

Role of Aged Garlic Extract Against Radiation Induced Oxidative Stress Associated with Some Biochemical Disorders in Male Albino Rats

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Abstract: This study was conducted to clarify the potential role of AGE against damages induced in rats due to exposure to gamma radiation. Adult male albino rats (214-230g). Eight groups, five healthy male rats each were used (20 irradiated and 20 Sham Irradiated), among which some were receiving via gavages distilled water, the others AGE at different doses (25 mg/kg and 50 mg/kg) and the rest vitamin E+Alpha Lipoic Acid. Blood samples were collected at day 8 post irradiation for biochemical assay. Exposure of rats to gamma radiation caused a significant increase in the level of total cholesterol (TC), triglycerides (TG), LDL-Cholesterol, Malondialdehyde (MDA), Nitrite (NO²⁻), Creatinine and AST, ALT, ALP and Bilirubin (Total Serum Bilirubin, Direct Bilirubin and Unconjugated Bilirubin) while a significant decrease was recorded in HDL-Cholesterol, serum total proteins, glutathione content (GSH), superoxide dismutase (SOD), catalase (CAT) activities and total protein level in organs tissues. In rats treated with AGE then exposed to radiation, the results showed an improvement in all previous parameters. It could be concluded that AGE might reduce the biological hazards in rats induced by gamma irradiation.

Keywords: γ -Radiation, Biochemical Disorders, Age, Antioxidant Enzymes, Rats

1. Introduction

All types of ionizing radiations generate ions which can lead to the formation of free radicals and reactive oxygen species (ROS). Excess production of free radicals or decrease in antioxidants level leads to oxidative stress. It is a harmful process that induces damage to cell structures, lipids, proteins, RNA and DNA which leads to a number of diseases [1-2]. Phytoconstituents and herbal medicine are important in the management of pathological conditions of those diseases

caused by free radicals [3].

AGE contains many important water-soluble organosulfur compounds with potent antioxidant and free radical scavenging activities. So far, AGE has been demonstrated to possess several physiological activities in experimental animals [2-3]. Recently, AGE has received particular attention because of studies that have reported that it is a highly efficient antioxidant and has free radical scavenging capacity [4-5].

ALA and Vitamin E have been reported to have highly

protective effect on lipid peroxidation and their positive effect includes protection against radiation damage [6-7].

In view of these considerations, the main objective of this study was to assess the role of AGE against radiation induced oxidative stress associated with some biochemical disorders in male albino rats using Vitamin E and Lipoic Acid as positive control group.

2. Material and Methods

2.1. Animals

Eighty healthy Albino male rats (*Rattus norvegicus*) of Wistar strain (3 to 4 months old) ranging from 214-230g body weight were obtained according to the ICH guidelines from animal lab Université des Montagnes, Bangangté and Douala University in Cameroon. Their acclimatization to laboratory conditions took place at room temperature, relative humidity and natural light-dark cycle (12 hours light and 12 hours dark). The rats were given *ad libitum* tap water and food of a commercial balanced diet. Five animals were housed per plastic cage containing paddy husk (procured locally) as bedding and fasted night before sacrifice. The experimental protocol and the maintenance of the experimental animals was done in accordance with the regulations of the Organization for Economic Cooperation and Development (OECD) guide since in Cameroon the ethics committee focuses only on clinical studies.

2.2. Chemical

Aged Garlic Extract (KYOLIC® Aged Garlic Extract™ Liquid) is prepared by soaking sliced raw garlic (*Allium sativum* Linn) with a quality plan program (QPP-003) in 15-20% aqueous ethanol for 20 months at room temperature. The extract is then filtered and concentrated under reduced pressure according to the guidelines of Good Manufacturing practices established by the World Health Organization. The garlic is grown under strictly controlled organic conditions (without herbicides or pesticides of any kind), harvested at full maturity, cleaned, sliced and stored in stainless steel tanks under carefully controlled conditions without the use of a heating process [8-10]. The content of water-soluble compounds is relatively high whereas that of oil-soluble compounds is relatively low [10]. The AGE used in this study is standardized with S-Allyl Cysteine and contained 30% extracted solids (300 mg/ml), and S-allyl cysteine present at 1.47 mg/ml.

2.3. Experimental Design

Two weeks after acclimatization and conditioning, the animals were randomly divided into four equal and double male rat groups in separate plastic cages, five rats each. Two negative control groups receiving 10 mL/kg of distilled water (I and II), two AGE-treated groups at dose of 25 mg/kg AGE (III and IV), two AGE-treated groups at dose of 50 mg/kg AGE (V and VI) and two positive control groups (receiving 50 mg/kg Vitamin+25 mg/kg of Lipoic Acid) (VII and VIII)

were used. Among the double groups, 20 were irradiated (rats of groups II, IV, VI and VIII) and 20 sham irradiated (rats of groups I, III, V and VII). The rats of each group were fed via gavage for 12 days (5 consecutive days prior to acute irradiation and one hour after irradiation on day 6 and for 7 consecutive days) and weighed daily during the experiment. The experimental protocol and the maintenance of the experimental animals was done in accordance with the standard ethical guidelines for laboratory animal use and care as described in the European Community guidelines; EEC Directive 86/609/EEC, of the 24th November 1986 [11].

2.4. Irradiation

The Albino Wistar rats were placed in collective cages made of plastic for whole-body exposure after at least two weeks of acclimatization and conditioning. Rats were exposed using the facilities provided by the Oncology and Radiotherapy department of the Douala General Hospital. Irradiation was delivered by an ALCYON-II model cobalt-60 teletherapy unit (General Electric/GE Healthcare). The rats in an area of 36 x 36 cm were exposed to a single dose of 4.5 Gy applied as single shot dose at a dose rate of 0.55 Gy/min. Five animals were irradiated at once and sham-irradiated animals were treated in the same manner but were not exposed to the source. After irradiation, the rats were brought back to the animal Lab of Douala University for the follow up and the tests.

2.5. Sample Collection

2.5.1. Blood Samples

The animals were put to fast during the night before their blood test (7th day post irradiation). The day of sacrifice (8th day post irradiation), arterio-venous blood was collected in dry tubes and allowed to clot (stand for 30 min) and centrifuged at 3 000 rpm for 15 min. The supernatant (serum) obtained was gathered in Eppendorf tubes and stored at -20°C for biochemical analysis of lipid profile (Cholesterol total, HDL Cholesterol and Triglyceride), alkaline phosphatase, transaminase enzymes (Aspartate transaminase and Alanine transaminase), Bilirubin (Total Serum Bilirubin and Direct Bilirubin) and Total proteins.

2.5.2. Tissue Samples

A vertical midline thoracic and abdominal incision was done to explore the rat's viscera. Because of administration of distilled water, AGE, Lipoic acid+vitamin E for consecutive days and whole body irradiation at 4.5 Gy, brain, lungs, aorta, heart, liver, spleen, kidneys, testis, thymus, vertebra, femur, skin and sternum of each rat was excised, cleaned from their surrounding fat and connective tissue, washed with normal saline, blotted with filter paper, examined macroscopically (form modification, size, consistency and color) and weighed.

2.6. Biochemical Assay

Liver biomarkers assessment: the levels of aspartate

transaminase (AST) and alanine transaminase (ALT) enzymes were estimated in the sera of the blood samples using commercial kits (Innesco GmbH-Wiedtalstrasse 11 & 18-D-53577 Neustadt/Wied–Germany) according to Kaplan [12] and alkaline phosphatase level estimated in accordance with Prahlad and Conaway method [13]. Also, serum total protein was determined using Biuret reaction [14] and Bilirubin was assayed according to calculation (Unconjugated Bilirubin) and the method of Balistreri and Shaw (Total Serum Bilirubin and Direct Bilirubin) [15] as well.

Lipid profile and creatinine: the second part of blood was allowed to clot and centrifuged to obtain serum for the determination of Total Cholesterol, HDL Cholesterol and Triglyceride according to the method used by Atsang A Kiki [16] and LDL Cholesterol according to the method of Nauck et al. [17] and the formula of Friedewald et al. [18]. The creatinine assay was done in accordance with Bartels and Bohmer method [19].

Lipid peroxidation, total Protein and antioxidants assessment in tissue homogenates: Homogenate 20% was prepared by adding 2 mL of 50 mM, Tris-HCl buffer to 0.40 g of each organs (brain, lungs, liver, spleen, left kidney, left testis and vertebra) and homogenate 10% by adding 1 mL of 50 mM Tris-HCl to 0.1g of aorta. Homogenate obtained was centrifuged at 3500 rpm for 25 minutes at 4°C after grinding in a mortar on ice tray. The supernatants were collected for the measurement of catalase (CAT), superoxide dismutase (SOD), Nitrite (NO_2^-), the levels of reduced glutathione (GSH), and malondialdehyde (MDA). GSH was determined in accordance with the method of Ellman [20] and SOD activity according to the method of Misra and Fridovich [21]. CAT activity was estimated by measuring the decomposition of hydrogen peroxide, according to the method of Sinha [22] and Nitrite (NO_2^-) assay according to Slack [23]. The marker of lipid peroxidation (malondialdehyde: MDA), was determined according to the method of Wilbur et al. [24].

2.7. Statistical Analyses

Results were expressed as Mean±Standard Error of the Mean (SEM). Comparison of means was done by Dunnett test as post hoc test. P values less than 0.05 were considered statistically significant. Statistical evaluation was conducted using one way analysis of variance (ANOVA) software Graph Pad Prism 5.03. With the α risk of 5%, statistically significant differences are reported in the tables and figures with an asterisk (*), the highly statistically significant differences are marked with two stars (**) and statistically highly significant differences are indicated by three stars (***)

3. Results

3.1. Liver Biomarkers Assessment

3.1.1. Alanine Transaminase (ALT)

After γ -radiation, the level of alanine transaminase

increased significantly ($p < 0.001$) in order of 60% (115.2 ± 2.24 Vs 72 ± 2.24 U/L) in the group "Irradiation+Distilled Water". This rate decreased significantly ($p < 0.001$) in the range of 50.69% (56.8 ± 2.24 Vs 115.2 ± 2.24 U/L) and 42.36% (66.4 ± 2.24 Vs 115.2 ± 2.24 U/L) in the groups "Irradiation 25 mg / kg AGE" and "Irradiation+50 mg / kg AGE" compared to the group "Irradiation+Distilled Water". The decrease in this rate is also significant ($p < 0.01$) in the range of 34.86% (56.8 ± 2.24 Vs 87 ± 2.24 U/L) by comparing the group "Irradiation+25 mg / kg AGE" to the positive control group "Irradiation+Vitamin E and Lipoic Acid" (Figure 1).

