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The Potential Therapeutic Effect of Ferulic Acid in Mitigating Oxidative Stress Induced by γ-Irradiation in Male Rats

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THE TESTIS is considered as one of the most sensitive organs in the body to ionizing radiation because of the rapidly dividing germinal epithelium. Seminal oxidative stress (OS) causes damage of the sperm plasma membrane and loss of its DNA integrity, therefore, the need for an effective therapeutic agent is evident. The present study investigated the mechanism(s) of potential therapeutic effect of ferulic acid (FA) on radiation-induced testicular damage.

Mature male albino rats were either exposed to single dose γ-radiation (5Gy) and/ or treated with FA (50mg/ kg body wt, orally), daily for seven days post-irradiation. FA significantly reversed OS effects of γ-rays that was evidenced by increasing malondialdehyde (MDA) and decreasing ferric reducing antioxidant power (FRAP) and catalase (CAT) activity. In addition, alterations in some trace elements such as zinc (Zn), cupper (Cu), iron (Fe) and manganese (Mn) were observed. Furthermore, sperm head abnormalities noticeably increased in the γ-irradiated group; in contrast, FA treatment ameliorated these alterations.

In conclusion, FA exhibited curative effect against radiation induced testicular damage.

Keywords: Ferulic acid, γ-rays, oxidative stress, trace elements, testes.

Ionizing radiation is used in a large number of therapeutic, industrial and other applications for the generation of nuclear power, developing new varieties of high-yielding crops and enhancing storage period of food materials (Maurya and Devasagayam, 2011).

Radiotherapy (RT) is considered as a curative medical intervention, depends on the generation and uses of reactive oxygen species (ROS) to eradicate tumours but non-target tissues are also damaged (Said *et al.,* 2012). RT is a major factor contributing to male infertility by destroying the process of spermatogenesis (Ahmed and Tawfik, 2012). Over the years, infertility has been remarked and increased in both males and females. The increase in male infertility has become a source of inclusive concern (Ekhoye *et al*., 2013).

Many elements such as Zn, Cu, Fe & Mn are essential in the biological system; they are mostly present in trace amounts. Most of these elements act as cofactors in important vital processes such as; cellular respiration, cellular utilization of oxygen, maintenance of cell membrane integrity, sequestration of free radicals, and DNA and RNA reproduction (Chan *et al.,* 1998). Moreover, these trace elements act as activators or cofactors for antioxidant capacities and preventing the accumulation of pathological concentration of oxygen radicals or in repairing damage caused by irradiation (Ali *et al.,* 2013and Nada *et al.,* 2012). Moreover, the presence of Zn at the cellular level is essential for the cell growth and division in gonads, which occurs continuously. So that, Zn-deficiency causes testicular atrophy, reductions in libido and sperm production, atrophy of seminiferous tubules and complete inhibition of spermatogenesis (Visweswaran and Krishnamoorthy, 2012).

FA (4-hydroxy-3-methoxy cinnamic acid) is ubiquitous phenolic compound of plant tissues constituting a bioactive ingredient of many foods (Soobrattee *et al.,* 2012). It displayed antioxidant and cytoprotective effects and acts as a potential treatment for many humans disorders including Alzheimer's disease, cancer, cardiovascular diseases, diabetes mellitus and skin disease (Mancuso and Santangelo, 2014).

Therapeutic potentiality of FA on an antioxidant system of liver and intestine of γ-irradiated male rats was reported before (Tawfik *et al.,* 2010). Certain study indicated that oral supplementation of FA can significantly mitigate diabetes-associated oxidative impairments in rat testis (Roy *et al*., 2013). This study was designed to evaluate the potential therapeutic effect of FA against radiation-induced testicular damage together with studying its effects on different OS markers.

Materials and Methods

Chemicals

FA, 2,4,6-tri[2-pyridyl]-s-triazine (TPTZ), N-butanol, trichloroacetic acid (TCA) and thiobarbituric acid (TBA) were purchased from (Sigma-Aldrish Chemical Co., St Louis, MO, USA). All other chemicals and solvents were of the highest grade commercially available.

