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Amelioration of Oxidative Stress Induced by Gamma Irradiation in Rats Using *Spirulina platensis*

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Abstract: Radiation exposure of living organisms is known to produce many harmful effects in biological systems due to generation of free radicals. Many antioxidants have been investigated as hepato-protectors against ionizing radiation induced injury since they reduce the oxidative effect of the reactive oxygen species on normal cells. *Spirulina platensis* is a potent scavenger of a variety of free radicals. The aim of this study was to investigate the radio-protective effect of *Spirulina platensis* algae *a*gainst oxidative stress and tissue injury caused by gamma radiation.

Rats irradiated at 5 Gy delivered as single dose produced a significant decrease in albumin, total protein and globulin levels as compared to normal control rats. However, γ-irradiated rats pre-treated with *Spirulina* increased significantly albumin, total protein and globulin levels as compared to gamma irradiated rats (5 Gy). Rats irradiated at 5 Gy produced a significant increase in the activity of the liver enzymes, ALT, AST, ALP and GGT. Meanwhile, gamma irradiated rats pre-treated with *Spirulina platensis* decreased significantly ALT, AST, ALP and GGT as compared to gamma irradiated rats. Gamma irradiated rats increased significantly cholesterol, triglyceride, HDL and LDL as compared to normal control rats. Also, gamma irradiated rats pre-treated with *Spirulina platensis* decreased significantly cholesterol, triglyceride, HDL and LDL as compared to gamma irradiated rats. Kidney function tests, creatinine, urea and potassium increased significantly in γ-irradiated rats as compared to normal control rats. Meanwhile, in *Spirulina platensis* pre-treated animals before irradiation decreased significantly creatinine, urea and potassium as compared to gamma irradiated rats. .

Gamma irradiated rats (5 Gy) decreased significantly the antioxidant enzyme activity of GSH, GPX, CAT, and SOD as compared to normal control rats. Also, γ-irradiated rats pre-treated with *Spirulina* increased significantly GSH, GPX, CAT, and SOD as compared to γ-irradiated rats.

It was concluded that administration of *Spirulina platensis* algae possess a radio protective capacity against ionizing-radiation induced oxidative stress and organ injury. Thus, supplementation with *Spirulina platensis* may have a benefit for safe application of radiation technology in medicine and industry.

Key Words: Gamma irradiation, *Spirulina platensis*, Enzymes.

1. Introduction

Exposure to ionizing radiation causes many health hazardous effects. Such exposure produces biochemical lesions that initiate a series of physiological symptoms. Reactive oxygen species (ROS) such as superoxide (O_2^-), hydroxyl radical ($OH^\cdot$) and hydrogen peroxide (H_2O_2) created in the aqueous medium of living cells during irradiation cause lipid peroxidation in cell membrane and damage to cellular activities leading to a number of physiological disorders situation and dysfunction of cells and tissues [1,2]. ROS are the cause of certain disease such as cancer tumors, cardiovascular diseases, and liver dysfunction [3]. Ionizing radiation passing through living tissues generates free radical that can induce DNA damage. The damaging effects of ionizing radiation on DNA lead to cell death and are associated with an increased risk of cancer [4].

To maintain the redox balance and to protect organs from these free radicals action, the living cells have evolved an endogenous antioxidant defense mechanism which includes enzymes like catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GSHpx), in addition to reduced glutathione (GSH) and metallothioniens (MTs). Radiation exposure alters the balance of endogenous defense systems. Appropriate antioxidant intervention seems to inhibit or reduce free radicals toxicity and offer a protection against the radiation damage. A number of dietary antioxidant has been reported to decrease free radical attack on biomolecules [5].

Spirulina platensis is a blue-green microalgae has a spiral cellular structure, and has an extraordinary capacity to survive under conditions that are much too harsh for other algae. Habitats with extensive *Spirulina* growth include the Pacific Ocean near Japan and Hawaii, large

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fresh water lakes in Africa, North America, Mexico, and South America. Two species of *Spirulina* that are most commonly used in nuritional supplements are *Spirulina platensis* and *Spirulina maxima* [6].

Spirulina, contains large amounts of protein (70% dry weight) [7], carotenoid (4000 mg/kg) chlorophyll, and phycocyanin [8], omega-3 and omega-6 polyunsaturated fatty acids, γ–linolenic acid, sulfolipids, glycolipids, polysaccharides, provitamins, vitamin A [9], vitamin E [10], various B vitamins and minerals, including calcium, iron, magnesium, manganese, potassium, zinc [6] and selenium [11]. The present study has been carried out in order to access the radio-protective efficiency role and the antioxidant effect of natural biochemical ingredients present in *Spirulina platensis* against oxidative stress and tissue injury in rats caused by gamma radiation.

