

# Lycopene Protects the Structure of the Small Intestine against Gamma-Radiation-induced Oxidative Stress

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**The small intestine displays numerous morphological and functional alterations after exposure to ionizing radiations. Oxidative stress and changes in monoamines levels may contribute toward some of these alterations. The objective of the current work is to evaluate the efficacy of lycopene on radiation-induced damage in the small intestine. Lycopene (5 mg/kg BW) was given to male albino rats, via gavages for 7 days before whole body exposure to gamma ray (6 Gy). Irradiated animals, sacrificed 7 days after irradiation, showed sloughing villi, ulcers, and ruptured goblet cells, shrinkage of submucosa layers, more fibers and fibroblasts. Histopathological changes were associated with a significant increase in thiobarbituric acid reactive substances (TBARS) and alteration in xanthine oxidoreductase system (XOR). In parallel, significant decreases in reduced glutathione (GSH) content, superoxide dismutase (SOD) and catalase (CAT) activities were recorded. Gamma irradiation has also induced a significant decrease in the level of monoamines: serotonin (5-HT), dopamine (DA), norepinephrine (NE), and epinephrine (EPI) associated with an increase in monoamine-oxidase (MAO) activity. Lycopene pretreatment has significantly improved the oxidant/antioxidant status, which was associated with significant regeneration of the small intestine, and improved monoamines levels. Based on these results, it is concluded that lycopene may protect the small intestine against radiation-induced damage. Copyright © 2009 John Wiley & Sons, Ltd.**

*Keywords:* radiation; lycopene; small intestine; monoamines; oxidative stress.

## INTRODUCTION

Radiation therapy is an essential therapeutic modality in the management of a wide variety of tumors, but its immediate and delayed side effects on the normal tissues limit the effectiveness of the therapy (Grdina *et al.*, 2002). Moreover, the increased focus on treatment-related side effects in cancer survivors and the need for medical countermeasures against radiologic or nuclear accidents or terrorism have resulted in a resurgence of interest in the mechanisms of, and ways to modify, radiation injury.

The effect of whole body irradiation is mainly due to the damage of gastrointestinal epithelium and bone marrow progenitor cells, both of which are critically important for survival. The normal physiological processes are impaired through damage to such rapidly proliferating cells. Regarding the small intestine, acute morphological changes are associated with motor dysfunction (Frisby *et al.*, 2007). Many gross symptoms such as anorexia (loss of appetite), nausea, vomiting, and diarrhoea are characteristically present. In this line, El-Tahawy (2009) has demonstrated that exposure to ionizing radiation induces a decrease in the level of small intestine monoamines – dopamine, norepineph-

rine, epinephrine and serotonin – which are important regulators of intestinal motility (Baglolle *et al.*, 2005). Furthermore, irradiation enhances the activity of monoamine oxidases (MAO-A and MAO-B) (El-Tahawy, 2009) – enzymes bound to the outer membrane of mitochondria that catalyze the oxidative deamination of monoamines – and consequently plays a pathophysiological role by enhancing the generation of oxidant species (Richards *et al.*, 1996).

The detrimental effects of ionizing radiation are associated, also, with alteration in the xanthine oxidoreductase (XOR) system through the conversion of xanthine dehydrogenase (XDH) into xanthine oxidase (XO) (Srivastava *et al.*, 2002). The XOR system consists of two inter-convertible forms, xanthine oxidase (XO) and xanthine dehydrogenase (XDH), the latter accounts for about 90% of the total activity of XOR and has no role in the initiation or potentiation of oxidative damage in the cells. In many pathological conditions, however, XDH is converted to XO associated with an increase in the production of superoxide anion ( $O_2^{\bullet-}$ ). Superoxide anion can be converted spontaneously or enzymatically into hydrogen peroxide ( $H_2O_2$ ) and then into the highly reactive hydroxyl radical ( $\bullet OH$ ), that initiate the lipid peroxidation chain reaction (Wardman and Candeias, 1996). Superoxide anion may react, also, with nitric oxide (NO) to generate the cytotoxic peroxy nitrite anion ( $ONOO^-$ ), which can react with carbon dioxide, leading to protein damage via the formation of nitrotyrosine (Huie and Pasmaja, 1993).