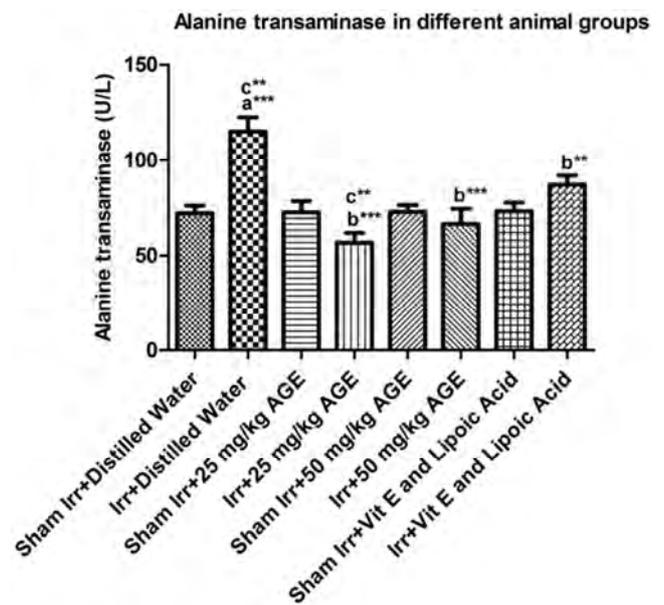


Figure 1. Effects of γ -radiation and AGE on Alanine transaminase rate.

Each bar represents the Mean±ESM, n=5. Significant differences are:

- a* $P < 0.05$; a** $P < 0.01$; a*** $P < 0.001$: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* $P < 0.05$; b** $P < 0.01$; b*** $P < 0.001$: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c* $P < 0.05$; c** $P < 0.01$; c*** $P < 0.001$: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.1.2. Aspartate Transaminase (AST)

The irradiation resulted in a significant increase of aspartate transaminase ($p < 0.01$) in the group "Irradiation+Distilled Water" in order of 18.28% (159.2 ± 3.56 Vs 134.6 ± 5.38 U/L) and a significant decrease in the groups "Irradiation+25 mg / kg AGE" ($p < 0.001$) and "Irradiation+50 mg / kg AGE" ($p < 0.05$) respectively in order of 35.36% (87 ± 4.68 Vs 134.6 ± 5.38 U/L) and 13.22% (116.8 ± 1.69 Vs 134.6 ± 5.38 U/L). Animals receiving AGE at doses of 25 and 50 mg / kg, showed a significant decrease ($P < 0.01$ and $P < 0.05$) in aspartate transaminase levels compared to the group "irradiation+Distilled Water" (Figure 2). This decrease

was respectively in order of 45.35% (87±4.68 Vs 159.2±3.56 U/L) and 26.63% (116.8±1.69 Vs 159.2±3.56U/L). Similarly, compared to the group "Irradiation+Vitamin E and Lipoic Acid" a significant decrease (p<0.01) was observed in the groups "Irradiation+25 mg / kg AGE" and "Irradiation+50 mg / kg AGE" in the range of 42.15% (87±4.68 Vs 150.4±4.17 U/L) and 22.34% (116.8±1.69 Vs 150.4±4.17 U/L).

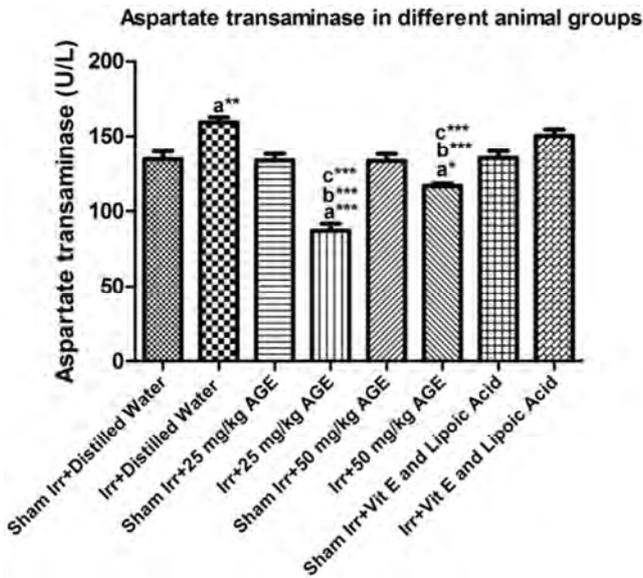


Figure 2. Effects of γ -radiation and AGE on Aspartate transaminase rate.

Each bar represents the Mean±ESM, n=5. Significant differences are:

- a*P<0.05; a**P<0.01; a***P<0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b*P<0.05; b**P<0.01; b***P<0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c*P<0.05; c**P<0.01; c***P<0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.1.3. Alkaline Phosphatase (ALP)

The effects of γ -radiation and AGE intake are shown in Figure 3. This figure reveals that alkaline phosphatase increased significantly (p<0.001) in the group "Irradiation+Distilled Water" in order of 40.96% (70.2±0.8 Vs 49.8±0.66 U/L) and significantly decreased (p<0.001) in the groups "Irradiation+25 mg / kg AGE", "Irradiation+50 mg / kg AGE" and "Irradiation+Vitamin E and Lipoic Acid" respectively in order of 36.55% (31.6±0.68 Vs 49.8±0.66 U/L), 22.89% (38.4±0.93 Vs 49.8±0.66 U/L) and 18.07% (40.8±1.11 Vs 49.8±0.66 U/L). Compared to "Irradiation+Distilled Water" group, figure 3 shows a significant decrease (p<0.001) in the rate of alkaline phosphatase in order of 54.99% (31.6±0.68 Vs 70.2±0.8 U/L) and 45.30% (38.4±0.93 Vs 70.2±0.8 U/L) in the groups receiving AGE at doses of 25 and 50 mg / kg. Compared to the positive control group

"Irradiation+Vitamin E and Lipoic Acid", the decline was not significant (P> 0.05) in the group "Irradiation+50 mg / kg AGE" and significant (p<0.001) in order of 22.55% (31.6±0.68 Vs 40.8±1.11 U/L) in the group "Irradiation+25 mg / kg AGE".

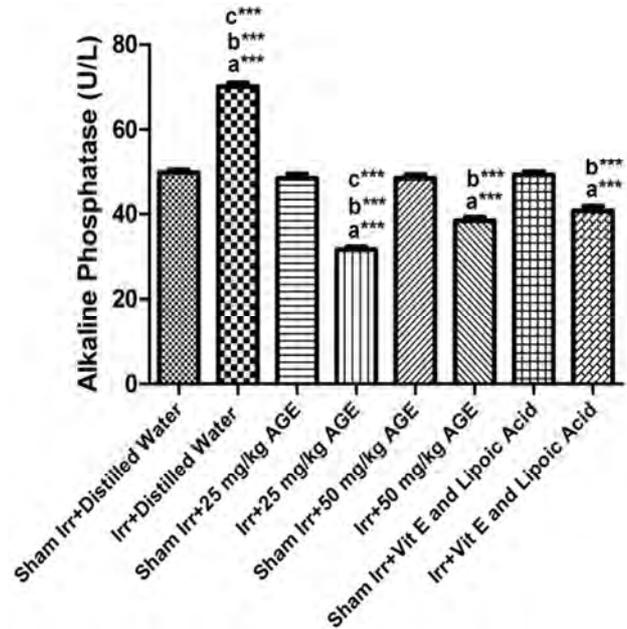


Figure 3. Effects of γ -radiation and AGE on Alkaline Phosphatase level.

Each bar represents the Mean±ESM, n=5. Significant differences are:

- a*P<0.05; a**P<0.01; a***P<0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b*P<0.05; b**P<0.01; b***P<0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c*P<0.05; c**P<0.01; c***P<0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.1.4. Serum Total Protein

It is clear from Figure 4 that the irradiation caused a significant increase (P<0.001) in total serum protein in order of 46.40% (9.57±0.28 Vs 6.53±0.65mg/dL) in the group "Irradiation+25 mg / kg AGE" and a significant decrease (P<0.01) in the range of 43.86% (3.67±0.58 Vs 6.53±0.65 mg/dL) in the "Irradiation+Distilled Water" group compared with the negative control group ("Sham Irradiation+Distilled Water"). Among the irradiated groups, a significant increase (P<0.001) in serum protein was observed in the groups "Irradiation+25 mg / kg AGE" and "Irradiation+50 mg / kg AGE" respectively, in order of 160.80% (9.57±0.28 Vs 3.67±0.58 mg/dL) and 115.05% (7.89±0.59 Vs 3.67±0.58 mg/dL). In addition, compared to the positive control group ("Irradiation+Vitamin E and Lipoic Acid"), a significant increase (P<0.001) in serum proteins was observed in animals of the group "Irradiation+25 mg / kg AGE" in order of 98.55% (9.57±0.28 Vs 4.82±0.36 mg/dL) and in order of 63.72%

(7.89 ± 0.59 Vs 4.82 ± 0.36 mg/dL) in those of the group "Irradiation+50 mg / kg AGE".

