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Role of Sodium Selenite in Ameliorating the Oxidative Stress of Gamma Radiation Exposure.

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Abstract

Back ground: This work aims to investigate the role of Sodium Selenite ($NaSeO_3$) in ameliorating the oxidative stress of gamma radiation exposure. The relation between the antioxidant status, the histopahological changes and the immunohistological expression of *p53* was evaluated.

Materials and methods: Adult male Swiss albino mice weighing 25-30g were used in this work. Lipid peroxidation and GSH activity levels were estimated in liver and intestinal tissues. Histopathological observations in addition to the immunohistological expression of *p53* were also assayed. Experimental animals treated daily with 0.7µg /ml /kg body weight of $NaSeO_3$ for two weeks. Some animals were exposed to 5Gy γ-irradiation and others exposed to 5Gy γ-irradiation and treated with $NaSeO_3$.

Results: Due to ROS production, 5Gy γ-radiation induced a highly significant increase in lipid peroxidation and a significant decrease in GSH activity level in liver and intestine tissues. $NaSeO_3$ supplementation revealed NS change in lipid peroxidation of liver and intestine tissues, while GSH levels recorded a significant increase as compared to the control group. Combined treatments with NaSeO3 supplementation and 5Gy γ-radiation revealed a significant amelioration in lipid peroxidation and GSH levels as compared to the irradiated groups. The histopathological observations went parallel to the biochemical records, while *p53* expression was treatments and organs dependent.

Conclusion: $NaSeO_3$ supplementation recorded ameliorated effects against cellular damage caused by radiation oxidative stress.

Introduction

Radiation is known to produce various reactive oxygen species (ROS) in biological systems such as superoxide, hydrogen peroxide and hydroxyl radical and various types of tissue damage due to free radical reactions (Adler *et al.,* 1999). Reactive oxygen species (ROS) and free radicals induced by partial reduction of oxygen (O_2) react with cellular macromolecules (i.e., nucleic acids, lipids, proteins, and carbohydrates) (Sies, 1986) and induce their damage. In response to ionizing radiation induced DNA damage, cell cycle checkpoints and DNA repair are activated to protect the genome (Zhou and Elledge, 2000 ; Friedberg, 2003).The damage is properly repaired and the irradiated cells can resume proliferation or regenerate or develop tissues undergo apoptosis in response to ionizing radiation. *p53* plays an essential role in ionizing radiation induced apoptosis.

p53 is a tumor-suppressor gene located on the short arm of chromosome 17 and has an important function in the regulation of the cell cycle and in promoting tumorigenesis (Okusa *et al.*, 1996 ; Roviello *et al.*, 1999). This gene encodes for the *p53* protein, which increases the time necessary for DNA repair by slowing down the cell cycle at the G1-S transition, and suppresses tumor growth by causing apoptosis (Lanfrancone *et al*., 1994; Ryan *et al.*, 2001). Alteration or inactivation of *p53* by mutation can allow a cell to escape from normal into

uncontrolled growth leading to cancer development. *p53* mutations are a very common genetic change in a variety of human tumors (Ryan *et al*., 2001; Starzynska *et al.*, 1992). The wild-type *p53* protein has a short half-life and is removed rapidly from the nucleus. On the contrary, mutant *p53* with a prolonged half-life accumulates in the nucleus, where it could be detected by immunohistochemistry. Therefore, the accumulation of the *p53* protein may be considered an indicator of p53 gene mutation (Okusa *et al*., 1996; Starzynska *et al*., 1992).

The essential trace element selenium is of fundamental importance to human health. Its amount in vegetables and fruits is highly dependent on the soil content. As a constituent of selenoproteins, selenium has several structural and enzymatic roles; in the latter context it is best known as an antioxidant. Although investigation of selenium's role in health promotion has focused on its antioxidant activity (Holben and Smith ,1999), it has diverse biological functions, including the ability to suppress cell proliferation (Ganther ,1999), enhance immune response (Kiremidjian-Schumacher and Roy 1998), alter the metabolism of carcinogens (Ip ,1998), and induce apoptosis (Ganther ,1999). Providing selenium in its inorganic (e.g., selenite and selenate) or organic [e.g., selenocysteine and selenomethionine (Se Met)] forms has been found to meet nutritional needs. The biological activity of selenium actually reflects its expression in various compound forms (Ip, 1998). Kuchan and Milner (1992) provided rather compelling evidence that intracellular concentrations of glutathione were instrumental in determining the ability of selenite to alter cellular proliferation. In this study, we evaluated the immunohistochemical expression of *p53* in liver and intestine tissues. The relationship between *p53* expression, histopathologic features and the GSH and MDA levels as affected by γ- radiation exposure and/ or Sodium selenite (selenium) consumption.