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Efficient defense and repair mechanisms exist in living cells to protect against oxidant species. Superoxide dismutase (SOD) catalyzes the reduction of  $O_2^{\cdot-}$  to hydrogen peroxide ( $H_2O_2$ ), the majority of which is broken down to oxygen and water by CAT. In addition to CAT, glutathione peroxidase (GSH-Px) in presence of adequate amount of reduced glutathione (GSH) can also break down  $H_2O_2$  (Sun *et al.*, 1998).

Radiation damage, is to a large extent, caused by the overproduction of reactive oxygen species (ROS), including superoxide anion ( $O_2^{\cdot-}$ ), hydroxyl radical ( $\cdot OH$ ), and hydrogen peroxide ( $H_2O_2$ ), that overwhelm the levels of antioxidants, resulting in oxidative stress and cellular damage. If this damage is irreparable, then injury, mutagenesis, carcinogenesis, accelerated senescence, and cell death can occur (Spitz *et al.*, 2004).

Lycopene – a carotenoid found in tomatoes, water melon, pink guava, pink grapefruit and papaya – has a structure similar to that of the well-known antioxidant beta-carotene, but its antioxidant activity in neutralizing singlet oxygen has been shown to be much stronger (Tsen *et al.*, 2006). Several studies confirmed the antioxidant (Rao *et al.*, 2007; Wood *et al.*, 2008) and antitumor (Fornelli *et al.*, 2007; Huang *et al.*, 2008) capacity of lycopene.

Meanwhile, the antioxidant capacity of lycopene offers protection against gamma-radiation-induced damage to cell membranes (Saada and Azab, 2001). A study lead by Srinivasan *et al.* (2007) even concluded that lycopene could be developed as effective radioprotector during radiotherapy of cancer patients. In favor of this postulation, Puri *et al.* (2005) found that the addition of lycopene to radiotherapy and chemotherapy in patients with high-grade glioma results in a positive outcome.

In view of these considerations, the main objective of this study was to assess the role of lycopene in protecting the normal architecture of the small intestine from radiation-induced damage. In parallel, the efficacy of lycopene on radiation-induced oxidative stress and the alterations in monoamine metabolism have been evaluated.

## MATERIAL AND METHODS

All animal procedures were performed in accordance with the Ethics Committee of the National Research Center and in accordance with the recommendations for the proper care and use of laboratory animals (NIH publication No. 85–23, revised 1985).

Irradiation was performed through the use of a Canadian Gamma Cell-40 ( $^{137}Cs$ ) at the National Center for Radiation Research and Technology (Cairo, Egypt). The dose rate of Gamma cell (0.5 Gy/minute) was calculated according to the Dosimetry Department in our Institute (NCRRT), where 0.5Gy is emitted from the Cesium source/minute.

Lycopene purchased from Sigma Chemical Co., (St. Louis, MO, USA) was dissolved in pure sesame oil. Rats received 5 mg/Kg body weight, by gavages, according to Saada and Azab (2001).

Male Albino rats (130–140 g) purchased from the Egyptian Holding Company for Biological Products and Vaccines (Cairo, Egypt) were used. Animals were

housed under standard conditions of light and temperature and allowed free access to standard pellet diet and tap water. Animals were randomly divided into four groups. Control group: animals neither exposed to radiation nor treated with lycopene. Lycopene group: animals received lycopene (5 mg/Kg/day) during 7 successive days. Irradiation group: rats were whole body exposed to 6 Gy applied in one dose. Lycopene+ irradiation group: rats received lycopene (5 mg/Kg/day) during 7 successive days before irradiation.