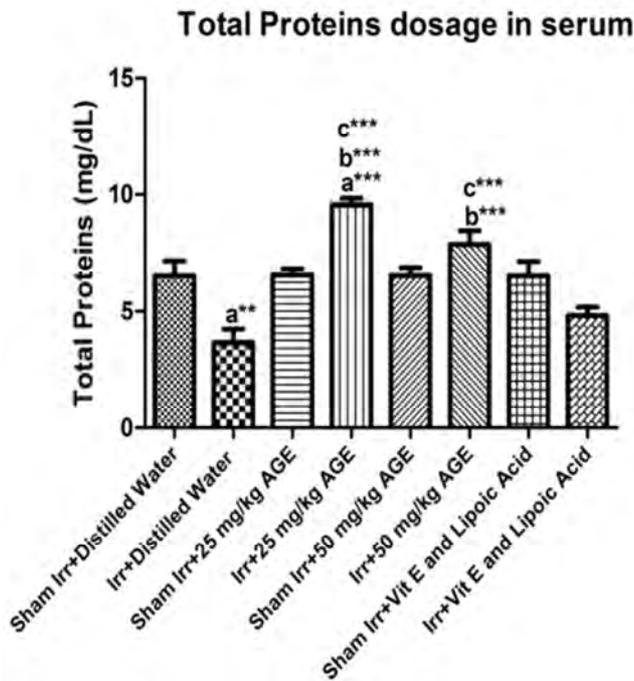


Figure 4. Effects of γ -radiation and AGE on total serum protein.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- a* P <0.05; a** P <0.01; a*** P <0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* P <0.05; b** P <0.01; b*** P <0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c* P <0.05; c** P <0.01; c*** P <0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.1.5. Total Serum Bilirubin

After irradiation, Figure 5 shows significant increase (P <0.001) in the rate of total bilirubin in animals of "Irradiation+Distilled Water" group in order of 50% (2.64 ± 0.25 Vs 1.76 ± 0.11 mg/dL), similarly, a significant decrease (P <0.001) in the range of 57.84% (0.74 ± 0.08 Vs 1.76 ± 0.11 mg/dL) in groups treated with AGE at a dose of 25 mg / kg. Moreover, this rate decreased significantly (P <0.001) in order of 71.89% (0.74 ± 0.08 Vs 2.64 ± 0.25 mg/dL) and 47.65% (1.38 ± 0.15 Vs 2.64 ± 0.25 mg/dL) in groups "Irradiation+25 mg / kg AGE" and "Irradiation+50 mg / kg AGE" compared to the group "Irradiation+Distilled Water". The rate of total bilirubin has also declined significantly (P <0.001 and P <0.01) in the groups "Irradiation 25 mg / kg AGE" and "Irradiation 50 mg / kg AGE" respectively in order of 66.15% (0.74 ± 0.08 Vs 2.19 ± 0.09 mg/dL) and 36.95% (1.38 ± 0.15 Vs 2.19 ± 0.09 mg/dL) compared to the positive control group "Irradiation+Vitamin E and Lipoic Acid".

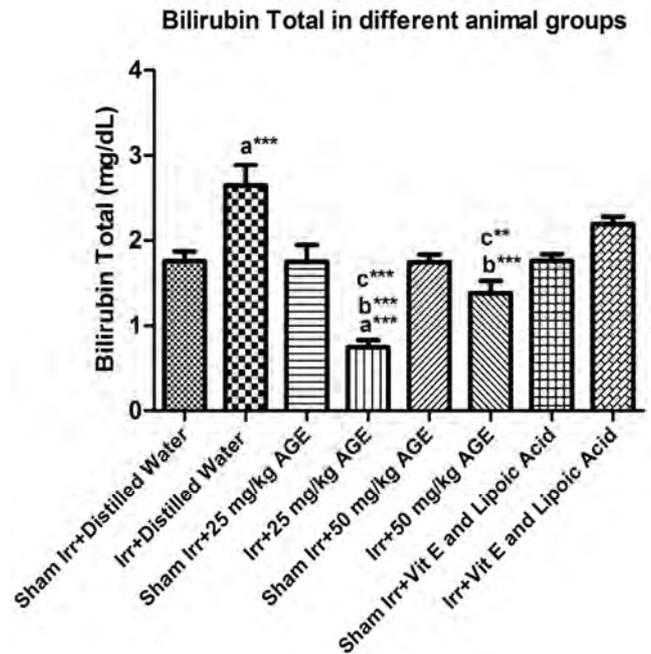


Figure 5. Effects of γ -radiation and AGE on total Bilirubin rate.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- a* P <0.05; a** P <0.01; a*** P <0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* P <0.05; b** P <0.01; b*** P <0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c* P <0.05; c** P <0.01; c*** P <0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.1.6. Direct Bilirubin

Figure 6 shows the effect of irradiation and AGE administration on direct bilirubin. Compared to the negative control group, irradiation resulted in a significant increase of direct bilirubin levels (P <0.01) in the range of 35.43% (0.60 ± 0.04 Vs 0.45 ± 0.03 mg/dL) in "Irradiation+Distilled Water" group and a significant decline (P <0.001) in the range of 68.16% (0.14 ± 0.04 Vs 0.45 ± 0.03 mg/dL) and 45.29% (0.24 ± 0.14 Vs 0.45 ± 0.03 mg/dL) in the groups "irradiation+25 mg / kg AGE" and "irradiation+50 mg / kg AGE". A significant decrease (P <0.001) in the range of 76.49% (0.14 ± 0.04 Vs 0.60 ± 0.04 mg/dL) and 59.60% (0.24 ± 0.14 Vs 0.60 ± 0.04 mg/dL) was noticed comparing groups "Irradiation+25 mg / kg AGE" and "Irradiation+50 mg / kg AGE" to the group "Irradiation+Distilled Water". The decrease in direct bilirubin rate was significant (P <0.001) in the group "Irradiation+25 mg / kg AGE" in order of 58.72% (0.14 ± 0.04 Vs 0.34 ± 0.02 mg/dL) and non-significant (P >0.05) in the group "Irradiation+50 mg / kg AGE" in order of 29.07% (0.24 ± 0.14 Vs 0.34 ± 0.02 mg/dL) compared to the positive control "Irradiation+Vitamin E and Lipoic Acid".

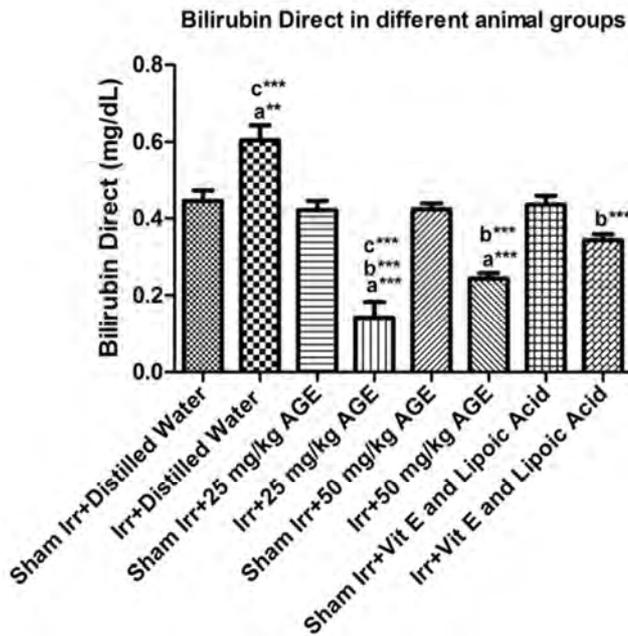


Figure 6. Effects of γ -radiation and AGE on Direct Bilirubin.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- a* P <0.05; a** P <0.01; a*** P <0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* P <0.05; b** P <0.01; b*** P <0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c* P <0.05; c** P <0.01; c*** P <0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.1.7. Unconjugated Bilirubin

Figure 7 shows the effect of irradiation and AGE intake on direct bilirubin. Indeed, compared to the negative control "Sham Irradiation+Distilled Water" a significant increase (P <0.01) was observed in the group "Irradiation+Distilled Water" in order of 54.95% (2.04 ± 0.23 Vs 1.31 ± 0.13 mg/dL); and a significant decrease (P <0.01) in the range of 54.34% (0.6 ± 0.09 Vs 1.31 ± 0.13 mg/dL) in the irradiated group AGE at a dose of 25mg / kg. The comparison of groups "Irradiation+25 mg / kg AGE" and "Irradiation+50 mg / kg AGE" with the "Irradiation+Distilled Water" group showed a significant decrease (P <0.001) in the range of 70.53% (0.6 ± 0.09 Vs 2.04 ± 0.23 mg/dL) and 44.11% (1.14 ± 0.13 Vs 2.04 ± 0.23 mg/dL) in these groups. This reduction remained significant (P <0.001et P <0.01) comparing the groups "Irradiation+25 mg / kg AGE" and "Irradiation+50 mg / kg AGE" with the group "Irradiation+Vitamin E and Lipoic Acid" respectively in order of 67.53% (0.6 ± 0.09 Vs 1.85 ± 0.09 mg/dL) and 38.42% (1.14 ± 0.13 Vs 1.85 ± 0.09 mg/dL).

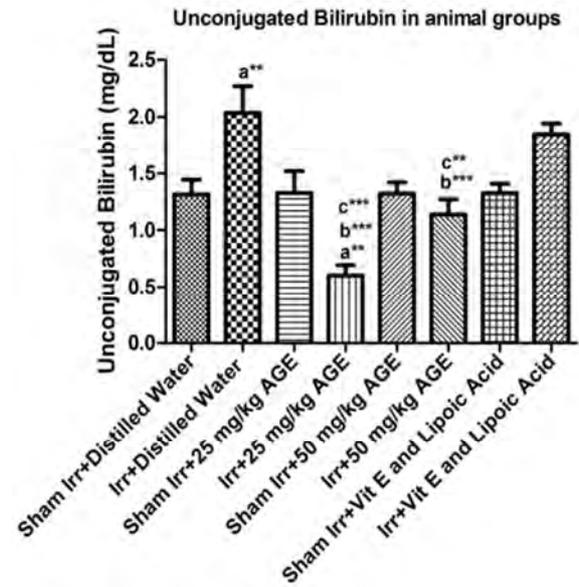


Figure 7. Effects of γ -radiation and AGE on Unconjugated Bilirubin rate.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- a* P <0.05; a** P <0.01; a*** P <0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* P <0.05; b** P <0.01; b*** P <0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c* P <0.05; c** P <0.01; c*** P <0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.2. Lipid Profile

3.2.1. Total Cholesterol

Figure 8 shows the effects of irradiation and AGE on total cholesterol over time. It is clear from this figure that irradiation resulted in a significant increase compared to the negative control ("Sham Irradiation+Distilled Water") of total cholesterol in groups "Irradiation+Distilled Water" (p <0.01) in order of 24.05% (104.2 ± 1.39 Vs 84.00 ± 4.39 mg/dL) and "Irradiation+25 mg / kg AGE" (p <0.05) in order of 8.33% (91.0 ± 5.5 Vs 84.00 ± 4.39 mg/dL). AGE intake caused a significant decrease (p <0.001) in total cholesterol respectively of about 35.12%, (67.6 ± 1.08 Vs 104.2 ± 1.39 mg/dL) and 28.21% (74.8 ± 1.93 Vs 104.2 ± 1.39 mg/dL) in the groups "Irradiation+25 mg / kg AGE" and "Irradiation+50 mg / kg AGE". Comparing these two groups to positive control "Irradiation+Vitamin E and Lipoic Acid", a significant decline in order of 25.71% (67.6 ± 1.08 Vs 91.0 ± 5.5 mg/dL) and 17.8% (74.8 ± 1.93 Vs 91.0 ± 5.5 mg/dL) was noticed in the groups "Irradiation+25 mg / kg AGE" (p <0.001) and "Irradiation+50 mg / kg AGE" (p <0.05).