2. Materials and Methods

Animals

Male Westar rats weighing 150-180 g were obtained from the animal farm of the Egyptian Holding Company for Biological Products and Vaccines, Egypt. Experimental animals were housed in cages with free access to drinking water and diet and maintained in the animal care facility throughout the duration of the experiment. The animals were kept at 22–24°C with the 12 h light/dark cycle. The food composition contents of experimental basal diet were casein, corn, vitamin, mineral and cellulose, respectively by 12, 10, 1, 4 and 5g/100g [12].

Animal husbandry and experimentation were consistent with the Public Health Guide for the Care and Use of Laboratory Animals and in accordance with protocols approved by the local experimental animal ethics committee. During the whole experiment, rats will be kept separate in well aerated cages; diet and water will be supplied ad-lib

***Spirulina platensis* extracts powder**

Spirulina platensis in a powder form (food grade) was purchased from Nature's Way Products, INC. Springville, Utah 84663 USA. The rats will be fed daily by *Spirulina platensis* at dose level of 400 mg/kg dissolved in water for 45 consecutive days.

Irradiation Processing

Animals were placed in a specially designed well-ventilated acrylic container and the whole body of the animals were exposed to 5 Gy, given at a dose rate of 0.84 Gy/min from the biological irradiator gamma cell-40, Cesium-137 source (Atomic Energy Agency, Canada), belonging to National Center for Radiation Research and Technology, Cairo. The irradiation time for a dose of 5 Gy was 4.2 minutes.

Experimental Design

Animals were divided into four groups, each group containing seven rats.

Animals in group 1: were served as control group and no treatment was given to these rats. This group will be fed daily by only basal diet for 45 consecutive days.

Animals in group 2: will be fed daily by only basal diet, after 10 days the whole body of the animals will be exposed to a dose of 5 Gy of gamma irradiation and continued up to 45 days after radiation exposure.

Animals in group 3: will be fed daily by only basal diet + *Spirulina platensis* daily by gavages at dose level of 400 mg/kg dissolved in water for 45 consecutive days.

Animals in group 4: will be fed daily by only basal diet + *Spirulina platensis* daily by gavages at dose level of 400 mg/kg dissolved in water for 10 consecutive days before irradiation exposure and continued up to 45 days after radiation exposure.

Collection of samples

Animals were sacrificed at the end of the experiment (12 h after over night fasting). Blood samples were collected and put into chilled non-heparinized tubes, which were centrifuged at 3000 rpm for 10 min at 4 ºC. The sera were frozen at -20 ºC for the following measurements. The serum levels of Cholesterol was measured by the enzymatic colorimetric method of [13], Triglyceride (TG) were measured by the enzymatic colorimetric method of [14], High density lipoprotein (HDL) was determined by the method of [15], Low density lipoprotein (LDH), Proteins profile (total protein was measured colorimetricaly by the method of [16], albumin was measured by a modified bromocresol green colorimetric method of [17], globulin, and A/G ratio), Urea was measured by the Berthelot enzymatic colorimetric method of [16], Creatinine [18], Sodium and Potassium were measured by Flame Photometry (Hitachi 775, Hitachi Co., Ltd., Hitachi, Japan).Total bilirubin [19], as well as the activity of Alanine Aminotransferase (ALT) measured by the kinetic method of [20], Aspartate Aminotransferase (AST) was measured by the kinetic method of [20], Alkaline Phosphatase (ALP) was measured according to the kinetic method of [21], and Gamma-Glutamyltransferase (GGT) according to the method of [22]. Also, the activity of the Antioxidant Enzymes, Catalase (CAT) according to the method of [23], Sodium Peroxidase (SOD) was measured by [24], Glutathione Peroxidase (GPX) was measured by [25], and Glutathione (GSH) was measured according to the method of [26], using kits from bio-Merieux, France.

3. Results and Discussion

Biochemical Studies:

Influence of *Spirulina platensis* and/or gamma irradiation on total bilirubin, albumin, total protein, globulin and A/G ratio in different rat groups.

Rats irradiated at 5 Gy delivered as single dose produced a significant decrease ($p \leq 0.05$) in albumin, total protein and globulin levels by 54.5, 60.4 and 70 %, respectively as compared to normal control values (Table 1).

However, γ-irradiated rats pre-treated with *Spirulina platensis* increased significantly albumin, total protein and globulin levels by 155.6, 178.1 and 207.1 %, respectively as compared to γ-irradiated animals. Irradiated rats (5 GY)

increased significantly ($p \leq 0.05$) total bilirubin by 33.9 % as compared to normal control animals. Meanwhile, γ-irradiated rats pre-treated with *Spirulina platensis* decreased significantly total bilirubin by 26.8 % as compared to γ-irradiated rats.