Six animals from each group were sacrificed on the 7th day post-irradiation. Blood was collected and ileum tissues were removed for biochemical and histological investigations. XO and XDH were determined according to Kaminski and Jewezska (1979). SOD and CAT activities were determined according to Minami and Yoshikawa (1979) and Aebi (1984), respectively. The content of GSH was determined according to Beutler *et al.* (1963). The extent of lipid peroxidation was assayed by the measurement of TBARS according to Yoshioka *et al.* (1979). The content of catecholamine, epinephrine (EPI), nor epinephrine (NE) and dopamine (DA) were estimated fluorometrically according to Maurer *et al.* (1973). The content of serotonin (5-HT) was assayed by the fluorometric method of Ciarlone (1978). The activity of monoamine oxidase (MAO-A+MAO-B), was measured according to the method of Ozaki *et al.* (1960). Protein contents, was measured by the method of Lowry *et al.* (1951).

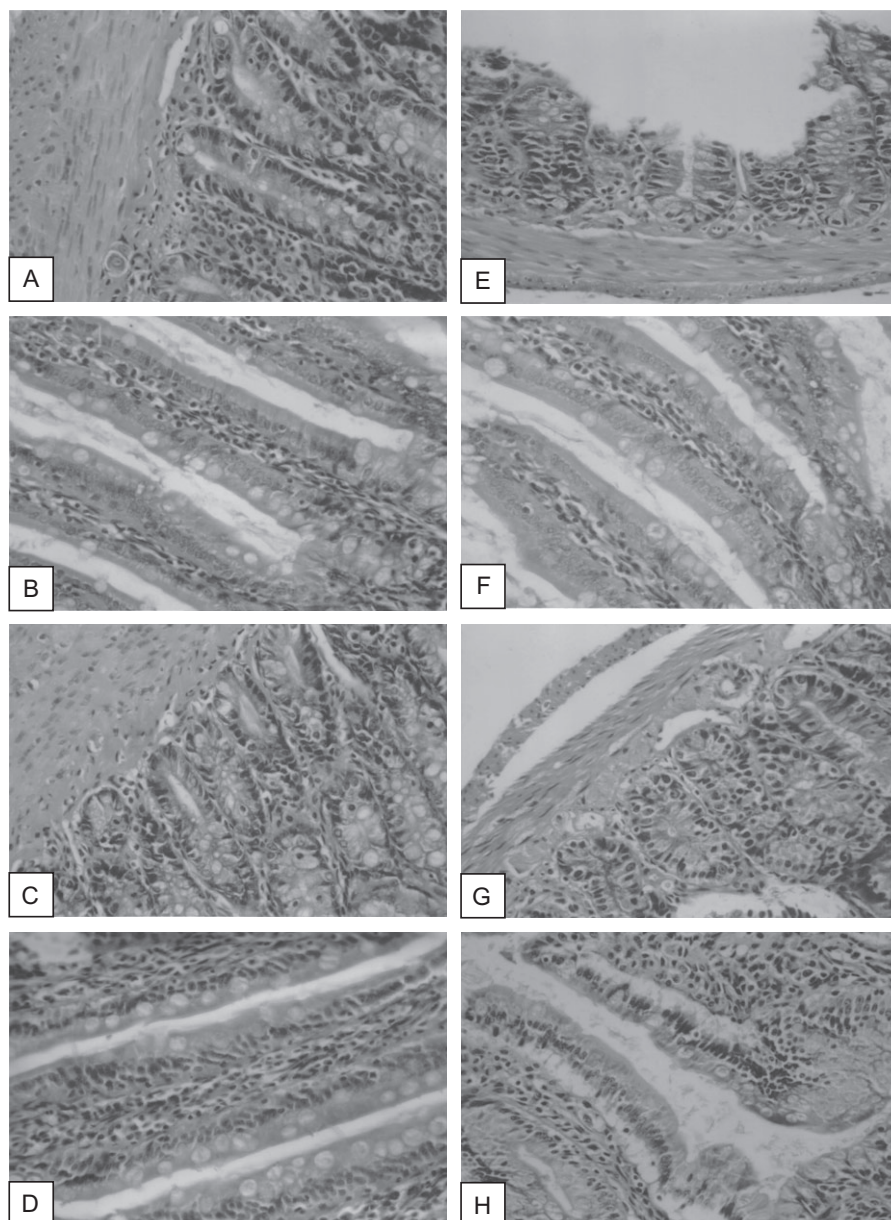
Samples of small intestine were excised immediately, fixed in 10% formalin, processed routinely for paraffin embedding and sectioned at 4  $\mu$ m. Sections were stained with haematoxylin and eosin and mounted with Canada balsam according to Lewis and Knight (1977). The sections were examined by Olympus light microscope to detect the histological changes induced by any of the treatments described previously.