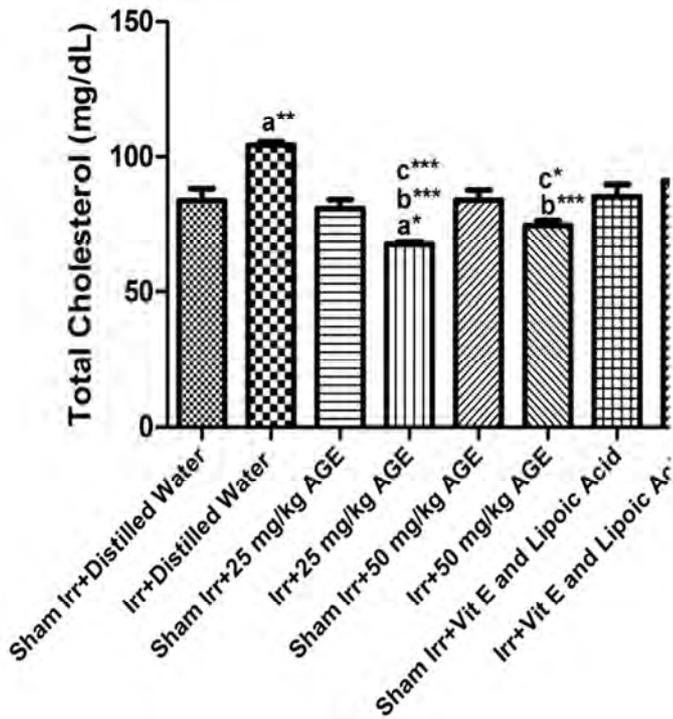


Figure 8. Effects of γ -radiation and AGE on Total Cholesterol.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- a* P <0.05; a** P <0.01; a*** P <0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* P <0.05; b** P <0.01; b*** P <0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c* P <0.05; c** P <0.01; c*** P <0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.2.2. HDL Cholesterol

The effects of γ -radiation and AGE intake on HDL cholesterol are shown in Figure 9. This figure shows that, HDL cholesterol significantly decreased (p <0.05) in order of 33.33% (18.8 ± 1.93 Vs 28.2 ± 2.85 mg/dL) in the "Irradiation+Distilled Water" group compared to the negative control ("Sham Irradiation+Distilled Water"). After irradiation, the administration of AGE lead to the increase of total cholesterol in the range of 92.55% (36.2 ± 0.86 Vs 18.8 ± 1.93 mg/dL) in the group "Irradiation+25 mg / kg AGE" (p <0.001) and to 64.89% (31 ± 2.72 Vs 18.8 ± 1.93 mg/dL) in the group "Irradiation+50 mg / kg AGE" (p <0.01) compared to the group "Irradiation+Distilled Water". This increase is significant compared to the positive control "Irradiation+Vitamin E and Lipoic Acid" in order of 77.45% (36.2 ± 0.86 Vs 20.4 ± 2.25 mg/dL) in the group "Irradiation+25 mg / kg AGE" (p <0.001) and 51.96% (31 ± 2.72 Vs 20.4 ± 2.25 mg/dL) in the group "Irradiation+50 mg / kg AGE" (p <0.05).

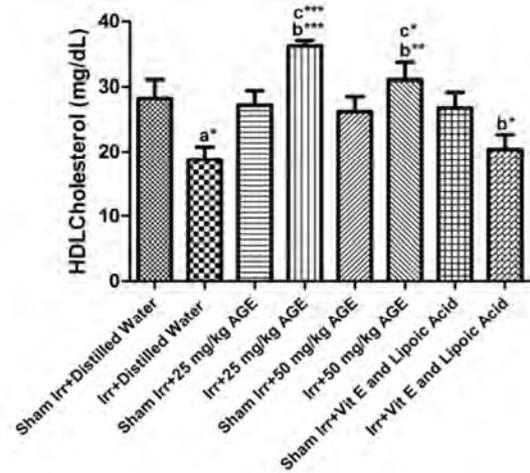


Figure 9. Effects of γ -radiation and AGE on HDL Cholesterol.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- a* P <0.05; a** P <0.01; a*** P <0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* P <0.05; b** P <0.01; b*** P <0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c* P <0.05; c** P <0.01; c*** P <0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.2.3. Triglyceride

The effects of γ -radiation and AGE administration on triglycerides have been shown in the following figure.

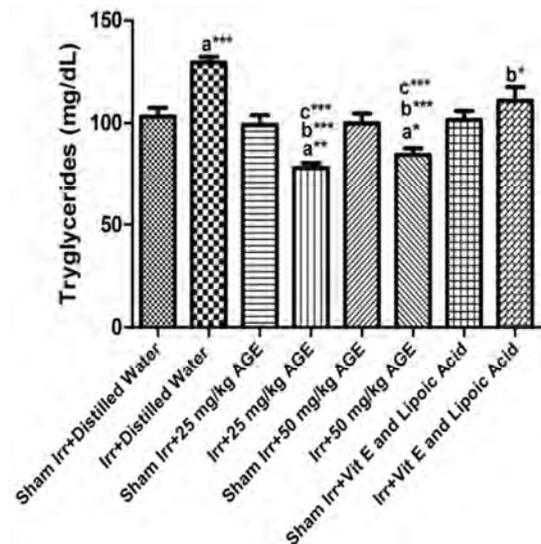


Figure 10. Effects of γ -radiation and AGE on HDL Cholesterol.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- a* P <0.05; a** P <0.01; a*** P <0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b* P <0.05; b** P <0.01; b*** P <0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or

- $c^*P<0.05$; $c^{**}P<0.01$; $c^{***}P<0.001$: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

The irradiation caused a significant increase ($p<0.001$) of triglycerides in order of 25.63% (129.4 ± 2.73 Vs 103 ± 4.28 mg/dL) in the group "Irradiation+Distilled Water" and a significant decrease in order of 24.27% (78 ± 2.41 Vs 103 ± 4.28 mg/dL) in the group "Irradiation+25 mg / kg AGE" ($p<0.01$) and in the range of 18.06% (84.4 ± 2.3 Vs 103 ± 4.28 mg/dL) in the group "Irradiation+50 mg / kg AGE" ($p<0.05$). Compared to the group "Irradiation+Distilled Water", AGE intake after γ -radiation resulted in a significant decrease ($p<0.001$) in the groups "Irradiation+25 mg / kg AGE" and "Irradiation 50 mg / kg AGE" respectively in order of 39.72%, (78 ± 2.41 Vs 129.4 ± 2.73 mg/dL) and 34.78% (84.4 ± 2.3 Vs 129.4 ± 2.73 mg/dL). This decrease was also significant ($p<0.001$) in comparing these two groups with positive control group "Irradiation+Vitamin E and Lipoic Acid" in order of 29.6% (78 ± 2.41 Vs 110.8 ± 6.58 mg/dL) and 23.83% (84.4 ± 2.3 Vs 110.8 ± 6.58 mg/dL) (Figure 10).

3.2.4. LDL Cholesterol

Figure 11 shows a significant change in LDL cholesterol after γ -radiation through an increase ($p<0.01$) in the range of 69.32% (59.6 ± 2.11 Vs 35.2 ± 5.63 mg/dL) in the "Irradiation+Distilled Water" group and a decrease ($p<0.05$) in the range of 54.55% (16 ± 1.58 Vs 35.2 ± 5.63 mg/dL) in the group "Irradiation+25 mg / kg AGE". In irradiated groups, a significant decrease was observed ($p<0.001$) in the groups receiving AGE at doses of 25 and 50 mg / kg; respectively in order of 73.15% (16 ± 1.58 Vs 59.6 ± 2.11 mg/dL) and 55.37% (26.6 ± 3.41 Vs 59.6 ± 2.11 mg/dL) compared to the group "Irradiation+Distilled Water". Comparing these two groups to irradiated positive control group receiving vitamin E and Lipoic acid shows a significant decline in order of 67.08% (16 ± 1.58 Vs 48.6 ± 5.6 mg/dL) in animals of the group "irradiation+25 mg / kg AGE" ($P<0.001$) and in the range of 45.27% (26.6 ± 3.41 Vs 48.6 ± 5.6 mg/dL) in animals of the group "irradiation+50 mg / kg AGE" ($P<0.01$).