Animals

The study was conducted according to the ethical guidelines (Ain Shams University, Cairo, Egypt). 40mature male albino rats (12-13 weeks old age) were obtained from Nile Pharmaceutical and Chemical Industries-Nile (NIPH), El Sawah, Cairo, Egypt. Rats were housed in an air-conditioned atmosphere at a temperature of 25℃ with alternatively 12-h light and dark cycles. Animals were acclimated for three days before experimentation. They were kept on a normal standard requirement of food and water *ad-libitum*.

Gamma-radiation

Whole body gamma-irradiation of rats was carried out using a ^{137}Cesium-source, Gamma Cell-40 biological irradiator, at the NCRRT, Nasr City, Cairo, Egypt. The animals were exposed to a single dose of (5Gy) gamma rays with a dose rate of 0.125Gy/ min. This dose represents the sub-lethal dose for rats according to the study of Adaramoye *et al*. (2010).

Experimental design

Animals were divided into four groups and treated for seven days as follows; the first group served as control. The second irradiated group received distilled water (5ml/ kg body wt, orally for seven days) then exposed to a single dose of whole-body irradiation with 5Gy gamma rays. The third group was given FA (50 mg/ kg body wt, orally for seven days), according to Roy *et al*. (2013) protocol**.** The last group was exposed to a single dose of whole-body γ-rays (5Gy), and then after 1 h, started the orally administered of FA for seven days). Seven days after irradiation, all rat groups were sacrificed; blood samples were collected from the heart puncture and allowed blood to clot for serum

separation. Coda epididymis and testes organs were dissected; washed with ice-cold saline and then testes were weighed.

Tissue collection and processing

Serum was separated by centrifugation at 3000xg for 15min and kept frozen at-80℃ until assessment of testosterone hormone. Samples of testis tissues were homogenized at 1:5(w/v) in phosphate buffer (pH 7.4) with homogenizer (Glas-Col, USA) after that the supernatant was obtained by centrifugation at 10,000xg for 15min (Cooling centrifuge, Hettich, MIKRO-22R, Germany) then stored at -80℃ until the biochemical analysis of the different suggested biomarkers.

Circulating levels of serum testosterone

According to the manufacturer instructions of the enzyme-linked immunosorbent assay (ELISA) kit, Alpico, USA, the circulating level of serum testosterone was estimated using Stat Fax-2100 Microplate Reader, Awareness Technology, USA.

Evaluation of the reproductive functions of the rats

The caudal epididymis of each rat was minced in 3ml phosphate buffer (pH 7.8). The filtrate of suspension was mixed with 0.05% eosin-Y (10:1) for 30min. Spermatozoa (n= 200) of each animal were counted by ordinary microscope at 40X-magnification lens using a blue-green filter (Leitz, Germany). Evaluation of sperm heads abnormalities were made according to the criteria of Wyrobek *et al*. (1984). Mutation factor and mutation index were calculated as the following: Mutation factor= frequency of abnormal sperm heads (treated)/ frequency of abnormal sperm heads (control). Mutation index= frequency of abnormal sperm heads (treated-control)/ frequency of abnormal sperm heads (control) according to Ekaluo *et al.* (2010).

Measurement of OS markers

Lipid peroxidation was determined by the estimation of thiobarbituric acid reactive substances (TBARS) measured as MDA according to the method of Yoshika *et al.* (1979). Furthermore, CAT assay was described by Beers and Sizer (1952).

Total antioxidant activity assay

The total antioxidant activity was measured by spectrophotometrically by the FRAP assay according to the method of Benzie and Strain (1999).

Trace elements analysis

Zn, Cu, Fe and Mn concentrations were measured in testicular tissue. The digestion process used Milestone MLS-1200 Mega and High Performance Microwave Digestor Unit (Italy). Each organ (0.5-1g) was put in special vessel with 6ml nitric acid and 1ml hydrogen peroxide. After complete digestion, samples were diluted to suitable concentrations appropriate for metals analysis by Thermo Scientific iCE 3000 series Atomic Absorption Spectrophotometer (AAS), England (IAEA, 1980 and Kirgbright, 1980).

Statistical analysis

Data are expressed as the mean± S. E, and were analysed by one-way analysis of variance (ANOVA) followed by Tukey-Kramer as a post-hoc test.

The 0.05 level of probability was used as the criterion for significance. All statistical analyses were done and graphs were sketched using GraphPad Prism (ISIH software, USA) version 5 software.

