other body tissues (**Elkady and Ibrahim, 2014**).

Moreover, radiation-induces cardiovascular disruption might be due to endothelial damage via production of reactive oxygen species (**Hatoum et al., 2006**). In addition, the inflammatory vascular damage due to radiation is also via oxidative stress and activation of nuclear factor-kappa B (**Weintraub et al., 2010**). **Hayashi et al. (2005)** proposed the indirect association of inflammation with radiation-induced vascular damage comes from studies showing elevated levels of the proinflammatory cytokines IL-6, CRP, TNF-α, and INF-γ and also increased the levels of the anti-inflammatory cytokine IL-10, in the Japanese atomic bomb survivors. Moreover, data regarding the main networks activated after IR exposure, cytokines exhibit pivotal roles in invasiveness and fibrosis radiation-related and radio-immune combined therapies (**Maggio et al., 2015**).

The current results showed a radioprotective potential of blueberry supplementation before γ-irradiation in the tested parameters (LDH, CPK and IL-6) relative to the control γ-irradiated group. These results were in agreement with

Blumeberg et al. (2015) who reported that consumption of a purified mixture of anthocyanins (i.e. bioactive polyphenol of edible berries) led to significant decreases in C-reactive protein (CRP), soluble vascular cell adhesion molecule1 (sVCAM-1), and plasma IL-1β in patients with hypercholesterolemia. **Ashour et al. (2011)** detected that bilberry significantly inhibits doxorubicin-induced elevations in serum activity of LDH, CPK and CK-MB, as well as troponin I levels.

The putative mechanism of radiomodifying action of berries resides in its bioactive contents especially anthocyanins. Anthocyanins act as novel cardioprotectants by maintaining vascular permeability, reducing inflamatory responses and platelet aggregation, and offer superior vascular protection compared to other cardioprotective drugs (**Duthie et al., 2006 and Neto, 2007**). Also, **Freitas et al. (2013)** suggested that phenolic and flavonoids found in fruits as black grape juice are great antioxidants because their molecular structures contain hydroxyl groups which provide electrons to stabilize free radicals and ROS, restoring the redox state of cardiomyocytes.

The results of the current study revealed marked elevation in liver transaminases (ALT and AST) and alkaline phosphatase (ALP) in γ-irradiated animals compared to control group, which could be attributed to hepatic damage induced by gamma rays. The liver, which was used for bio-transformation and detoxification of materials is particularly susceptible to oxidative stress. These findings stand in well agreement with several previous studies of **El-Missiry et**

al. **(2007), Eydan** *et al.* **(2011) and Farag & Darwish (2016)** who suggested to be due to the damage of structural integrity of the liver resulted in the leakage of these enzymes from the cytosol into the blood stream.

The mechanism of γ-irradiation induced liver injury clarified by **Kalpana** *et al.* **(2011**) who suggested that levels of the lipid peroxidation indicator MDA have been shown to increase in a variety of biological systems including the liver after gamma radiation exposure. Also, **Choi** *et al.* **(2007)** reported that lipid peroxidation reactions can occur at both of cell membrane and mitochondria membranes, and either can subsequently trigger cell death through apoptosis (caspase-mediated apoptotic cell death) and/or autophagy (LC-3-mediated autophagic cell death). **Marnett (1991)** demonstrated that such free radical-mediated lipid peroxidation is harmful not only because damaged lipids disrupt membrane structure and function, but also because the process produces potentially mutagenic and carcinogenic by products.

In the present work, BBJ consumption by rats before irradiation decreased the serum liver enzymes (ALT, AST and ALP) when compared to irradiated rats, indicating hepato-protective properties of the BBJ. The observed decrease in the activity of these hepatic enzymes of BBJ supplemented group before irradiation could be attributed to the high content of naturally occurring polyphenols with antioxidant and free radical scavenging activity. The present data agreed with **Wang** *et al.* **(2013)** who demonstrated that BBJ consumption by rats attenuates CCl4-induced hepatotoxicity evaluated by

increased expression of metallothionein, increased SOD activity, reduced oxidative stress, and decreased levels of α-smooth muscle actin and collagen III in the liver. These suggest that attenuation of hepatotoxicity by BBJ might be through its enhancement of the antioxidative capability of the liver. **Ozcelik** *et al.* **(2014)** also reported that consumption of blue berry significantly decreases liver arginase activity and ornithine levels in addition to serum transaminases with marked increase in nitric oxide and glutathione levels during the acetamino-phen-induced liver injury. Therefore, hepatoprotective effect efforded by blue berry can be attributed to its antioxidant and anti-inflammatory activities.

In the present study, elevation of serum urea and creatinine was observed in γ-irradiated rats when compared to control group. These results came similar to previous investigations by **Barakat** *et al.* **(2011) and Abd El Kader** *et al.* **(2015).** These effects caused by the interaction of cellular membranes with gamma rays or action of free radicals may be related to extensive breakdown of renal architecture **(Hussein, 2008)**.

The observed increase in serum urea could be due to increase in glutamate dehydrogenase enzyme as a result of irradiation, and this may increase carbamayl phosphate synthetase activity leading to increase in urea concentration **(Ramadan** *et al.,* **2001)**. **Robbins** *et al.* **(2001)** reported the impaired detoxifica-tion function of the liver by irradiation could also contribute in the increase of urea in the blood. **Ferguson and Waikar (2012)** reported that creatinine produces through metabolic processes in the

muscles and is freely filtered by the glomerulus without renal tubular reabsorption, and increased levels in serum is an indicator of reduced GFR and or increased muscle protein catabolism. **Abdelhalim and Moussa (2013)** reported elevation of serum creatinine level of the irradiated rats group might indicate nephritis and renal dysfunction due to impairment of glomerular selective properties, and proposed that oxidative stress is linked to the organ damage following exposure to ionizing radiation**. El-Kashef and Saada (1988**) attributed the increase in serum creatinine to the interaction of ionizing radiation with the sites of biosynthesis.