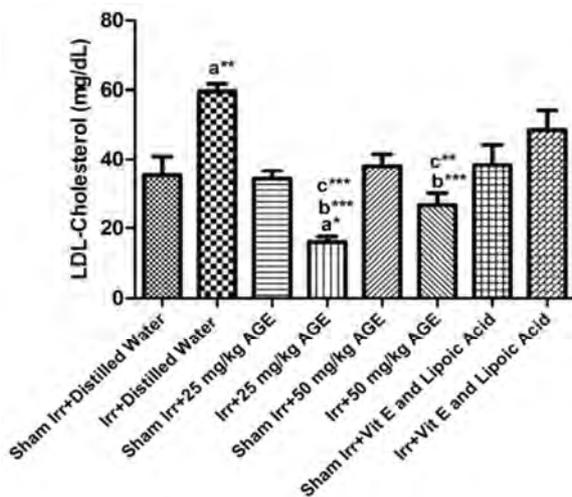


Figure 11. Effects of γ -radiation and AGE on HDL Cholesterol.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- $a^*P<0.05$; $a^{**}P<0.01$; $a^{***}P<0.001$: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- $b^*P<0.05$; $b^{**}P<0.01$; $b^{***}P<0.001$: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- $c^*P<0.05$; $c^{**}P<0.01$; $c^{***}P<0.001$: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.3. Creatinine

The effects of radiation and AGE on creatinine levels are shown in Figure 12. Comparison of the groups with the negative control "Sham Irradiation+Distilled Water" revealed a significant increase of creatinine level ($P<0.01$) in order of 51.65% (1.84 ± 0.14 Vs 1.21 ± 0.05 mg/dL) in the group "Irradiation+Distilled Water" while a significant decrease of the range of 53.30% (0.57 ± 0.07 Vs 1.21 ± 0.05 mg/dL) occurred in the group "Irradiation+25 mg / kg AGE". Furthermore, a significant decrease ($P<0.001$) in the creatinine level was observed in the animals irradiated and receiving AGE at doses of 25 mg / kg and 50 mg / kg compared to those of group "Irradiation+Distilled Water". This decrease was respectively in the range of 69.21% (0.57 ± 0.07 Vs 1.84 ± 0.14 mg/dL) and 55.82% (0.81 ± 0.16 Vs 1.84 ± 0.14 mg/dL). Similarly, compared to positive control irradiated receiving Vitamin E and Lipoic Acid, a significant decline of creatinine level ($P<0.001$) was also observed in the group "Irradiation+25 mg / kg AGE" respectively in order of 39.66% (0.57 ± 0.07 Vs 0.94 ± 0.14 mg/dL) and a non-significant reduction ($P> 0.05$) in the range of 13.43% (0.81 ± 0.16 Vs 0.94 ± 0.14 mg/dL) observed in the group "Irradiation+50 mg / kg AGE".

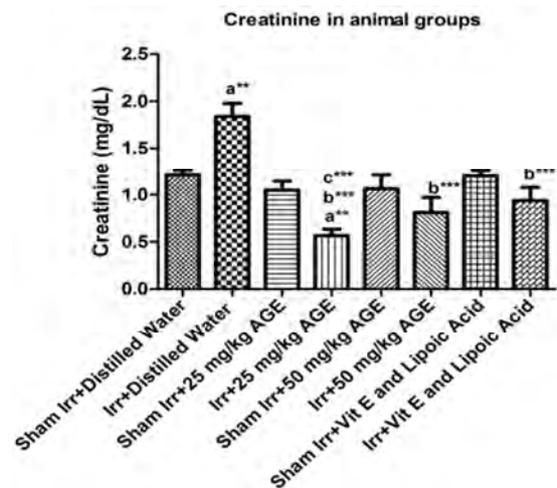


Figure 12. Effects of γ -radiation and AGE on creatininerate.

Each bar represents the Mean \pm ESM, n=5. Significant differences are:

- $a^*P<0.05$; $a^{**}P<0.01$; $a^{***}P<0.001$: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or

- $b^*P<0.05$; $b^{**}P<0.01$; $b^{***}P<0.001$: when comparing groups to “Irradiation+Distilled Water Group” (b) or
- $c^*P<0.05$; $c^{**}P<0.01$; $c^{***}P<0.001$: when comparing groups to “Irradiation+Vitamin E and Lipoic Acid Group” (c).

3.4. Oxidative Stress Assessment in Tissue Homogenates

3.4.1. Reduced Glutathione (GSH)

Irradiation and AGE intake have led to a significant

decrease in glutathione reduced levels in the groups “Irradiation+Distilled Water” and “Irradiation+Vitamin E and Lipoic Acid” and a significant increase in groups “Irradiation+25 mg/kg AGE” and “Irradiation+50 mg/kg AGE”. The decline was most significant in the group “Irradiation+Distilled Water” than in the group “Irradiation+Vitamin E and Lipoic Acid” and the increase more important in the group “Irradiation+25 mg/kg AGE” than in the group “Irradiation+50 mg/kg AGE” (Table 1).

Table 1. Effects of γ -radiation and AGE on glutathione reduced rate ($\mu\text{mol}/\text{mg}$ of tissue).

Organs	Sham Irradiation+Distilled Water	Irradiation+Distilled Water	Sham Irradiation+25 mg/kg AGE	Irradiation+25 mg/kg AGE
Lungs	126.9±2.20	58.46±5.74 a ^{***} , b ^{***} , c ^{***}	143.65±5.40	205.27±2.97 a ^{***} , b ^{***} , c ^{***}
Testis	29.12±2.4	11.99±1.46 a ^{***} , c ^{***}	32.35±2.02	42.14±1.38 a ^{**} , b ^{***} , c ^{***}
Brain	25.09±0.62	12.13±1.43 a ^{**} , c [*]	25.77±1.49	37.21±4.09 a ^{**} , b ^{***} , c ^{***}
Vertebrum	22.16±2.7	13.82±1.38	23.65±3.81	31.24±2.28 b ^{***} , c [*]
Liver	151.96±2.54	108.85±3.46 a ^{***}	156.78±5.36	251.12±5.18 a ^{***} , b ^{***} , c ^{***}
kidney	145.22±1.46	62.15±2.94 a ^{***} , c ^{***}	126.15±1.33	175.19±2.38 a ^{***} , b ^{***} , c ^{***}
Spleen	143.5±3.7	82.78±4.7 a ^{***} , c ^{***}	143.85±2.38	209.87±2.03 a ^{***} , b ^{***} , c ^{***}
Heart	141.22±2.26	58.96±3.89 a ^{***} , c ^{***}	141.65±2.23	290.06±2.27 a ^{***} , b ^{***} , c ^{***}
Aorta	84.96±5.95	38.96±3.28 a ^{***} , c ^{**}	80.53±4.85	119.71±5.12 a ^{***} , b ^{***} , c ^{***}

Table 1. Continue.

Sham Irradiation+50 mg/kg AGE	Irradiation+50 mg/kg AGE	Sham Irradiation+Vitamin E and Lipoic Acid	Irradiation+Vitamin E and Lipoic Acid
146.26±2.93	164.61±4.85 a ^{***} , b ^{***} , c ^{***}	141.44±5.36	117.26±4.31 b ^{***} ,
30.56±2.47	35.55±3.40 b ^{***} ,	31.32±2.31	27.84±2.41 b ^{***} ,
25.62±1.3	30.6±1.01 b ^{***} , c [*]	25.49±1.02	20.93±3.87 b [*]
21.5±2.98	26.46±2.01 b ^{**}	21.15±3.13	19.57±1.53
166.29±5.27	192.43±5.36 a ^{***} , b ^{***} , c ^{***}	133.81±5.39	120.62±4.94 a ^{***} ,
119.28±2.56	146.06±3.89 b ^{***} , c ^{***}	118.93±3.27	91.28±4.97 a ^{***} , b ^{***} ,
142.24±1.91	167.42±4.22 a ^{***} , b ^{***} , c ^{***}	142.30±4.05	107.81±4.62 a ^{***} , b ^{***}
142.75±3.51	210.62±3.68 a ^{***} , b ^{***} , c ^{***}	148.19±2.8	84.94±3.79 a ^{***} , b ^{***} , c ^{***}
81.76±3.46	96.06±6.39 b ^{***} , c ^{***}	80.21±2.66	64.91±6.51 a [*] , b ^{**} ,

Each bar represents the Mean±ESM, n=5. Significant differences are:

- $a^*P<0.05$; $a^{**}P<0.01$; $a^{***}P<0.001$: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- $b^*P<0.05$; $b^{**}P<0.01$; $b^{***}P<0.001$: when comparing groups to “Irradiation+Distilled Water Group” (b) or
- $c^*P<0.05$; $c^{**}P<0.01$; $c^{***}P<0.001$: when comparing groups to “Irradiation+Vitamin E and Lipoic Acid Group” (c).

3.4.2. Superoxide Dismutase (SOD)

Irradiation and AGE administration induced a significant decrease in superoxide dismutase levels in groups “Irradiation+Distilled Water” and “Irradiation+Vitamin E and Lipoic Acid” and a significant increase in groups “Irradiation+25 mg/kg AGE” and “Irradiation+50 mg/kg AGE”. The decline was most significant in the group “Irradiation+Distilled Water” than in the group “Irradiation+Vitamin E and Lipoic Acid” and the increase more important in the group “Irradiation+25 mg/kg AGE” than in the group “Irradiation+50 mg/kg AGE” (Table 2).

Table 2. Effects of γ -radiation and AGE on Superoxide Dismutase rate ($\mu\text{mol}/\text{mg}$ of proteins).

Organs	Sham Irradiation+Distilled Water	Irradiation+Distilled Water	Sham Irradiation+25 mg/kg AGE	Irradiation+25 mg/kg AGE
Lungs	24.4±0.41	18.38±0.15 a ^{***} , b ^{***} , c ^{***}	24.45±0.42	34.43±0.32 a ^{***} , b ^{***} , c ^{***}
Testis	49.6±0.51	40.2±0.37 a ^{***} , c ^{***}	50.73±0.21	81.88±0.53 a ^{***} , b ^{***} , c ^{***}
Brain	76.83±0.70	55.15±0.16 a ^{***} , c [*]	75.7±0.53	112.65±0.25 a ^{***} , b ^{***} , c ^{***}
Vertebrum	14.9±0.62	8.1±0.42 a ^{***} , c ^{***}	14.1±0.50	25.2±0.57 a ^{***} , b ^{***} , c ^{***}
Liver	17.18±0.67	13.38±0.69 a ^{***}	17.53±0.46	26.63±0.48 a ^{***} , b ^{***} , c ^{***}
kidney	17.63±0.54	12.5±0.67 a ^{***}	17.55±0.61	23.23±0.61 a ^{***} , b ^{***} , c ^{***}
Spleen	45.93±0.55	32.68±0.98 a ^{***} , c ^{***}	52.8±0.41	96.13±0.49 a ^{***} , b ^{***} , c ^{***}
Heart	50.39±0.39	34.3±0.75 a ^{***} , c ^{***}	57.63±0.39	90.65±0.32 a ^{***} , b ^{***} , c ^{***}
Aorta	30.09±0.49	22.03±0.50 a ^{***} , c ^{***}	33.71±0.62	49.45±0.43 a ^{***} , b ^{***} , c ^{***}

Table 2. Continue.