Results were presented as mean  $\pm$  SD ( $n = 8$ ). Experimental data were analyzed using one way analysis of variance (ANOVA). Duncan's multiple range test was used to determine significant differences between means. The statistical analysis systems (SAS) package was used for statistical analysis. Differences between means were considered significant at  $P \leq 0.05$ .

## RESULTS AND DISCUSSION

Exposure of mammals to ionizing radiations, leads to the development of a complex, dose-dependent series of changes, including injury to different organs which cause changes in the structure and function of cellular components, resulting in tissue damage and death. Radiation produced marked intestinal mucosal injury, a decrease in the number of villi, villus height, a decrease in the number of crypts cells, and damage of epithelial and goblet cells (Akpolat *et al.*, 2009). Oxidative stress with subsequent production of ROS has been postulated as one of the mechanisms of radiation toxicity (Finkel and Holbrook, 2000).

In the present study, the small intestine of control (Fig. 1A, B) and rat receiving lycopene (5 mg/Kg BW/day) for 7 successive days (Fig. 1C, D) showed normal architecture. Whole body exposure of rats to gamma radiations (6 Gy) resulted into sloughing villi, ulcers,



**Figure 1.** Photomicrographs of rats small intestine sections (ileum). A, B **control**, C, D, **lycopene**: showing muscularis mucosa opened into crypts, components cell types in crypts base (crypts base columnar cells and paneth cells, striated border columnar cells and goblet cells). The simple columnar epithelium also contains goblet cells in villi. E, F **irradiation**: showing sticking of submucosa layers, ill defined, sloughing crypts, ulcers and ruptured villi. G, H **lycopene+irradiation**: showing improved submucosal layers, regenerated muscularis mucosa opened in crypts, normal shape crypts with various cell types and regenerated villi with normal shape (H&E) (A, C, E, G x400) (B, D, F, H x 1000).

and ruptured goblet cells, shrinkage of submucosa layers, more fibres and fibroblasts (Fig. 1E, F). The histopathological changes observed in the small intestine of irradiated rats could be primarily attributed to radiation-induced oxidative stress and increased lipid peroxidation; one of the major mechanisms of tissue injury. Confirming this postulation a significant increase ( $P \leq 0.05$ ) in the level of TBARS (Table 2) associated with a significant decrease ( $P \leq 0.05$ ) in the activity of SOD and CAT, and in the content of GSH (Table 2) was recorded in the small intestine of irradiated rats. The elevated level of TBARS might probably result from the interaction of the excess of  $\cdot\text{OH}$ , resulting from the radiolysis of water upon exposure to ionizing radiation, with polyunsaturated fatty acids in the phospholipids portion of cellular membranes (Spitz *et al.* 2004). The significant decrease ( $P \leq 0.05$ ) in the activity

of SOD and CAT might also be attributed to the excess of ROS, which interacts with the enzyme molecules causing their denaturation and partial inactivation (Kregel and Zhang, 2007). The depletion in GSH may be due to its reaction with free radicals resulting in the formation of thiyl radicals that associate to produce oxidized glutathione (GSSG). GSH can, also, react with peroxynitrite anion ( $\text{ONOO}^-$ ) to form S-nitrosoglutathione (Roy *et al.*, 2006).