Materials and methods

Animals

Adult male Swiss albino mice weighing 25-30g were purchased from the breeding unit of the Egyptian Organization for Biological Products and Vaccines, Cairo and were used in this study. The animals were maintained on a commercial standard pellet diet and tap water *ad libitum*.

Exposure of Animals to γ-Radiation

Mice were irradiated by whole body gamma irradiation using a Canadian ^{137}Cs Gamma Cell-40 at the National Centre for Radiation Research and Technology (NCRRT), Cairo, Egypt. The dose rate was 0.61 Gy/min.

Sodium Selenite supplementation

Sodium Selenite ($NaSeO_3$) was obtained from South Egypt Drug Industries Company (SEDCO) dissolved in distilled water at dose level 0.7µg /ml /kg body weight. $NaSeO_3$ supplemented daily for two weeks.

Groups under investigation.

G1: Non irradiated non treated animals, served as control.

G2: Non irradiated and treated daily with $NaSeO_3$ for two weeks.

G3: Whole body gamma irradiated mice with 5Gy.

G4: Animals treated with $NaSeO_3$ before exposure to5Gy γ-irradiation.

Animals were sacrificed by cervical dislocation after one day of the last $NaSeO_3$ and / or γ-irradiation treatment. Liver and the small intestine were dissected out for the present investigation.

Biochemical analyses.

For biochemical analyses small intestine and liver tissues were dissected out, and homogenized in ice cold phosphate buffer (0.1M/pH 7.4) to give 10% homogenates for determination of reduced glutathione (GSH), and lipid peroxidation as malonadialdehyde (MAD). The level of Lipid peroxidation was ascertained by

measuring malonadialdehyde level (MDA) content according to the method described by Ohkhawa *et al*. (1979). Glutathione (GSH) content was assayed calorimetrically according to the procedure of Moron *et al*. (1979).

Histopathology.

For histopathology samples of intestine and liver tissues were fixed in 10% formaldehyde. These samples were then dehydrated in ascending series of alcohol cleared in xylene and embedded in paraffin wax. Sections of 5 µm thickness were cut and subsequently stained with Hx.& E. dye.

Immunohistochemistry.

For immunohistochemistry, samples of intestine and liver tissues were fixed in 4% formaldehyde in phosphate-buffered saline (pH 7.4), before dehydration in alcohols and embedding in wax. Tissue sections were cut using a microtome at a thickness of 3 µm. Immunohistochemistry was performed using P53 Ab-1(clone PAb 240) mouse monoclonal antibody purchased from lab Vision Corporation. Immunohistochemistry was performed using anti mouse IgG (H+L) streptavidin peroxidase and diaminobenzidine as the immunodetection substrate.

In immunohistochemistry, slides were heated to 65°C in an Incubator for 60 min. The slides were then taken directly from the incubator and deparaffinized in three changes of xylene for 5 min each, followed by three rinses in absolute ethanol (ETOH) for 2 min each. To eliminate staining due to endogenousperoxidase, sections were treated with an ETOH / H_2O_2 (45 ml ETOH/3 ml H_2O_2) block for 10 min at 42°C. Slides were hydrated in decreasing concentrations of ethanol and rinsed in PBS. From this point in the assay, all antibody and complex incubations were carried out in a humidity chamber at 42°C. Slides were pre-incubated for 10 min in 5% NHS diluted in PBS/2% BSA, followed by incubation for 45 min with primary antibody. Slides were then rinsed in PBS and subsequently incubated in the presence of the secondary antibody for 20 min (Vector). Slides were rinsed in PBS, followed by a 20-min incubation in pre-mixed Elite Universal Kit reagents as recommended by the product insert (Vector). The PBS rinse was repeated and sections were developed in the enzyme substrate DAB solution.

P53 immunoreactivity was recorded according to their intensity in Browne colure. Using light microscopy, certain cells exhibited noticeably stronger immunoreactivity than the rest. These cells were classified as strongly stained.

Statistical analysis

Data were analyzed by Student's *t*-test. Values are expressed as mean ± SE.

Results

Effect of NaSeO3 in the prevention of lipid peroxidation

MDA is an aldehyde end product of poly unsaturated fatty acids and related esters that it used to assess lipid peroxidation. NaSeO3 administration recorded NS change in liver and intestine tissues in comparison to control tissues. From table (1) whole body exposure of experimental animals to 5Gy . -radiation predicted a highly significant increase in lipid peroxidation ($p< 0.001$) as compared to control group. Treatment of the experimental animals by NaSeO3 followed by whole body exposure to 5Gy . -radiation induced amelioration in lipid peroxidation compared to the irradiated group.