Sham Irradiation+50 mg/kg AGE	Irradiation+50 mg/kg AGE	Sham Irradiation+Vitamin E and Lipoic Acid	Irradiation+Vitamin E and Lipoic Acid
24.35±0.19	29.08±0.12 a***, b***, c***	24.4±0.58	20.78±0.48 a***, b***, c***
52.43±0.39 a***,	60.5±0.14 a***, b***, c***	49.75±0.14	42.95±0.54 a***, b***, c***
74.8±0.60 a*,	89.03±0.59 a***, b***, c***	70.93±0.13 a***,	53.15±0.53 a***, b*,
14.16±0.53	19.35±0.23 a***, b***, c***	14.45±0.33	11.05±0.23 a***, b***
17.48±0.48	21.7±0.39 a***, b***, c***	17.43±0.24	15.28±0.38
17.3±0.71	19.85±0.51 b***, c***	16.93±0.63	14.23±0.62 a**,
56.23±0.63	78.28±0.54 a***, b***, c***	57.25±0.45	43.05±0.38 a**, b***, c***
57.6±0.52	70.68±0.25 a***, b***, c***	54.13±0.48	43.35±0.67 a***, b***
34.12±0.35	40.34±0.57 a***, b***, c***	32.05±0.28	26.8±0.33 a***, b***,

Each bar represents the Mean±ESM, n=5. Significant differences are:

- a*P<0.05; a**P<0.01; a***P<0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b*P<0.05; b**P<0.01; b***P<0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c*P<0.05; c**P<0.01; c***P<0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.4.3. Catalase (CAT)

Irradiation and AGE administration have led to a significant decrease in catalase levels in groups "Irradiation+Distilled Water" and "Irradiation+Vitamin E and Lipoic Acid" and a significant increase in groups "Irradiation+25 mg/kg AGE" and "Irradiation+50 mg/kg AGE". The decline was most significant in the group "Irradiation+Distilled Water" than in the group "Irradiation+Vitamin E and Lipoic Acid" and the increase more important in the group "Irradiation+25 mg/kg AGE" than in the group "Irradiation+50 mg/kg AGE" (Table 3).

Table 3. Effects of γ -radiation and AGE on Catalase rate (μ moles H_2O_2 /minute/mg of protein).

Organs	Sham Irradiation+Distilled Water	Irradiation+Distilled Water	Sham Irradiation+25 mg/kg AGE	Irradiation+25 mg/kg AGE
Lungs	3.50±0.32	2.13±0.18 a*,	3.52±0.27	4.74±0.41 a*, b***, c***
Testis	6.84±0.63	5.36±0.18 a**,	6.82±0.37	9.13±0.57 b***, c***
Brain	12.48±0.78	9.02±0.92 a*,	12.49±0.84	20.17±0.77 a***, b***, c***
Vertebrum	9.65±0.34	5.56±0.67 a**,	9.69±0.86	14.19±0.95 a**, b***, c***
Liver	5.59±0.48	2.93±0.74 a*,	5.58±0.69	9.66±0.36 a***, b***, c***
kidney	3.79±0.28	1.99±0.15 a***, c**	3.88±0.32	5.53±0.14 a***, b***, c***
Spleen	3.23±0.34	1.85±0.24 a*,	3.28±0.53	4.42±0.26 b***, c**
Heart	7.18±0.40	4.00±0.36 a**, c*	7.26±0.39	9.42±0.67 a*, b***, c**
Aorta	3.15±0.39	2.41±0.10	3.18±0.37	5.13±0.15 a***, b***, c***

Table 3. Continue.

Sham Irradiation+50 mg/kg AGE	Irradiation+50 mg/kg AGE	Sham Irradiation+Vitamin E and Lipoic Acid	Irradiation+Vitamin E and Lipoic Acid
3.51±0.29	4.04±0.26 b***, c**	3.51±0.43	2.45±0.15
6.82±0.49	7.93±0.30 b**, c*	6.81±0.25	5.88±0.56
12.49±0.91	16.01±0.79 a*, b***, c***	12.67±0.55	9.91±0.57
9.67±0.64	11.79±0.97 b***, c***	9.65±0.82	6.03±0.69 a*,
5.65±0.15	7.15±0.97 b***, c*	5.53±0.14	4.75±0.50
3.85±0.20	4.47±0.41 b***,	3.73±0.43	3.41±0.09 b**,
3.26±0.09	3.65±0.40 b**,	3.23±0.21	2.79±0.24
7.73±0.77	8.24±0.20 b***,	7.08±0.46	6.37±0.86 b*,
3.16±0.37	4.13±0.39 b**, c**	3.13±0.14	2.65±0.34

Each bar represents the Mean±ESM, n=5. Significant differences are:

- a*P<0.05; a**P<0.01; a***P<0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b*P<0.05; b**P<0.01; b***P<0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c*P<0.05; c**P<0.01; c***P<0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.4.4. Nitrite (NO^2)

Irradiation and AGE administration induced a significant increase in nitrite levels in groups "Irradiation+Distilled Water" and "Irradiation+Vitamin E and Lipoic Acid" and a significant decrease in groups "Irradiation+25 mg/kg AGE" and "Irradiation+50 mg/kg AGE". The increase was most significant in the group "Irradiation+Distilled Water" than in the group "Irradiation+Vitamin E and Lipoic Acid" and the decline more important in the group "Irradiation+25 mg/kg AGE" than in the group "Irradiation+50 mg/kg AGE" (Table 4).

Table 4. Effects of γ -radiation and AGE on Nitrite rate ($\mu\text{mol}/\text{mL}$).

Organs	Sham Irradiation+Distilled Water	Irradiation+Distilled Water	Sham Irradiation+25 mg/kg AGE	Irradiation+25 mg/kg AGE
Lungs	0.115±0.015	0.163±0.006	0.108±0.018	0.038±0.007 a**, b***, c***
Testis	0.035±0.004	0.054±0.006	0.034±0.006	0.014±0.002 a*, b***, c**
Brain	0.025±0.002	0.034±0.004	0.025±0.002	0.014±0.001 a*, b***, c***
Vertebrum	0.058±0.007	0.096±0.006 a*,	0.051±0.013	0.031±0.001 b***, c*
Liver	0.135±0.008	0.175±0.008 a*	0.133±0.002	0.054±0.014 a***, b***, c***
kidney	0.158±0.022	0.247±0.004 a**, c*	0.15±0.009	0.065±0.012 a**, b***, c***
Spleen	0.068±0.008	0.109±0.002 a***, b***, c**	0.069±0.004	0.032±0.002 a***, b***, c***
Heart	0.76±0.03	1.18±0.13 a*,	0.74±0.12	0.38±0.02 a*, b***, c**
Aorta	0.119±0.025	0.197±0.025 a*,	0.113±0.026	0.055±0.003 b***, c**

Table 4. Continue.

Sham Irradiation+50 mg/kg AGE	Irradiation+50 mg/kg AGE	Sham Irradiation+Vitamin E and Lipoic Acid	Irradiation+Vitamin E and Lipoic Acid
0.112±0.016	0.079±0.013 b***,	0.115±0.012	0.127±0.015
0.034±0.009	0.030±0.003 b*,	0.037±0.003	0.041±0.004
0.025±0.004	0.020±0.003 b**,	0.026±0.001	0.029±0.001
0.053±0.011	0.041±0.008 b***,	0.058±0.003	0.067±0.007
0.134±0.003	0.097±0.012 a*, b***, c***	0.137±0.01	0.152±0.005
0.152±0.022	0.098±0.025 b***, c**	0.157±0.006	0.182±0.005 b*,
0.069±0.005	0.055±0.006 b***, c**	0.068±0.004	0.081±0.005 b**,
0.72±0.12	0.5±0.05 b***, c*	0.72±0.12	0.91±0.09
0.114±0.003	0.078±0.008 b***,	0.117±0.002	0.144±0.014

Each bar represents the Mean±ESM, n=5. Significant differences are:

- a*P<0.05; a**P<0.01; a***P<0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b*P<0.05; b**P<0.01; b***P<0.001: when comparing groups to "Irradiation+Distilled Water Group" (b) or
- c*P<0.05; c**P<0.01; c***P<0.001: when comparing groups to "Irradiation+Vitamin E and Lipoic Acid Group" (c).

3.4.5. Malondialdehyde (MDA)

Irradiation and AGE administration have led to a significant increase in Malondialdehyde levels in groups "Irradiation+Distilled Water" and "Irradiation+Vitamin E and Lipoic Acid" and a significant decrease in groups "Irradiation+25 mg/kg AGE" and "Irradiation+50 mg/kg AGE". The increase was most significant in the group "Irradiation+Distilled Water" than in the group "Irradiation+Vitamin E and Lipoic Acid" and the decrease more significant in the group "Irradiation+25 mg/kg AGE" than in the group "Irradiation+50 mg/kg AGE" (Table 5).

Table 5. Effects of γ -radiation and AGE on Malondialdehyde rate ($\mu\text{mol}/\text{mg}$ of tissue).

Organs	Sham Irradiation+Distilled Water	Irradiation+Distilled Water	Sham Irradiation+25 mg/kg AGE	Irradiation+25 mg/kg AGE
Lungs	1.34±0.19	1.81±0.05a*, c**	1.33±0.14	0.84±0.11 a*, b***,
Testis	1.09±0.17	1.46±0.05	1.09±0.15	0.36±0.15 a*, b***, c**
Brain	1.72±0.15	2.09±0.23	1.71±0.10	1.12±0.05 a**, b***, c***
Vertebrum	4.54±0.84	6.46±0.59	4.29±0.84	1.71±0.26 a**, b***, c***
Liver	1.09±0.17	1.46±0.05	1.09±0.15	0.36±0.15 a*, b***, c**
kidney	2.89±0.23	3.63±0.39	2.79±0.23	1.83±0.27 b***, c**
Spleen	2.20±0.10	3.25±0.12 a***, c**	2.18±0.07	1.15±0.05 a***, b***, c***
Heart	5.68±0.12	8.37±0.70 a***,	5.63±0.19	2.45±0.18 a***, b***, c***
Aorta	2.15±0.05	3.34±0.25 a***	2.14±0.07	0.93±0.17 a***, b***, c***

Table 5. Continue.