Results

Effect of FA on testes/ body wt relative ratio and serum testosterone level

Seven days post irradiation; the animals exhibited a decrease in their testes/ body wt relative ratio reaching about 47.2% of the control value. Treatment with FA post γ-irradiation nearly normalized this decrease and converted it from 47.2 % to 111.1% as compared to control group.

Animals treated with FA exhibited non-significant change as compared to control animals, Table 1. In the irradiated group, a noticeable decrease in serum testosterone level was observed reaching 16.2% as compared to control group.

However, treatment with FA post γ-irradiation increased the serum testosterone level to 36.4% as compared to control. However, Animals treated with FA exhibited non-significant change, Table 1.

TABLE 1. Effect of FA on testes/ body wt relative ratio and testosterone hormone level in rats exposed to whole body γ-radiation.

Rat groups	Testes/ body wt relative ratio	Serum testosterone (ng/ml)
Control	1.08± 0.0561	1.54± 0.042
IRR	0.52± 0.046[a]	0.25± 0.023[a]
FA	1.10± 0.109[b]	1.65± 0.066[b]
IRR+ FA	1.20± 0.048[b]	0.78± 0.074[a,b]

Male rats were exposed to single dose of whole body γ-radiation (5Gy).
FA was given orally in a dose of (50 mg/kg body wt once daily for 7 days).
Data expressed as Mean ± SE (n=6).
Statistical analysis was done using one-way ANOVA followed by Tukey-Kramer as a post-hoc test.
a: significantly different from the corresponding control group at $P< 0.05$.
b: significantly different from corresponding irradiated group at $P< 0.05$.

Effect of FA administration on sperm head abnormality

As shown in Table 2. male adult rats exposed to γ-rays exhibited significant increase in sperm head abnormalities to the 26% more than the control group. Although, FA administration post irradiation ameliorated the sperm abnormalities from 26% to 20% more than the control, this difference is still significant in comparison control group.

Moreover, FA administration post γ-rays with exposure of rats produced reduction in the values of mutation factor and mutation index as compared with the respective control group. In contrast, treatment with FA alone showed non-significant change in sperm abnormalities, the values of mutation factor and mutation index (Table 2).

TABLE 2. Effect of FA on sperm head abnormalities frequency in rats exposed to whole body γ-radiation.

Rat groups	Frequency of sperm head abnormalities (%)	Increase in sperm head abnormalities percentage	Mutation Factor	Mutation Index
Control	9.75	0	1.00	0
IRR	35.83[a]	↑26 **%**	3.67	2.67
FA	12.25[b]	2.5 **%**	1.26	0.26
IRR+FA	29.50[a,b]	↓20 **%**	3.03	2.03

Legends as in Table 1.
Increase in sperm head abnormalities percentage according to control group.

Oxidative stress biomarkers

Gamma-irradiation induced OS in rat testes was assessed by determination of MDA content as well as CAT activity. As shown in Fig. 1. radiation stimulated significant increase in testicular MDA content by 158% as compared to the control group. Treatment of animals with FA post exposure to γ-rays retained level of MDA nearly toward the control value. Further, testicular CAT activity was significantly decreased after irradiation to 46.5% as compared to the control values. Post-treatment of the irradiated group with FA significantly maintained CAT activity similar to the control values. Testicular MDA level and CAT activity were not displayed any significant differences between control and FA alone treated group.