Effect of NaSeO3 on the GSH levels activity.

Table (2) shows the effect of NaSeO3 on the level of GSH activity of liver and intestine tissues. Treatment of the experimental animals with NaSeO3 only influences a significant change as compared to control level. Exposure of the experimental animals to 5Gy of . -radiation, a significant decrease in reduced glutathione was noticed either in liver or intestine tissues reaching to -29.80% and -34.21% respectively. Non significant change was observed in NaSeO3 irradiated group (5Gy) as compared to control group and significant increase was detected in comparison to control group.

Histopathological observations.

Liver

The results of the microscopic investigation showed that liver of mice treated with 5 Gy γ-radiations (Fig1C) displayed erosion of the endothelial cell of the central vein (↑) and fragmentation of the hepatic cells (↕). In addition many of the hepatocytes manifested pyknotic nuclei. Liver tissue in mice treated with NaSeO3 recorded some hepatic cells atrophy in addition to the presence of some pyknotic nuclei (Fig 1B) and cell vaculation due to either NaSeO3 or NaSeO3 & 5 of γ-radiation exposure (Fig 1 B&D).

Intestine

In Fig (2) the histopathological observations in intestine tissue of mice exposed to 5 Gy γ-radiations was evaluated (G). Compact and shortening of intestinal villi (High magnification) were observed and decrease in goblet cells was detected. Treatment of experimental animals with NaSeO3 (F) showed normal appearance of intestinal tissue as compared to control tissue. Treatment of the experimental animals with NaSeO3 followed by 5Gy γ-radiation (H), some normalization in intestinal tissues was appeared.

Immunohistochemical detection of *p53*.

Liver

Fig (3) illustrates the immunoreactivity of *p53* in liver tissue. Control normal one (A) did not detect any immunoreactivity of *p53* expression. Exposure of experimental anim-als to 5Gy of γ-radiation (B), expression of *p53* was observed in many of the hepatocytes (↑) which suffered from cytoplasmic vacuolation. Treatment of mice with NaSeO3 (C) revealed marked expression of *p53* in many of the hepatocyes compared to other treatment and more pronounced when liver tissue treated with NaSeO3 and exposed to 5 Gy γ-radiation (D).

Intestine

The intestinal *p53* expression effected by different treatments was recorded in fig (4). Control intestine express *p53* only in the muscularis externa region. Exposure to 5 Gy revealed highly *p53*-positive cells which mainly towards the base of the small intestinal crypts (F). Treatment of the experimental animals with NaSeO3 revealed a negative expression in intestinal *p53* (G). Mild *p53* expression was recorded in some intestinal villi cells when the experimental animals were treated with NaSeO3 and exposed to 5 Gy γ-radiation (H).

Table (1): Effect of NaSeO3 on MDA levels of mice exposed to γ-radiation.

Organs	Groups			
	Control	**NaSeO3**	**Radiation**	**NaSeO3+Radiation**
Liver	104.14 ± 0.42	103.62 ± 0.42 ^{NS}	184.82 ± 0.57 ***	143.46 ± 1.38 ***
% of change	100 %	-1.41 %	77.47 %	37.76 %
Intestine	94.40 ± 0.35	93.47± 0.26 ^{NS}	121.62 ± 0.69 ***	106.09 ± 0.40 **
% of change	100 %	-0.99 %	28.83 %	12.38 %

***Significantly different at P< 0.001 **significantly different at P<0.01

Values are the mean of 5 observations ± S.E

Table (2): Effect of NaSeO3 on GSH levels activity of mice exposed to γ-radiation.

Organs	Groups			
	Control	**NaSeO3**	**Radiation**	**NaSeO3+Radiation**
Liver	104.47 ± 0.38	162.22 ± 0.47 ***	73.34 ± 0.19 ***	101.45 ± 2.57 NS
% of change	100 %	55.28 %	- 29.80 %	-2.89 %
Intestine	161.42 ± 0.36	218.22± 0.40***	106.20 ± 0.46 ***	166.52 ± 2.63 NS
% of change	100 %	35.19 %	- 34.21 %	3.16 %

Legends as in table (1)