Sham Irradiation+50 mg/kg AGE	Irradiation+50 mg/kg AGE	Sham Irradiation+Vitamin E and Lipoic Acid	Irradiation+Vitamin E and Lipoic Acid
1.33±0.12	1.11±0.13b**,	1.34±0.09	1.19±0.03 b**,
1.09±0.11	0.80±0.19 b*,	1.08±0.20	1.20±0.18
1.72±0.06	1.51±0.08 b**,	1.71±0.05	1.89±0.07
4.25±0.36	3.47±0.18 b**,	4.38±0.18	5.31±0.20
1.09±0.11	0.80±0.19 b*,	1.08±0.20	1.20±0.18
2.76±0.26	2.32±0.14 b*,	2.82±0.45	3.40±0.19
2.19±0.14	1.89±0.22 b***, c**	2.20±0.15	2.54±0.12 b**,
5.57±0.21	4.74±0.40 b***, c***	5.56±0.24	7.01±0.51
2.12±0.08	1.81±0.32 b***, c**	2.12±0.09	2.75±0.26

Each bar represents the Mean±ESM, n=5. Significant differences are:

- a*P<0.05; a**P<0.01; a***P<0.001: when comparing groups to control (Sham Irradiation+Distilled Water) (a) or
- b*P<0.05; b**P<0.01; b***P<0.001: when comparing groups to “Irradiation+Distilled Water Group” (b) or
- c*P<0.05; c**P<0.01; c***P<0.001: when comparing groups to “Irradiation+Vitamin E and Lipoic Acid Group” (c).

4. Discussion

In this study, male rats were used to investigate the possible effect of AGE administration against the deleterious consequences produced by γ -radiation. The present study indicated that exposure of rats to 4.5Gy γ -radiation induced an increase in ALP activity in liver tissue. The same results were obtained by Sanaa *et al.* on the first and seventh day post-exposure day using a dose of 6.5Gy [25]. The increase observed can be due to the release of ALP from different tissues associated with the obstruction of the blood stream to the liver [26]. The change in the tissue permeability due to irradiation could enhance the release of the most sensitive biomarker enzymes from their subcellular sites of production to extracellular process and consequently to blood circulation [27-28]. Radiation exposure induced changes in the amino acid residue and catalytic activity of ALP explaining the changes noticed [29-30]. Furthermore, the liver always react to an injury by synthesizing more enzymes which enter the circulation, raising the enzyme level in serum [31].

The male rats irradiated showed elevation of serum levels of ALT, AST, ALP and Bilirubin (Total Serum Bilirubin, Direct Bilirubin and Unconjugated Bilirubin) as compared with saline control group. In agreement with our results, El-Kafif *et al.* explained that this increase may be ascribed to the radiation-induced damage to hepatic parenchymal cells as well as extra hepatic tissues with a subsequent release of the enzymes into the blood stream [32]. It may also be attributed to the structural damage in spleen, lymphnodes and mature lymphocytes [33]. Moreover, the destruction of erythrocytes due to ionizing radiation and the release of their enzymes cannot be excluded as a causative factor for the rise in these enzymes [34]. The increased activity of serum ALP by gamma-irradiation agrees with Tabachnick *et al.* who attributed it to the enzyme release from the tissues to the blood stream or to liver disturbances [35], particularly due to defects in cell membrane permeability [36]. The variation in transaminases activities may be due to certain damage in some tissue like heart, liver, kidney and skeletal muscles. Fahim *et al.* mentioned that whole body gamma-irradiation of rats showed significant changes in the activities of transaminases which are dependent on the time lapses after irradiation and the type of tissue containing the enzyme [37]. These results may be attributed to the state of hypoxia of parenchyma for contracting fibrous tissue and the increased

permeability of hepatic cell membrane due to radiation exposure with release of ALT enzyme to circulation. The elevation in the serum activity of ALT, a liver cytoplasmic enzyme indicates anecrotic lesions in the liver cells [38]. It is also a sign of liver parenchymal cell destruction induced by whole body gamma irradiation [39].

The clinical and diagnostic values associated with changes in blood enzymes concentrations such as AST, ALT, ALP and bilirubin have long been recognized [40]. Increased levels of these diagnostic markers of hepatic function in irradiated rats are implicative of the degree of hepatocellular dysfunction caused by the radiation [39]. The increase in the levels of serum bilirubin reflected the depth of jaundice and the increase in transaminases was the clear indication of cellular leakage and loss of functional integrity of the cell membrane [41]. Omran *et al.* revealed that significant elevation in AST, ALT, ALP and bilirubin were recorded post exposure to gamma-radiation which reflects detectable changes in liver functions [42]. Such elevation was in agreement with [43]. They reported that this elevation is directly due to the interaction of cellular membranes with gamma-rays or through an action of free radicals produced by this radiation.

Oral administration of AGE one hour after irradiation on day 6 after acclimatization significantly reduced radiation toxic effect on serum levels of AST, ALT, ALP and Bilirubin (Total Serum Bilirubin, Direct Bilirubin and Unconjugated Bilirubin) compared to untreated rats. The reduction was significant in groups receiving AGE at a dosage of 25 mg/kg compare to those receiving it at a dosage of 50 mg/kg or to those receiving Vitamin E and Lipoic Acid after irradiation. In agreement with results of the present study, some authors revealed that administration of AGE caused a significant reduction in the serum levels of AST and ALT in rats treated with cadmium [44]; lead [45] and doxorubicin [46]. The reduction of the liver enzymes in AGE pre-treated rats may be due to its antioxidant effect that reduces the free radical-induced oxidative damage in the liver, there by stabilizing the membrane permeability and reducing the leakage of enzymes into the blood [47]. Similarly, reduction in serum levels of AST and ALT enzymes was reported with administration of other herbal plants [48]. Garlic also exhibits a wide range of properties including hepatoprotective effects [49-50]. Earlier studies revealed that AGE protects against liver injuries with SAC and SAMC [51-53].

An important function of serum protein synthesized and secreted by several cell types is the maintenance of the normal distribution of body water by controlling the osmotic balance between the circulating blood and the membrane of tissues, and the transport of lipids, hormones and inorganic materials [54-55]. Blood serum protein is a fairly labile biochemical system, precisely reflecting the condition of the organism and the changes happening to it under influence of internal and external factors [56].

The present study revealed that, there was significant decrease in serum total proteins post irradiation probably due

to the damage of vital biological processes or to changes in the permeability of liver, kidney and other tissues resulting in leakage of protein via the kidney [57-60]. The slow rate in synthesis of all protein fractions after irradiation can explain the decrease in blood total protein [61-62]. This decrease coincides with the decrease in serum t-protein reported by other workers in irradiated rats, which may be due to radiation damage to the liver [63]. The decrease in protein in irradiated rats might be the result of either damage of biological membranes or to changes in the permeability of the liver [32, 64-65]. Several investigations indicated that exposure to radiation increases free radical activity. The generation of free radicals is considered to be the primary cause of damaging effects. Radiation induced lipid peroxidation reduce protein synthesis and cause disturbances in the enzyme activity of the liver [66].

In the present study, there was a decrease in contents of total proteins in serum of rats irradiated with gamma radiation, indicating liver injury [67-68]. These results are in accordance with other studies using high-energy radiation from cobalt source [69]. Therefore, it is suggested that oxidative stress as a result of gamma-irradiation is linked to the organ damage following exposure to ionizing radiation. Kempner explained that this decrease in proteins level may be due to gamma-irradiation can damage or inactivate proteins by two different mechanisms. First, it can rupture the covalent bonds in target protein molecules as a direct result of a photon depositing energy into the molecule. Second, it can act indirectly, link with a water molecule, producing free radicals and other non-radical reactive oxygen species that are in turn responsible for most (99.9%) of the protein damage [55, 70].

Oral administration of AGE one hour after irradiation on day 6 after acclimatization has caused a significant increase in serum total proteins in AGE groups. The increase was more important in "Irradiation+25 mg/kg AGE" group than in "Irradiation+50 mg/kg AGE" group or "Irradiation+Vitamin E and Lipoic Acid". AGE and SAC were shown to scavenge ROS [71] and to inhibit lipid peroxide formation in several studies [10, 72]. These antioxidant effects can be due to allixin, SAC, SMAC and diallylpolysulfides, whose radical-scavenging action increased with the number of sulfur atoms [73]. Or, due to N-fructosyl arginine and N-fructosyl glutamate which showed antioxidant effects by spin resonance spectroscopy [9].

The deleterious effects of ionizing radiation on biological system are mainly mediated through the generation of reactive oxygen species (ROS) in cells as a result of water radiolysis [74]. ROS and oxidative stress may contribute to metabolic and morphologic changes in human and animals [75]. The uncontrolled ROS production could induce modification of lipids [74, 76]. Lipid profile includes total lipids as cholesterol, triglycerides and lipoproteins as HDL-C, LDL-C [77]. Most lipids circulate through the bloodstream as lipoproteins. Lipoproteins are lipid-protein complexes that contain large insoluble glycerides and cholesterol with a superficial coating of phospholipids and

proteins synthesized in the liver [78]. All lipoproteins carry all types of lipid, but in different proportions, so that the density is directly proportional to the protein content and inversely proportional to the lipid content [79].

In the present study, γ -radiation induced decrease in HDL Cholesterol level and significant increase in total cholesterol, triglycerides and LDL cholesterol level. These results are in agreement with those of Markevich and Kolomiitseva, Zahran *et al.*, Abbady *et al.*, Kafafy *et al.*, Said and Azab and Nada who reported an increase of lipids in plasma level of rats post irradiation [80-84]. They also attributed the hypercholesterolemia conditions to the stimulation of cholesterol synthesis in the liver after gamma-irradiation. Roushdy *et al.* found that the elevation in cholesterol level might be due to disturbance in the metabolism of bile pigments and lipid due to liver damage resulting from radiation exposure [85]. Bok, *et al.* attributed this hypercholesterolemia to the increase of activation of β -hydroxy-3-methyl-glutaryl CoA (HMG-CoA) reductase enzyme, the key regulatory enzyme in the reduction of the overall process of cholesterol synthesis [86-87]. Sedlakova *et al.* explained that the increase in serum triglyceride level after irradiation might result from inhibition of lipoprotein lipase activity, leading to reduction in uptake of triacylglycerols [88]. Mahmoud attributed the hyperlipidemic state under the effect of gamma-irradiation, to the stimulation of liver enzymes responsible for the biosynthesis of fatty acids by gamma radiation and mobilization of fats from adipose tissue to blood stream [89]. While Chaialo *et al.* and Feurgard *et al.* suggested that the degeneration effect on hepatic cell and biomembranes led to acceleration in lipid metabolism after irradiation resulting in releasing of structural phospholipids [90-91]. Also the increase in serum triglycerides level after irradiation might result from inhibition of lipoprotein lipase activity, leading to reduction in the uptake of triacylglycerols [88] in addition to decreased fatty acid oxidation [92].