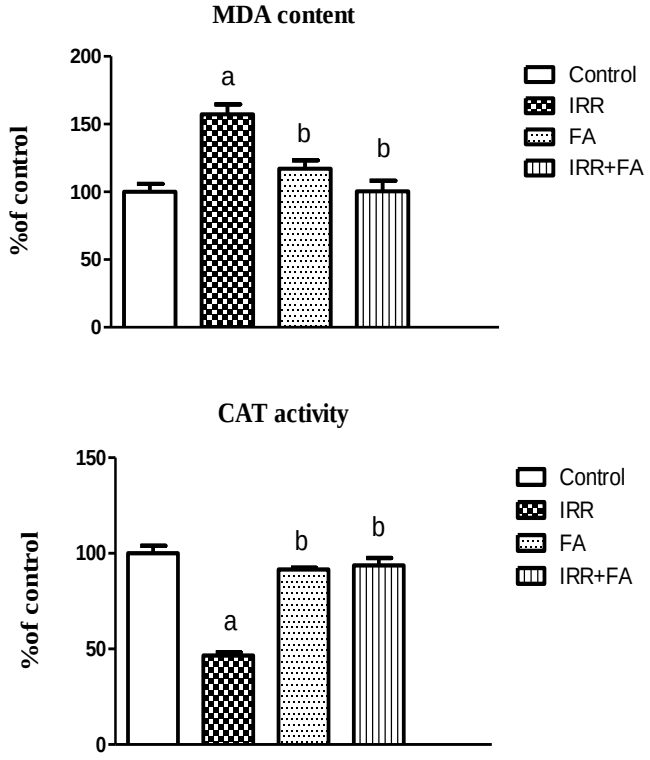

Fig. 1. Effects of FA on MDA content and CAT activity in rats exposed to whole body γ-radiation.

Legends as in Table 1.

Total antioxidant assay

The total antioxidant activity was measured by the FRAP assay; γ-irradiation induced a significant reduction in antioxidant activity by 71% as compared to control group. Conversely, treatment with FA post γ-irradiation treatment with FA reduced FRAP from71% to 88%, as compared to control value. While, FA treated animals exhibited non-significant change as compared to control animals, Table 3.

TABLE 3. Effect of FA on FRAP assay in rats exposed to whole body γ-radiation.

Rat groups	FRAP (mmol/g tissue)
Control	3.37± 0.13
IRR	2.40± 0.09[a]
FA	3.80± 0.10[b]
IRR+ FA	2.97± 0.13[b]

Legends as in Table 1.

***Testicular trace elements concentrations*:**

In the group exposed to γ-radiation, a significant decrease in testicular-Zn content was observed (75%) as compared to control group. However, treatment with FA post-irradiation converted the testicular-Zn content from 75% to 100% as compared to control, Table 4.

TABLE 4. Effects of FA on testicular Zn, Cur, Fe and Mn contents in rats exposed to whole body γ-radiation.

Rat groups	Zn (ug/g)	Cu (ug/g)	Fe (ug/g)	Mn (ug/g)
Control	26.80 ± 1.40	0.94± 0.08	26.70± 0.84	1.20± 0.08
IRR	20.00± 0.40[a]	1.90± 0.10[a]	81.30± 7.20[a]	3.05± 0.20[a]
FA	28.10± 1.60[b]	1.00± 0.06[b]	35.60± 3.20[b]	1.10± 0.08[b]
IR+FA	26.80± 1.70[b]	1.10± 0.02[b]	23.90± 0.97[b]	1.40± 0.08[b]

Legends as in Table 1.

In parallel a continuous significant elevation in testicular-Cu content by nearly 202% as compared to control. Furthermore, percentage change of testicular-Cu content in rats treated with FA post **γ**-irradiation could significantly decrease from 202% to117% as compared to control animals, Table 4. On the other hand, treatment of the irradiated rats with FA for seven days post irradiation turned the testicular Fe content to 89.5% instead of 304.5%

of respective control. Also, γ-irradiation caused a marked increase in testicular-Mn content by about 254% of control group. In contrast, treatment with FA post γ-radiation exposure significantly decreased this elevation by 117% as compared to control group. Animals treated with FA exhibited non-significant change in trace elements (Zn, Cu, Fe & Mn) contents as compared to control animals.

Discussion

Many studies demonstrated that, the damaging properties of γ-radiation within biological systems are intermediated by the production of ROS in cells after water radiolysis (Kamat *et al*., 2000 and Said *et al*., 2012). The generated ROS destroy important biological molecules for instance nucleic acid, proteins, lipids as well as cell membranes (Maurya and Devasagayam, 2013). Physiological spermatogenesis could be disturbed and induce male infertility. Current study verified a significant reduction in relative testes/ body wt ratio in response to whole body γ-radiation. These results further support that previously obtained by Liu *et al.* (2011), who indicated that, this reduction donated the wicked effect of the ionizing-radiation on both body and testis wt. Alternatively, administration of FA post γ-irradiation compensates the reduction in relative testes wt. In this study, the irradiated male rats exhibited lower levels of serum testosterone than those of the control group. This result is in harmony with previous study reported by Ahmed and Tawfik (2012), who stated that testicular injury induced by γ-radiation leads to reduction in testosterone hormone level. On the other hand, rats treated with FA post γ-irradiation minimized the decline in testosterone level. The present results confirmed the previous studies which revealed that FA ameliorates OS-induced serum testosterone decline through its antioxidant sparing action (Roy *et al*., 2013).