Increased levels of these diagnostic markers of hepatic function in irradiated rats are implicative of the degree of hepatocellular dysfunction caused by the radiation [27]. Results of the current study go in parallelism with previous studies that revealed a potential hepatoprotective effect of *Spirulina platensis* (C-phycocyanin) in rats [28].

The effect of *Spirulina* in maintaining normal hepatic functions are well documented [29]. Co-treatment of irradiation and *Spirulina platensis* resulted in a significant improvement in all the tested parameters (albumin, total protein, bilirubin and globulin) towards the normal values of the control [30].

Table 1: Influence of *Spirulina platensis* and/or gamma irradiation on total bilirubin, albumin, total protein, globulin and A/G ratio in different rat groups.

Treatments	T. Bilirubin (mg/dl)	Albumin (g/dl)	T. protein (g/dl)	Globulin (g/dl)	A/G Ratio
Basal diet (Control)	**0.54±0.13^{c}**	**3.3±0.13^{a}**	**5.3±0.68^{b}**	**2.0±0.11^{c}**	**0.62±0.03^{d}**
Basal diet + 5 Gy	**1.83±0.09^{a}**	**1.8±0.09^{c}**	**3.2±0.16^{c}**	**1.4±0.08^{d}**	**1.28±0.06^{b}**
Basal diet + *Spirulina platensis*	**0.49±0.15^{c}**	**3.6±0.15^{a}**	**6.2±0.49^{a}**	**2.6±0.21^{b}**	**1.38±0.07^{a}**
Basal diet + 5 Gy + *Spirulina platensis*	**0.86±0.17^{b}**	**2.8±0.17^{b}**	**5.7±0.23^{b}**	**2.9±0.21^{a}**	**0.96±0.04^{c}**

Values are represented as mean ± SD of 4 replicates. Means marked with the same superscript letters are not-significant ($p>0.05$), whereas others with different superscript letters are significant ($p<0.05$).

Influence of *Spirulina platensis* and/or gamma irradiation on enzyme activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) in different rat groups

Rats irradiated at 5 Gy produced a significant increase in the activity of the liver enzymes, ALT, AST, ALP and GGT by 791, 755, 324 and 608 %, respectively as compared to normal control animals (Table 2). Meanwhile, γ-irradiated rats pre-treated with *Spirulina platensis* decreased significantly ($p \leq 0.05$) ALT, AST, ALP and GGT by 64.5, 64.1, 55.8 and 72.6 %, respectively as compared to γ-irradiated rats.

In the present study, Gamma irradiation caused a marked increase in serum levels of AST, ALT, ALP and GGT indicating liver injury. These results are in accordance with other studies [31, 32]. The increase in serum transaminase activities and ALP is expected as a consequence for the increase in activities of the liver enzymes. These findings are supported by previous finding reported by [33, 34] who explained that changes in the enzymatic activities after irradiation may be due either to the release of enzymes from radiosensitive tissues or to changes in its synthesis and may be related to the extensive breakdown of liver parenchyma and renal tubules

Table 2: Influence of *Spirulina platensis* and/or gamma irradiation on enzyme activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) in different rat groups.

Treatments	ALT (U/L)	AST (U/L)	ALP (U/L)	GGT (U/L)
Basal diet (Control)	**15.6±0.94^{c}**	**18.9±1.14^{c}**	**33.4±2.67^{c}**	**27.5±1.92^{c}**
Basal diet + 5 Gy	**123.5±7.4^{a}**	**142.7±8.55^{a}**	**108.3±6.49^{a}**	**167.2±16.71^{a}**
Basal diet + *Spirulina platensis*	**12.4±0.99^{c}**	**16.5±1.32^{c}**	**31.2±0.99^{c}**	**23.2±1.41^{c}**
Basal diet + 5 Gy + *Spirulina platensis*	**43.8±4.83^{b}**	**51.2±5.66^{b}**	**47.8±4.78^{b}**	**45.8±5.33^{b}**

Values are represented as mean ± SD of 4 replicates. Means marked with the same superscript letters are not-significant ($p>0.05$), whereas others with different superscript letters are significant ($p<0.05$).

[35] Reported that *Spirulina platensis* resulted in a significant improvement in ALT, AST, cholesterol and triglyceride levels toward to normal values of the control rats.

Co-treatment of irradiation and *Spirulina platensis* resulted in a significant improvement in all the tested parameters towards the normal values of the control [30].