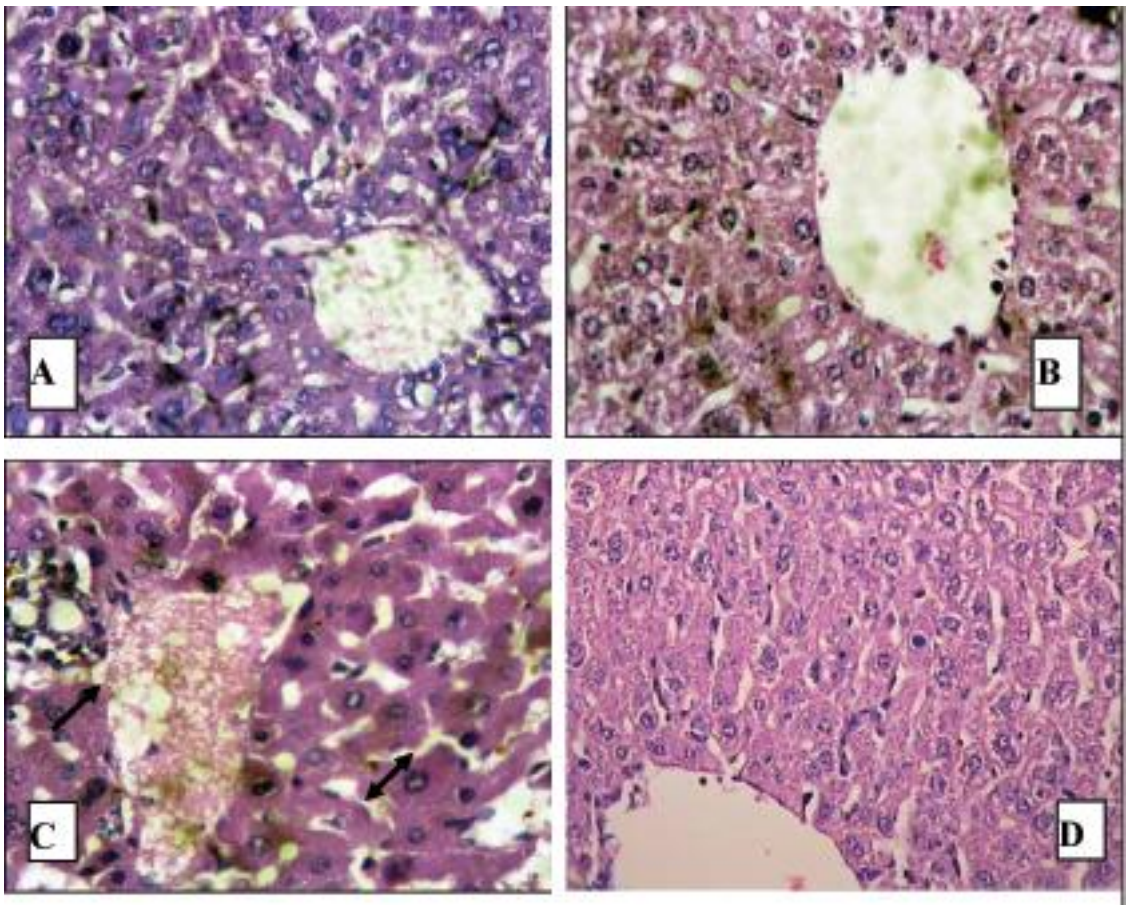
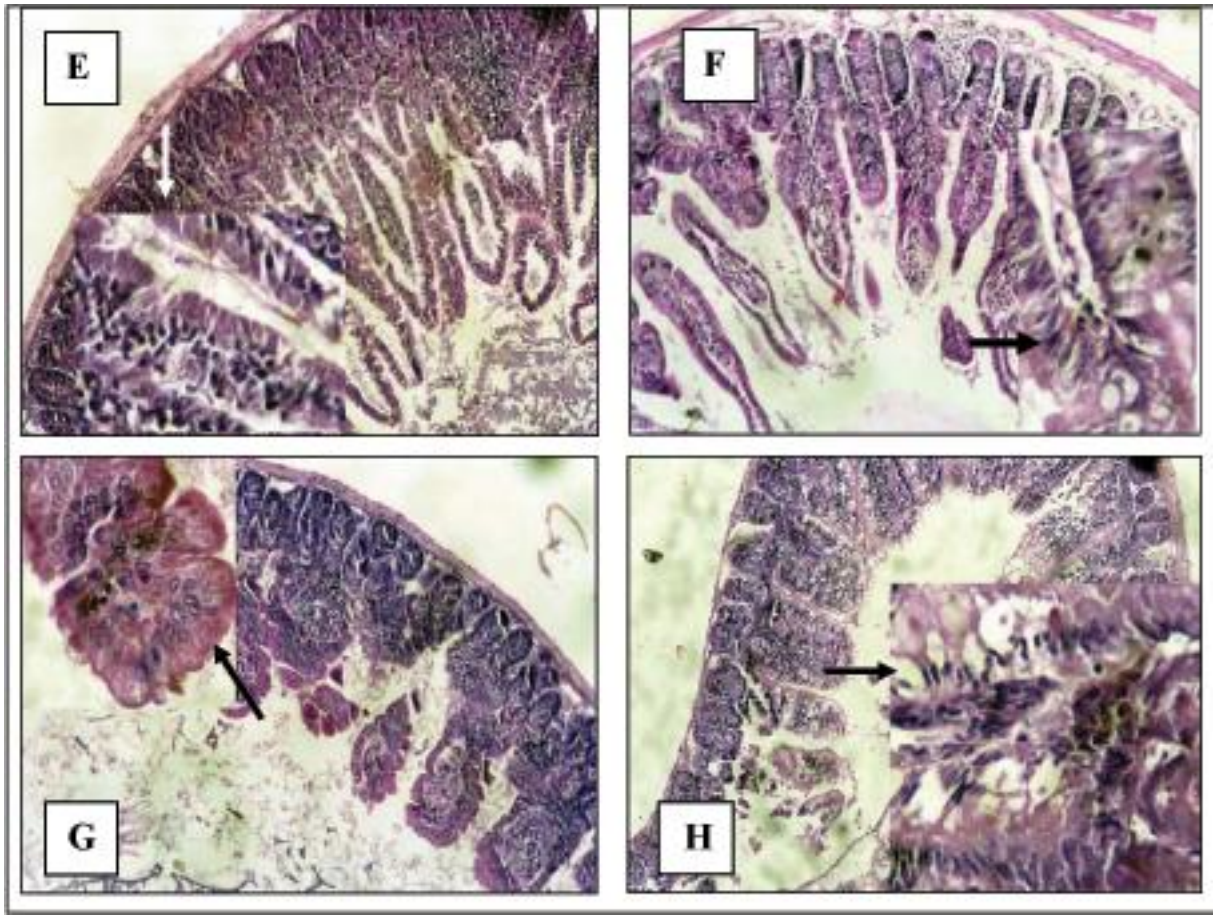