Several studies reported that there are correlation between the chromosomal aberration and DNA-fragmentation (DNA damage) in sperm and its specific abnormal morphology especially for head abnormalities (Alam *et al*., 2011). In the present study, γ-irradiation of rats induced significant elevation of sperm head abnormalities. The current result is in agreement with these obtained by Ahmed and Tawfik (2012), who verified the effect of γ-irradiation and the abnormal forms of sperm (sperm head abnormalities) due to the spermatogenesis disruption. Also, seminal-OS reduced sperm motility and function through

damaging its DNA and membrane integrity (Celik-Ozenci and Tasatargil, 2013). Alternatively, treatment of rats with FA post γ-irradiation ameliorated this significant elevation in sperm head abnormalities toward normal value. The result was on line with Kumar and Pruthi (2014) they revealed that, FA increased sperm viability.

In this study, it was found that acute radiation exposure of rats resulted in a significant increase in testicular lipid peroxides (represented as MDA) as well as a decrease of the antioxidant enzyme CAT activity. These results are comparable with those of Chen *et al*. (2002). In this context, Adaramoye *et al*. (2010) and El-Marakby *et al*. (2016) verified that exposure to γ-radiation leads to a significant increase in testicular lipid peroxidation associated with a marked decline in testicular CAT. Furthermore, a number of studies have reported that FA could scavenge free radicals, increase reduced glutathione content and constrains lipid peroxidation *in vivo* and *in vitro* (Gohil *et al*., 2012). It was reported that FRAP assay is considered as a measure of total antioxidant activity (Benzie and Strain, 1999). The results of the present work displayed that whole body γ-irradiation of rats significantly reduced FRAP assay that is in accordance with results of Maurya and Devasagayam (2011), they specified that γ-rays exposure leads to an increase in ROS levels and/ or a decrease in the activity of the antioxidant enzymes that scavenge these harmful free radicals. Animals treated with FA post γ-irradiation significantly improved antioxidant power as compared with respective control. These results further confirm those found by Prasad *et al*. (2006). FA stays in blood for longer than other antioxidants such as vitamin C (Srinivasan *et al*., 2007), inducing intrinsic antioxidant mechanisms such as superoxide dismutase (SOD), CAT and glutathione reductase (GR) activities. In addition, Dean *et al.* (1995) established that FA capability to modulate (phase II enzymes like glutathione transferase) and up regulate antioxidant enzymes (CAT, SOD and GR) is a reason for its curative role.

In addition, trace elements such as Zn, Cu, Fe & Mn are integral parts of enzymatic antioxidants. They play important roles in the catalytic and antioxidant activities of major enzymes. Also, deficiency of these trace elements (Zn & Cu) has been implicated with infertility (Nada *et al*., 2011 and Visweswaran and Krishnamoorthy, 2012). In the current study, γ-irradiation of rats induced decrease in testicular-Zn content. Zn derived from testis tissues that were