According to the data obtained, it appears that the detrimental damage of radiation in the small intestine is associated with the alteration of XOR system and conversion of XDH into XO activity (Table 2). The significant increase ( $P \leq 0.05$ ) in XO activity might be attributed to radiation-induced hypoxia where insufficient oxygen availability elevates calcium concentration, which activates a protease capable of converting

**Table 1. Effect of lycopene on xanthine oxidoreductase system (XO and XDH), thiobarbituric acid reactive substances (TBARS) contents, superoxide dismutase (SOD), catalase (CAT) activities and reduced glutathione (GSH) contents, in the small intestine of rats, 7 days post 6 Gy gamma irradiation**

Parameters	Rat groups			
	Control	lycopene	Irradiation	lycopene+ Irradiation
XO (mU/mg protein)	1.52 ± 0.075 <sup>a</sup>	1.50 ± 0.054 <sup>a</sup>	3.04 ± 0.064 <sup>b</sup>	2.30 ± 0.061 <sup>c</sup>
XDH (mU/ mg protein)	3.12 ± 0.161 <sup>a</sup>	3.18 ± 0.143 <sup>a</sup>	1.66 ± 0.089 <sup>b</sup>	2.34 ± 0.071 <sup>c</sup>
TBARS (n mol/g ww)	180 ± 7.14 <sup>a</sup>	170 ± 6.43 <sup>a</sup>	324 ± 16.07 <sup>b</sup>	230 ± 11.79 <sup>c</sup>
SOD (U/ mg protein)	21.6 ± 1.14 <sup>a</sup>	21.0 ± 1.07 <sup>a</sup>	9.0 ± 0.46 <sup>b</sup>	11.2 ± 0.54 <sup>c</sup>
CAT (U/ mg protein)	3.9 ± 0.089 <sup>a</sup>	4.0 ± 0.075 <sup>a</sup>	1.7 ± 0.107 <sup>b</sup>	2.7 ± 0.143 <sup>c</sup>
GSH (mg/g ww)	30.0 ± 1.61 <sup>a</sup>	29.5 ± 1.43 <sup>a</sup>	17.5 ± 1.11 <sup>b</sup>	24.0 ± 1.40 <sup>c</sup>

Values are expressed as means of 8 records ± Standard Error

Means with different superscripts are significantly different at the 0.05 level

**Table 2. The effect of lycopene on the levels of monoamines (Dopamine: DA, Norepinephrine: NE, Epinephrine: EPI, Serotonin: 5-HT), and monoamine oxidase (MAO) activities, in the small intestine of rats, 7 days post 6 Gy gamma irradiation**

Parameters	Rat groups			
	Control	lycopene	Irradiation	lycopene+ Irradiation
DA ( g/ g ww)	3.00 ± 0.054 <sup>a</sup>	2.90 ± 0.050 <sup>a</sup>	1.80 ± 0.043 <sup>b</sup>	2.40 ± 0.046 <sup>c</sup>
NE ( g/ g ww)	2.02 ± 0.043 <sup>a</sup>	2.00 ± 0.039 <sup>a</sup>	1.15 ± 0.054 <sup>b</sup>	1.62 ± 0.057 <sup>c</sup>
EPI ( g/ g ww)	2.03 ± 0.042 <sup>a</sup>	1.9 ± 0.357 <sup>a</sup>	0.97 ± 0.050 <sup>b</sup>	1.42 ± 0.046 <sup>c</sup>
5-HT ( g/ g ww)	6.00 ± 0.400 <sup>a</sup>	6.18 ± 0.275 <sup>a</sup>	3.00 ± 0.161 <sup>b</sup>	4.50 ± 0.239 <sup>c</sup>
MAO (mg consumed 5-HT/g ww/hr)	1.90 ± 0.089 <sup>a</sup>	1.85 ± 0.071 <sup>a</sup>	3.08 ± 0.125 <sup>b</sup>	2.66 ± 0.143 <sup>c</sup>