Fig (1): Liver sections of mice given NaSeO3 and subjected to γ-radiation. (H&E stain x 400). (A): Normal control liver tissue section. (B): Section in liver of mouse treated with NaSeO3. (C): Section in liver of mouse exposed to 5GY γ-radiation.(D): Section in liver of mouse treated with NaSeO3 and exposed to 5GY of γ-radiation.



B A.Fig (2): Intestine sections of mice given NaSeO3 and subjected to γ-radiation. (H&E stain x 100) (Arrow pointed to high magnification). (E): Normal control intestine tissue section. (F): Section in intestine of mouse treated with NaSeO3. (G): Section in intestine of mouse exposed to 5GY γ-radiation. (H):Section in intestine of mouse treated with NaSeO3 and exposed to 5GY γ-radiation.

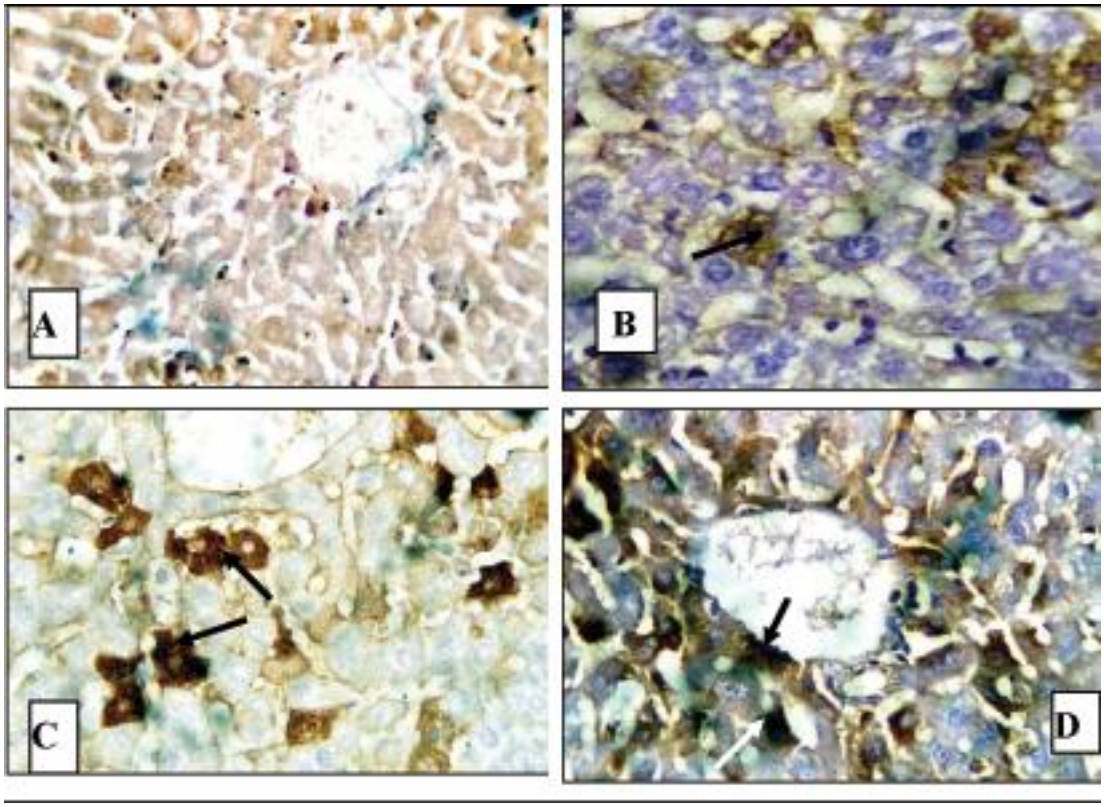


Fig (3): Staining of *P53* expression in liver sections by using Ab-1 mouse monoclonal antibody for immunohistochemical detection of murine *p53* in formalin fixed paraffin sections. Magnification was x400 for all figures. (A): Represent negative *p53* expression in control liver tissue section. (B): Expression of *p53* in liver tissue in animals exposed to 5 Gy γ-radiation. (C): Expression of *p53* in liver tissue when control mouse treated with NaSeO3. (D): Represent the expression of *p53* when control mouse treated with NaSeO3 and exposed to 5 Gy γ-radiations.