It has been reported that *Spirulina platensis* possess strong antioxidant and free radical scavenging properties [36]. The antioxidant and protective effects of *Spirulina* is owed to their content of antioxidant active constituents such as C-phycocyanins, β-carotene, vitamins, minerals, proteins, lipids and carbohydrates [37].

The hepatoprotective properties of *Spirulina platensis* are referrable to its antiinflammatory, antioxidant, membrane-stabilizing, and immunocorrecting actions. In this way the employment of *spirulina* is believed to be pathogenetically validated in chronic diffuse liver conditions, permitting stabilizing the process and preventing the transformation of chronic hepatitis into hepatocirrhosis [38].

Influence of *Spirulina platensis* and/or gamma irradiation on cholesterol, triglyceride, HDL and LDL in different rat groups.

As shown in Table (3), γ-irradiated rats increased significantly ($p \leq 0.05$) cholesterol, triglyceride, HDL and LDL by 48.9, 56.4, 68.5 and 13.1 %, respectively as compared to normal control rats. Also, γ-irradiated rats pre-treated with *Spirulina platensis* decreased significantly

Table 3: Influence of *Spirulina platensis* and/or gamma irradiation on cholesterol, triglyceride, HDL and LDL in different rat groups.

Treatments	Cholesterol (mg/dl)	Triglyceride (mg/dl)	HDL (mg/dl)	LDL (mg/dl)
Basal diet (Control)	**142.9±8.5^{c}**	**98.5±5.9^{c}**	**45.8±2.7^{c}**	**77.4±3.9^{b}**
Basal diet + 5 Gy	**279.7±13.9^{a}**	**226.2±18.0^{a}**	**145.4±9.9^{a}**	**89.1±4.8^{a}**
Basal diet + *Spirulina platensis*	**112.5±9.1^{d}**	**81.2±5.6^{d}**	**41.7±2.5^{c}**	**54.6±2.2^{d}**
Basal diet + 5 Gy + *Spirulina platensis*	**170.3±6.8^{b}**	**123.5±7.4^{b}**	**77.8±4.6^{b}**	**67.8±5.4^{c}**

Values are represented as mean ± SD of 4 replicates. Means marked with the same superscript letters are not-significant (p>0.05), whereas others with different superscript letters are significant (p<0.05)

cholesterol, triglyceride, HDL and LDL by 39.1, 45.4, 46.5 and 23.9 %, respectively as compared to γ-irradiated rats.

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Values are represented as mean ± SD of 4 replicates. Means marked with the same superscript letters are not-significant (p>0.05), whereas others with different superscript letters are significant (p<0.05).

Our results coincided with those of [31], who stated that serum cholesterol, HDL, LDL and triglycerides tend to be higher in irradiated rats than the control.

This imbalance induces hyperlipidemia through its multiple effects on lipid metabolism, including increased synthesis of cholesterol and triglyceride [39]. In the present study, marked significant elevation was observed in lipid (cholesterol and triglyceride) in irradiated rats. Our results are in agreement with those of [40, 34] who reported an increase of lipids in plasma level of rats post irradiation.

[35] Reported that *Spirulina platensis* resulted in a significant improvement in ALT, AST, cholesterol and triglyceride levels toward to normal values of the control rats.

The presence of antioxidant compounds like phycocyanin and β-carotene, linolenic acid and sulfated polysaccharide in *Spirulina* could be the cause of the properties and action of *Spirulina* on the decrease of plasma lipids levels. According to [41], phycocyanin causes hypocholesterolemic activity in rats. [42] Reported that β-carotene reduced the elevation of cholesterol and triglycerides of diabetic rats.

Influence of *Spirulina platensis* and/or gamma irradiation on kidney function (creatinine, urea, potassium and sodium) in different rat groups.

Kidney function tests, creatinine, urea and potassium increased significantly ($p \leq 0.05$) in γ-irradiated rats by 271.8, 716.7, and 72.9 %, respectively. Otherwise, they decreased the sodium level by 8 % as compared to normal control. Meanwhile, in *Spirulina platensis* pre-treated animals before irradiation decreased significantly ($p \leq 0.05$) creatinine, urea and potassium by 68.6, 60.5 and 20.3 %, respectively and increased significantly sodium content by 5.6 % as compared to γ-irradiated animals (Table 4).

In the present study, plasma urea and creatinine levels, which are considered as a markers of kidneys function were significantly elevated after exposure the animals to γ-irradiation indicating renal impairment [43]. Gamma irradiation decreased the Na content, but increased the K level in rats [44].

The increase in blood creatinine and urea has been reported after exposure to irradiation and secondary to renal damage [45]. In addition, the elevation in urea may be attributed to an increase in nitrogen retention or excessive protein breakdown [46].