Values are expressed as means of 8 records ± Standard Error

Means with different superscripts are significantly different at the 0.05 level

the dehydrogenase to oxidase form (McCord, 1985). Furthermore, the results showed that radiation-induced significant depletion in the content of GSH, which is essential for maintaining XDH in its reduced form (Kooij *et al.*, 1994).

In the present study, the significant decrease ( $P \leq 0.05$ ) in the levels of 5-HT, DA, NE, and E (Table 2) might be attributed to decreased synthesis resulting from radiation-induced damage to the ileal mucosa and reduction in net ilea absorption (Herrera *et al.*, 1995), where a decrease in the absorption of tryptophan would reduce the synthesis of serotonin, while a decrease in absorption of L-tyrosine may diminish the production of DA, NE and E. The results obtained in the present study, however, showed a significant increase ( $P \leq 0.05$ ) in the activity of MAO (Table 2), which suggests the possibility that radiation provokes the degradation of monoamines. The increase in the activity of monoamine oxidase might result from depletion in the absorption of sodium (Sarobe *et al.*, 2005).

It is well documented that dietary antioxidants play an important role in mitigating the damaging effects of oxidative stress on cells. Lycopene – a carotenoid highly present in tomatoes and tomato products – was shown to scavenge ROS and reactive nitrogen species (RNS) (Muzandu *et al.*, 2006) and to exhibit high singlet oxygen quenching ability (Rao and Rao, 2007). In this context, Rencuzogullari and Erdogan (2007) found that oral administration of lycopene reduces lipid peroxidation in cadmium-treated rats. Atessahin *et al.* (2007) mentioned that lycopene attenuates oxidative stress in

cyclosporine-treated rats. Wood *et al.* (2008) showed that the intake of lycopene modulates antioxidant activity in asthma and airway inflammation.

In the current study, the oral administration of lycopene, via gavages, for 7 successive days, before whole body gamma irradiation with 6 Gy, has reduced oxidative stress. The data obtained revealed a significant reduction ( $P \leq 0.05$ ) in the activity of XO and the level of TBARS (Table 1) with concomitant significant increase ( $P \leq 0.05$ ) in the activity of SOD and CAT, and in the content of GSH (Table 2), in comparison with their corresponding values in irradiated rats. Moreover, a significant increase ( $P \leq 0.05$ ) in the level of monoamines associated with a significant reduction ( $P \leq 0.05$ ) in the activity of MAO (Table 2) was recorded. Histological examination of sections in the small intestine revealed that the significant improvement in the oxidant/antioxidant status was associated with regeneration of small intestine tissue notified by amelioration in the structure of villi and crypt cells (Fig. 1G, H).

The results obtained corroborate the findings of Ito *et al.* (2004), who found that lycopene possesses a significant radioprotective effect on villi and crypts in the small intestine of abdominally radiated mice (15 Gy). The results confirm, also, the findings of Srinivasan *et al.* (2007) who establish that lycopene could be applied as a natural protector against gamma-radiation-induced damage.

According to the results obtained in the present study, it appears that pretreatment with lycopene attenuates the radiation-induced increase in the activity of

XO and MAO and maintain the activity of SOD and CAT, and GSH content. Consequently, lycopene would protect cellular membrane from radiation-induced lipid peroxidation so maintaining the architecture of small

intestine and preventing the release of monoamines. It could be concluded that lycopene pretreatment might be useful in protecting from radiation-induced oxidative damage.

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