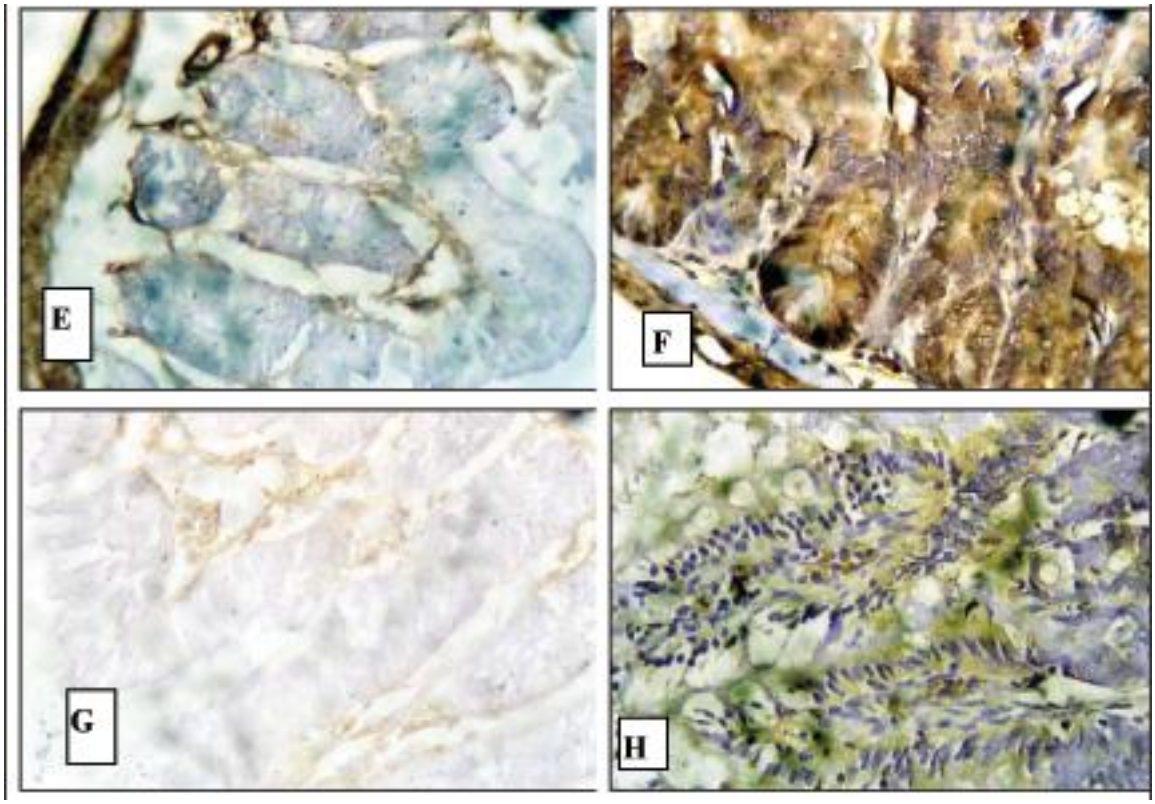


Fig (4): Staining of *p53*expression in intestine tissue sections by using Ab-1 mouse monoclonal antibody for immunohistochemical detection of murine *p53* in formalin fixed paraffin embedded intestine sections. Magnification was x400 for all figures. (E): Represent negative *p53* expression in control intestine tissue section. (F): Expression of *p53* in intestine tissue as affected by 5Gy of γ-radiation exposure. (G): Expression of *p53* in intestine tissue when control mouse treated with NaSeO3. (H): Represent the expression of *p53* in intestine tissue when control mouse treated with NaSeO3 and exposed to 5 Gy of γ-radiation.

Discussion

It is known that the exposure to Radiation produces various reactive oxygen species (ROS) in biological systems (Adler *et al.,* 1999) which react and damage cellular macromolecules (Sies, 1986).

In the current study a significant increase in lipid peroxiation was observed in liver and intestine tissues after whole body γ-irradiation due to oxidation of sulfhydryl group or due to the diminished activity of glutathione reductase (GR), (Sarkar *et al.*,1998). Also, Erden and Kahraman (2000) recorded decline in GR in liver tissue of animals exposed to irradiation and contributed this decline to the inactivation of SH groups existing at the active site of the enzyme molecule by $^{\cdot}OH$ and $^{\cdot}O_2$ which are formed as result of irradiation. Additionally Irshad and Chaudhuri (2002) indicated that there is a close relaion between depletion of GSH and antioxidant enzymes and increase in lipid peroxidation which leads to increase in MDA and the damage in liver tissue which is based on the excessive formation of ROS as well as the depletion of cellular antiox-idants which leads to histopathological observations. Atrophy in the endothelial cell of the central vein, the presence of fragmented hepatic cells and many of the hepatocytes have pyknotic nuclei (Li-Hua *et al.,* 2006). In addition, the exposure of

experimental animals to 5 Gy γ-radiation revealed compact and the shortening of intestinal villi and decrease in goblet cells. Jindal *et al*. (2006) observed that irradiation produced a significant decrease in crypt survival, mitotic figures and villus length; whereas goblet and apoptic cells showed a significant increase in irradiated animals. Becciolini *et al*. (1995) predicted that acute intestinal toxicity may occur in response to therapeutic or accidental exposure to ionizing radiation. At the histopathological level, it is characterized by a decrease in the depth of the intestinal crypts and the height of the villi. It is associated with basement membrane degradation, and ultimately leads to mucosal barrier breakdown and ulceration.