The current results indicated a significant increase in serum cystatin C and lipocalin-2 levels in γ-irradiated rats compared to control group, indicating kidney injury. The present data were in accordance with previous study of **Vijayasimha et al. (2013)**. **Parikh and Devarajan (2008)** reported that cystatin-C is assigned as a more reliable marker of GFR than creatinine, and can detect mild to moderate kidney affection. Cystatin-C is one of the major protectors of the intact glomerular basement membrane from damage by cysteine proteinases**.** Also, lipocalin-2 was identified as one of the earliest and most robustly induced proteins in the kidney after toxic kidney injury (**Devarajan, 2006).**

BBJ supplemention of rats prior to whole body γ-irradiation had a marked decrease in kidney function biomarkers (serum urea, creatinine, cystatin-C and lipocalin-2) when compared to γ-irradiated control group, indicating nephroprotective potential of BBJ. The present

findings were consistent with the study of **Nair et al. (2014)** who indicated that blueberry could protect against renal structural injury and dysfunction in metabolic syndrome animal model by inhibiting Toll-like receptors (TLR4) signaling-driven inflammation. This is, at least in part, a possible cause for the progression of glomerular and tubular injury, thereby contributing to renal dysfunction. Also, **Elks et al. (2011)** reported feeding of BB-enriched diet attenuate the development of hypertension-induced renal injury in rat model, proved by lowered blood pressure, preserved renal hemodynamics, and improved redox status in kidneys.

CONCLUSION

BBJ may serve as radioprotector against γ-irradiation induced cardio-hepato-nephrotoxicity possibly by ameliorating dyslipidemia, inhibiting lipid peroxidation, oxidative stress and inflammation and enhancing the antioxidant activity.

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قسم الفسيولوجياـ كلية الطب (بنات) ـ جامعة الأزهر ، * المركز القومي لبحوث و تكنولوجيا الإشعاع ـ هيئة الطاقة الذرية

خلفية البحث: فاكهة التوت الأزرق غنية بالمكونات النشطة بيولوجيا ، بما في ذلك مركبات الفلافونويد ، الأنثوسيانين ، والأحماض الفينولية ، ستيلبنس ، والعفص ، وكذلك المركبات الغذائية مثل السكريات والزيوت الأساسية والكاروتينات والفيتامينات و المعادن. وتوفر دراسات علمية عديدة أدلة كثيرة على أن المركبات النشطة بيولوجيا لديها القدرة على تقليل مخاطر الإصابة بأمراض القلب والأوعية الدموية وأمراض التآكل. وتعرض الجسم للإشعاع الأيوني يسبب الإجهاد التأكسدى من خلال تكوين الشوارد الحرة التى تؤدى إلى سلسلة من التفاعلات المسببة لتلف الأنسجة.

الهدف من البحث: دراسة التأثير الوقائي المحتمل للتوت الأزرق ضد إصابة القلب والكبد والكلى الناجم عن التعرض لأشعة جاما .

مواد و طرق البحث: تم تنفيذ الدراسة الحالية علي 40 من ذكور الجرذان البيضاء البالغة التى يتراوح وزنها بين 130-160جرام وتم تقسيمهم إلي أربع مجموعات متساوية : الأولى ضابطة، والثانية أعطيت عصير التوت الأزرق بجرعة 1 مل لكل 100جم من وزن الجسم بواسطة أنبوب عن طريق الفم لمدة 14 يوما متتالية، الثالثة تعرضت لجرعة واحدة من أشعة جاما (7 جراى)، والمجموعة الأخيرة أعطيت عصير التوت الأزرق بجرعة 1مل لكل 100جم من وزن الجسم بواسطة أنبوب عن طريق الفم لمدة 14 يوما متتالية قبل التعرض للإشعاع (7 جراى جرعة واحدة). فى نهاية التجربة تم تخدير الفئران كليا وجمع عينات الدم من الوريد العيني لقياس مستوى بعض الدلالات في مصل الدم (الكولسترول الكلى ـ الدهون الثلاثية ـ الدهون عالية الكثافة ـ الليبيدات الفوق مؤكسدة -لاكتات ديهيدروجينيز ـ كرياتين فوسفوكينيز ـ إنترلوكين-6 - إنزيمات الكبد ـ وظائف الكلى (اليوريا- الكرياتينين- سيتاتين-ج ـ ليبوكالين-2)

نتائج البحث: إعطاء التوت الأزرق للجرذان قبل التعرض للإشعاع أدى إلى إنخفاض كبير في مستوى الكولسترول الكلى و الدهون الثلاثية والليبيدات الفوق مؤكسدة، بينما ظهر ارتفاعا ذو دلالة إحصائية فى مستوى الدهون عالية الكثافة، كما أظهر إعطاء عصير التوت الأزرق انخفاضا كبيرا في مستوى الإنزيمات الدالة على إعتلال عضلة القلب، وإنخفاض الإنترلوكين المحفز للإلتهاب (لاكتات ديهيدروجينيز ـ كرياتين فوسفوكينيز ـ انترلوكين-6)، وتحسن وظائف الكبد (انخفاض مستوى الإنزيمات) وكذلك تحسن وظائف الكلى (إنخفاض كبير في مستوى اليوريا، و الكرياتينين، و سيتاتين-ج ، و ليبوكالين-2).

الإستنتاج: التوت الأزرق له دور ايجابى كمنتج طبيعي للحد من التوتر التأكسدي وحماية أعضاء الجسم من أشعة جاما.