The increase in cholesterol and triglycerides levels observed in this study after exposure to gamma radiation compared to control confirms previous reports which revealed that whole body exposure to gamma radiation induces hyperlipidemia [93-94]. They reported that increased level of serum cholesterol fractions was probably due to its release from tissues, destruction of cell membranes and increase rate of cholesterol biosynthesis in the liver and other tissues. The hyperlipidemic state observed after irradiation could be attributed to the mobilization of fats from the adipose tissues to the blood stream [95] in addition to mitochondrial dysfunction [96]. Chrysohoou *et al.* observed that total serum phospholipids, their fractions and cholesterol were significantly changed after radiation exposure [97]. Furthermore, some serum lipid polyunsaturated fatty acids were significantly altered, since these alterations are a sign of lipid peroxidation [93]. The elevation of serum triglycerides after exposure of rats to gamma irradiation comes in accordance with Ahmed and Abdel-Magied, [98-99]. The elevation in serum triglycerides may be related to destruction

of lipoprotein lipase activity in adipose tissue post-irradiation [100].

Oral administration of AGE one hour after irradiation on day 6 after acclimatization has caused a significant reduction in plasma TC, TG, LDL-Cholesterol and significantly increased plasma HDL-Cholesterol. These results were more important with AGE than with Vitamin E and Lipoic Acid and the effects observed have been more pronounced with the lower dose of AGE (25 mg/kg) than with the higher dose (50 mg/kg). Suggesting in accordance with Khalid S. Al-Numair that garlic extracts may have a beneficial effect on the blood lipid profile by improving lipid metabolic indices in rats' plasma [101]. The results of this study confirm the earlier hypolipidemic effects reported for garlic [102-111]. Moreover, previous studies have shown that ingestion of garlic appears to inhibit hepatic fatty acid synthesis by lowering key enzymes activities in supplying substrates, thus reducing lipid accumulation in the liver and TG level in plasma [112]. With respect to the cholesterol lowering property of garlic, it has been suggested that some constituents of garlic may act as inhibitors for some enzymes such as hydroxyl methyl glutaryl CoA reductase, which participates in cholesterol synthesis [113-114].

The increase in blood creatinine has been reported after exposure to irradiation and secondary to renal damage [91, 115-118]. Serum creatinine elevation by irradiation was attributed by El-Kashef and Saadato its interaction with the creatinine sites of biosynthesis [119]. The current study revealed an elevation in creatinine levels in response to whole body γ -radiation. According to Konnova *et al* [120] and Yildiz *et al* [121], the elevation of creatinine post irradiation might be due to the back leakage of the filtered creatinine, which may occur through the damaged tubular epithelium along the concentration gradient established by salt and water reabsorption [122].

The oral administration of AGE to rats one hour after irradiation on day 6 after acclimatization clarified that serum concentration of creatinine were significantly decreased. These effects have been more pronounced with AGE than with Vitamin E and Lipoic Acid administration. The reduction was significant in groups receiving AGE at a dosage of 25 mg/kg compare to those receiving it at a dosage of 50 mg/kg. Stipulating, garlic has ameliorative activity on creatinine. This amelioration is attributed to allicin [123]. The decrease in creatinine might cause a decrease in urinary protein excretion, attenuation of lipid derangements, decreased oxygen consumption and the hypertrophy of the kidney [124]. According to the decrease in creatinine, it can be assumed that, AGE retains the balance between lipogenesis and lipolysis in the kidney to counteract the hyperlipidemia associated renal damage in addition to maintaining cellular hydration leading to improvement of kidney function. Data suggest that the renoprotective effects of SAC and AGE are associated with their antioxidant properties [125]. Hence, they may be used to delay the progression of renal damage. This proves the AGE supplementation is helpful in preventing the progression of

radiation injuries and can thus be considered as nephroprotective [126]. Nevertheless, further studies are warranted to investigate the active principles responsible for the nephroprotective effect in AGE.

Ionizing radiations produced peroxidation of lipids leading to structural and functional damage to cellular membranous molecules directly by transferring energy or indirectly by generation of oxygen derived free radical (OH), superoxide (O_2^-) and nitric oxide (NO) which are the predominant cellular free radicals [127-128]. Oxidative stress leads to over production of NO, which readily reacts with superoxide to form peroxynitrite ($ONOO^-$) and peroxynitrous acid which they can initiate lipid peroxidation [129]. Under normal conditions, the inherent defense system, including the enzymes superoxide dismutase, which dismutates superoxide; catalase and glutathione peroxidase, which destroy toxic peroxides, and small molecules including glutathione, protects against oxidative damage. Excessive liver damage and oxidative stress caused by γ -radiation might be responsible for the depletion of GSH [130-132]. Irradiation has been reported to cause renal GSH depletion and lipid peroxides accumulation in different organs [133-135]. It was found that the level of elevation in lipid peroxidation after irradiation is in proportion to radiation dose and elapsed time [136]. Moreover, the formation of lipid peroxidation ultimately would alter the composition of the glomerular basement membrane [137]. Evidence of radiation induced organs injury via a mechanism of oxidative stress caused by increased MDA (a potential lipid peroxidation biomarker) and nitrite, reduced GSH levels and decreased activity of CAT, SOD were demonstrated by various studies [138-142]. Such oxidative stress was mediated through the generation of ROS that induced disturbance of membrane permeability and severe cell damage [143-144].

In the present study, radiation induced higher MDA level and nitrite, while decreasing SOD, CAT activities and GSH level in the homogenate of rat lungs, testis, brain, vertebra, liver, kidney, spleen, heart and aorta tissue. Increase MDA level enhanced the lipid peroxidation and increased ROS production with subsequent disturbance of membrane function and integrity [145]. These results are in accordance with those of Halliwell, and Gutteridge, [146] who observed a significant decrease in SOD and catalase activity after exposure to irradiation due to the excess production of hydroxyl radicals (the most potent oxidant stimulate the lipid peroxidation process) and other reactive oxygen species. SOD is an important endogenous antioxidant enzyme which acts as the first line defense system against ROS and converts the superoxide radicals to H_2O_2 . Glutathione peroxidase present in the cytoplasm of the cells removes H_2O_2 by coupling its reduction to H_2O with oxidation of GSH. Glutathione reductase regenerates GSH from oxidized glutathione in the presence of NADPH. GSH is a tripeptide and a powerful antioxidant present within the cytosol of cells and is the major intracellular non protein thiol compound. SH groups present in GSH react with H_2O_2 and the OH^\bullet radical and prevent tissue damage and GSH is also capable of

scavenging ROS directly or enzymatically via glutathione peroxidase [147]. The decrement of GSH level would be attributed to the decreased activity of Glucose-6- phosphate dehydrogenase that generates reduced NADPH which generates GSH from oxidized glutathione (GSSG) under the effect of glutathione reductase [148]. Moreover, Dahm *et al.* attributed the decrease in liver GSH content to the inhibition of GSH efflux across hepatocytes membranes [149]. The presence of adequate amount of GSH, SOD and catalase minimize lipids peroxidation [143].

The natural products-derived antioxidants were previously used to protect against radiation induced oxidative stress in several studies [150-152]. The water-soluble organosulfur compounds of AGE exhibited potent antioxidant and free radical scavenging activities [153-154].

In the present study, administration of AGE, one hour after irradiation on day 6 after acclimatization induced significant increase in CAT, SOD and GSH activities accompanied with significant decrease in MDA level and nitrite in radiation-treated rat's organs: lungs, testis, brain, vertebra, liver, kidney, spleen, heart and aorta. These effects have been more pronounced with the lower dose of AGE (25 mg/kg) than with the higher (50 mg/kg) or the administration of Vitamin E and Lipoic Acid. Suggesting in accordance with Khalid S. Al-Numair that garlic extracts may have a beneficial effect on antioxidant status by improving antioxidant metabolic indices in rat's plasma [101]. The protective effect of AGE might be mediated by its highly bioavailable and significant antioxidant compounds including S-allyl cysteine, S-allyl mercaptocysteine, allicin, and selenium that exhibited potent antioxidant activity [154]. The water-soluble S-allyl cysteine reduced the extent of lipid peroxidation and significantly enhanced antioxidant activities in vitro and in vivo [155]. Thus, AGE acts as a protective mechanism against oxidative stress [156-157] and could ameliorate the lipid peroxidation and oxidative damages of rat liver tissues induced by acute radiation through its antioxidant compounds; supporting the hypothesis that plant products are effective chemopreventive agents [158].

In accordance with present study, significant increase in CAT, SOD and GSH activities accompanied with significant decrease in MDA and nitrite level were reported in animals treated with AGE [46, 155, 159]. Garlic has been reported to modulate lipid peroxidation levels and enhance the status of antioxidant [158, 165-166]. Furthermore, Garlic pretreatment increased the activity of SOD and CAT and it scavenges superoxide radicals and reduced damage caused by free radicals [162]. Allium components have been reported to elevate the levels of SOD, GSH-Px and Catalase [163-164]. Other beneficial effects of garlic can be attributed to the presence of non-enzymatic antioxidants such as selenium and copper metals, vitamin C and other phytochemicals such as organosulphur compounds [165]. AGE increases cellular glutathione and other ROS scavenging enzymes in a variety of cells, including those in normal liver and mammary tissue [163, 166]. The radioprotective effects of AGE [167] are mediated via the ability of the extract, its organosulfur

components and phenolic compounds to scavenge free radicals [163] and enhance scavenging systems in the cell, including glutathione, SOD, catalase and glutathione peroxidase [163, 168].

5. Conclusion

On the basis of the data obtained, the present study revealed that AGE exerted a significant protection against oxidative stress induced by exposure of rats to γ -radiation through scavenging or neutralizing free radicals, and enhancement of antioxidant in addition to hepatoprotective and renal protective properties

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