In the current study supplementations of selenium in the form of $NaSeO_3$ revealed a non significant change in the MDA level in the liver and intestine tissues while a highly significant increase in GSH level was predicted because Selenium have its main role as an antioxidant in the enzyme selenium-glutathione-peroxidase production. This enzyme neutralizes hydrogen peroxide which is produced by some cell processes and would otherwise damage cell membranes (Roderick *et al.,* 2002).

Shani *et al.* (2003) postulated that histological examination of liver tissue showed normal pattern due to the treatment of experimental animals with $NaSeO_3$.

There is a great relation between the antioxidant status of the tissue cells and the *p53* expression. Involvement of plasma membrane and reactive oxygen species (ROS) generated by genotoxic stress free radicals caused damage to cellular membrane which in turn damage to biomolecules such as proteins and lipids of membrane which shown to initiate cascade of biochemical reactions and signalling events resulting in loss of cellular functions and eventually cell death (Pandey and Mishra, 1999, 2000 and 2003). Accumulated evidences suggest the active involvement of ROS as signalling molecule for the initiation and execution of apoptotic death has been shown that decrease in pool of intracellular glutathione (GSH), by lowering the cytoplasmic reducing capacity and increasing the MDA level and which leads to the *p53* expression resulting in apoptosis (Pandey and Mishra.,2003) . On the other hand when tissue cells are exposed to ionizing radiation, they initiate a complex response that includes the arrest of cell cycle progression in G1 and G2, apoptosis and DNA repair. DNA is an important subcellular target of ionizing radiation, but oxidative damage to plasma membrane lipids initiates signal transduction pathways that activate apoptosis and that may play a role in cell cycle regulation. How is DNA damage converted into intracellular signals for cell cycle arrest? The ataxia telangectasia mutant (ATM) protein and/or the DNA-dependent protein kinase (DNA-PK), that are both activated by DNA damage, may initiate cell cycle arrest by activating the *p53* tumor suppressor protein. The *p53* protein acts as a transcription factor and regulates expression of several components implicated in pathways that regulate cell cycle progression (Teyssier *et al*., 1999).