damaged by irradiation could be accumulated in other organ. This result is in harmony with that of Visweswaran and Krishnamoorthy (2012), who reported that Zn, a remarkable antioxidant, is an essential component of many metalloenzymes, its deficiency results in oxidative stress. On the other hand, γ-irradiation induced significant increase in testicular-Cu content. The increase of testicular-Cu may be attributed to re-synthesis of cuproenzymes. Moreover, the Zn & Cu are the metallic parts of Cu-Zn SOD, catalysing the dismutation of superoxide to H_2O_2, which must be removed by CAT and/ or glutathione peroxidase (Nada *et al*., 2012). These conclusions might explain the decrease of Zn due to excess utilization of metallo-enzymes after irradiation, or may be due to *de novo* synthesis of Zn-SOD and CAT or its accumulation in other organs. Furthermore, iron homeostasis has to be tightly controlled. Meanwhile, free iron has the ability to catalyse the generation of radicals which attack and damage cellular macro-molecules, promote cell death and tissue injury (Papanikolaou and Pantopoulos, 2005). In the present study, it was observed that after gamma irradiation of rats at a dose level of 5Gy, Fe content was significantly increased in testis (Nada *et al*., 2011) stated that, the accumulation of iron post-irradiation might result from disturbance in the biological functions of red blood cells including possible intravascular haemolysis and subsequent storage of Fe in other tissues. However, Nada *et al*. (2012) attributed the increase in value of Fe post-irradiation to the inability of bone marrow to utilize dietary available iron in diet and that released from destroyed red blood cells. Moreover, the increase of testicular-Fe content post-irradiation can further explain the increase in testicular MDA content as free Fe facilitates the decomposition of lipid hydro peroxides resulting in lipid peroxidation and the generation of $OH^{\bullet}$ radicals as well as accelerating the non-enzymatic oxidation of glutathione to form $O_2^{\bullet}$ radicals (Nada *et al*., 2012).

Conclusion

Based on the above stated study, it is possible to indicate that, FA could attenuate the severity of the biochemical, as well as the morphological disorders in testicular tissue induced by exposure to γ-rays. It is mainly through its free radical scavenging ability, in addition, enhancement of testicular antioxidant enzymes and elevation of testosterone level. Further findings must be undertaken to verify the present results in clinical settings.

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التأثير العلاجى المحتمل لحمض الفريوليك فى الحد من الإجهاد التأكسدى المحدث بالإشعاع الجامى فى ذكور الجرذان

رانيا عبدالمنعم جاويش ، و العلياء محمد سلام* ، و حنان عبدالحميد فهمى ، و أحمد شفيق ندا ، و هالة عثمان المسلمى*

قسم البحوث الدوائية الإشعاعية ، المركز القومي لبحوث و تكنولوجيا الإشعاع ، هيئة الطاقة الذرية المصرية ، ص. ب. ٢٩ مدينة نصر ، و *قسم الكيمياء الحيوية ، كلية الصيدلة ، جامعة عين شمس ، مصر.

تعد الخصية من أكثر الأعضاء تأثرا عند تعرضها للإشعاع المؤين ، ذلك لأن الإشعاع المؤين يدمر الخلايا المنتجة للحيوانات المنوية. كما أن زيادة معدلات الأكسدة فى السائل المنوى يؤدى إلى تدمير الغشاء البلازمى و الحامض النووى للحيوانات المنوية. و تشير الدراسة الحالية إلى الدور العلاجى لحمض الفريوليك ضد تلف الخصية نتيجة التعرض لأشعة جاما. تم علاج ذكور الجرذان المعرضة لخمسة جراى من أشعة جاما بخمسين مللى جرام من حمض الفريوليك لكل كيلوجرام من وزن جسم الجرذان لمدة سبعة أيام. و قد لوحظ ان التعرض لأشعة جاما يقلل من القدرة على إنتاج الحيوانات المنوية ، و ذلك من خلال قياس تشوهات رؤوس الحيوانات المنوية ، كما يزيد من معدلات الأكسدة [زيادة كمية المالون ثنائى الآلدهيد (MDA) و تقليل نشاط الكتلاز (CAT)] ، كما أن القدرة الكلية على عدم الأكسدة و التى تم تعينها من خلال قياس القدرة على إختزال الحديد الثلاثى (FRAP) انخفضت بنسبة إحصائية ملحوظة ، و قد لوحظ انخفاض شديد فى مستوى هرمون التستستيرون فى مصل دم الجرذان. كما أن تعرض الجرذان لأشعة جاما أحدث خللا فى كمية العناصر الشحيحة مثل (الزنك ، الحديد ، النحاس ، المنجنيز) فى نسيج الخصية. أوضحت الدراسة قدرة حمض الفريوليك العلاجية من خلال تحسين و معادلة الأثار السلبية الناجمة من التعرض لأشعة جاما; القدرة على الإنجاب و زيادة مستوى هرمون التستستيرون ، و زيادة نشاط الكتالاز و انخفاض كمية المالون ثنائى الآلدهيد ، و الحد من الخلل فى محتوي نسيج الخصية من العناصر الشحيحة التي تم تقديرها.