Co-treatment of irradiation and *Spirulina platensis* resulted in a significant improvement in all the tested parameters towards the normal values of the control [47].

Results of the present study showed that *Spirulina platensis* significantly decreased the elevated levels of creatinine and urea. It may be possible, that *Spirulina*, due to its potential antioxidant properties, improved renal function via attenuating oxidative stress- mediated decline

in kidney [48]. The nephroprotective effects of *Spirulina* have been reported against renal injury induced by gentamicin [49].

Table 4: Influence of *Spirulina platensis* and/or gamma irradiation on kidney function (creatinine, urea, potassium and sodium) in different rat groups.

Treatments	Creatinine (mg/dl)	Urea (mg/dl)	Potassium (mmol/L)	Sodium (mmol/L)
Basal diet (Control)	**0.78±0.09^{c}**	**18±2.16^{c}**	**3.7±0.19^{d}**	**137±13.7^{b}**
Basal diet + 5 Gy	**2.9±0.23^{a}**	**147±5.91^{a}**	**6.4±0.32^{a}**	**126±11.34^{c}**
Basal diet + *Spirulina platensis*	**0.75±0.08^{c}**	**23±2.07^{c}**	**4.7±0.42^{c}**	**136±10.88^{a}**
Basal diet + 5 Gy + *Spirulina platensis*	**0.91±0.06^{b}**	**58±6.38^{b}**	**5.1±0.32^{b}**	**133±7.98^{b}**

Values are represented as mean ± SD of 4 replicates. Means marked with the same superscript letters are not-significant ($p>0.05$), whereas others with different superscript letters are significant ($p<0.05$).

Influence of *Spirulina platensis* and/or gamma irradiation on reduced glutathione (GSH), glutathione peroxidase (GPX), catalase (CAT) and superoxide dismutase (SOD) in different rat groups.

Gamma irradiated rats (5 Gy) decreased significantly ($p\leq0.05$) the antioxidant enzyme activity of GSH, GPX, CAT, and SOD by 41.1, 56.2, 52.2 and 54.7, respectively as compared to normal control rats (Table 5).

Also, γ-irradiated rats pre-treated with *Spirulina platensis* increased significantly ($p\leq0.05$) GSH, GPX, CAT, and SOD by 56.8, 109.5, 84.3 and 93.1, respectively as compared to γ-irradiated rats (5 Gy).

The decrease in tissue antioxidant enzyme levels may be due to its consumption during the oxidative stress induced by irradiation and these findings are confirmed by other authors [50].

[35] Who reported that treatment of the normal rats with blue-green algae (*Spirulina platensis*) significantly increased the activities of CAT, SOD and GST as compared to those of the normal controls [51]. *Spirulina* treatment stimulates several antioxidants that raise the total antioxidant capacity of the body [52].

The preconditioning actions of *Spirulina platensis* can exert protective effects, by up regulation of the antioxidant system and the reduction in reactive oxygen species. It may propose that *Spirulina platensis* is an activator of antioxidant enzymes. Similarly, radioprotection by dietary vitamin A and β-carotene in mice exposed to gamma irradiation has been reported [38].

It was concluded that administration of *Spirulina platensis* algae possess a radio protective capacity against ionizing-radiation induced oxidative stress and organ injury. Thus, supplementation with *Spirulina* may have a benefit for safe application of radiation technology in medicine and industry.

Table 5: Influence of *Spirulina platensis* and/or gamma irradiation on glutathione (GSH), glutathione peroxidase (GPX), catalase (CAT) and superoxide dismutase (SOD) in different rat groups.

Treatments	GSH (U/L)	GPX (U/L)	CAT (U/L)	SOD (U/L)
Basal diet (Control)	**22.4±0.67^{a}**	**48±2.3^{b}**	**6.7±0.27^{b}**	**12.8±0.77^{b}**
Basal diet + 5 Gy	**13.2±0.55^{c}**	**21±1.0^{c}**	**3.2±0.19^{d}**	**5.8±0.47^{d}**
Basal diet + *Spirulina platensis*	**25.9±1.55^{a}**	**45±2.25^{a}**	**7.1±0.43^{a}**	**14.9±1.04^{a}**
Basal diet + 5 Gy + *Spirulina platensis*	**20.7±1.03^{b}**	**44±2.64^{a}**	**5.9±0.24^{c}**	**11.2±0.08^{c}**

Values are represented as mean ± SD of 4 replicates. Means marked with the same superscript letters are not-significant ($p>0.05$), whereas others with different superscript letters are significant ($p<0.05$).

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