In the current study exposure of experimental animals to 5Gy γ-radiation, expression of highly *p53*-positive cells in the small intestinal crypts and in many of the hepatocytes which suffered from cytoplasmic vacuolation were observed.

James *et al.* (1998) expressed that exposure to γ-radiation resulting strong *p53* expression and a higher frequency of apoptosis relative to the cells towards the top of the intestinal crypts and postulated that in apoptosis and a reduction in the fraction of proliferating cells; these cellular responses were associated with a time and dose-dependent increase in the expression of *p53*.

However the finding of Carol *et al.*, (1995) reported that *p53* protein accumulation was not detected in the hepatocytes of the irradiated mouse while the intestine tissue predict *p53* protein expression.

Treatment of mice with NaSeO3 revealed marked expression of *p53* in many of the hepatocyes as compared to other treatment for the role efficient apoptotic process of $NaSeO_3$ in normal tissues to prevent malignant transformation and help to correct age-related tissue damage (Zhang and Herman 2002). Also Shen *et al.,* (2000)

found that Se-induced oxidative stress and apoptosis are closely related to the intracellular level of GSH but the treatment of the experimental animals with $NaSeO_3$ revealed a negative expression of intestinal *p53*.

Pronounced expression of *p53* was noticed in liver and intestine tissues when the experimental animals treated with $NaSeO_3$ and exposed to 5 Gy γ-radiation.

The accumulation of *p53* protein in response to genotoxic stress like radiation exposure appears to be a means of inducing growth arrest and apoptotic cell death by the transcriptional regulation of other genes (Kern *et al*., 1991; Kastan *et al.,* 1992; El-Deiry *et al.,* 1993), and possibly by other direct mechanisms (Caelles *et al*., 1994) and the *p53* expression after genotoxic (Merritt et al., 1994 and Clarke *et al*., 1994). It is known that NaSeO3 was the main part of the tissue providing with selenium. Selenium activates certain pro-apoptotic genes linked to *p53*, NFκB and stress signal pathways in response to "danger signals" in mic liver (Huawei *et al.*, 2003). Since Selenium was the main one for its role as an antioxidant in the enzyme selenium-glutathione-peroxidase, which neutralizes hydrogen peroxide produced by some cell processes and would otherwise damage cell membranes. Selenium prevented radiation induced apoptosis, but did not decrease the levels of radiation induced *p53*; however selenium prevents radiation induced cell death by inhibiting *p53*-independent cell death pathways (Rafferty *et al*., 2003).

It is possible to conclude that NaSeO3 supplementation to mice exposed to ionizing radiation could ameliorate effects against cellular damage caused by radiation oxidative stress.

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دور ساليـنات الصوديم فى تخفيف الإجهاد التأكسدى الناتـج عن التعرض لأشعة جاما

نعمات حنفى أحمد
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تهـــدف هـــذه الدراســـه إلـى تحديـد دور ســـالينات الصـوديوم فـى تعـديل الإجهـاد التأكسدى نتيجـة التعرض لأشـعة جـــاما وقـد اســتخدمت الفــئران المهـقاء فى هذا العمل حيث تم قياس الجلوتاثيون والمالنالدهيد فى كل من الكبد والامعاء . كذلك درست التغيرات الباثولوجية و تعبير *p53* لنفس الانســـجة. وقد اوضحت النتائجززيادة المالنالدهيد ونقص الجلوتـاثيون فـى كـل مـن الكبـد والامعـاء نتيجـة تعـرض الفئـران لجرعـة مقدارها 5 جـراى. ونتيجة إعـطاء الفئران ســالينات الصوديوم أظـهرت تلك الانسجة تغير غير معنوى فى معدل المالنالدهيـد و زيـادة معنويـة فـى معـدل الجلوتـاثيون. وأسـفرت التغيـرات الباثولوجيـة عـن تغيرات مماثله فى كل من الكبد والامعاء. وقد أظهرت النتـائج المناعـيه الهستوكيمائية أن *p53* يختلف فى تعبيرة طبقا لاختلاف نـوع النسيج واختلاف نـوع المعـاملات. ومن النتـائج السابق ذكرها يمكننا ان نحد من أضـرار الإشـــعاع بتنــاول أطعمـة تحتـوى علـى ســـالينات الصوديوم.