Protective effects of curcumin against gamma radiation-induced ileal mucosal damage

Meryem Akpolat · Mehmet Kanter · Mustafa Cem Uzal

Abstract The major objective of this study was to test curcumin as a potential radioprotectant for the ileum goblet cells of the rat. Wistar albino rats were used in the study. Group A was the control group and group B was the single dose radiation group. Group C was the two dose radiation group (4 days interval). The rats in groups D and E were given a daily dose of 100 mg/kg of curcumin for 14 and 18 days, respectively. During the curcumin administration period, the rats in group D were exposed to abdominal area gamma ($\gamma$)-ray dose of 5 Gy on the 10th day and group E was exposed to same dose radiation on the 10th and 14th day. Irradiation and treatment groups were decapitated on the 4th day after exposure to single or two-dose irradiation and ileum tissues were removed for light and electron microscopic investigation. Single or two dose 5 Gy $\gamma$-irradiation caused a marked intestinal mucosal injury in rats on the 4th day. Radiation produced increases in the number of goblet cells. Curcumin appears to have protective effects against radiation-induced damage, suggesting that clinical transfer is feasible.

Keywords Radioprotection · Curcumin · Ileum · Goblet cell · Morphometry · Rat

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). Cell damage may develop, depending on dose and exposure time (Weiss et al. 1990). 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 in normal tissues (Denham et al. 2001).

The gastrointestinal tract is, after the bone marrow, the most sensitive organ to the effects of radiation. As a result of ionizing radiation, acute morphological changes of the intestine are observed within 24–48 h (Dalla 1968). Early radiation enteropathy develops during radiation therapy as a result of intestinal crypt cell death, disruption of the epithelial barrier, and mucosal inflammation (Wang et al. 2006).

Goblet cells are quantitatively the most important population of the small intestine epithelium after the columnar cells, among which they are intercalated (Becciolini et al. 1997). The gastrointestinal tract is covered by a mucus layer secreted by goblet cell, which arise from pluripotent stem cells present at the base of crypt. During migration in the crypt towards the villus, the goblet cells mature and lose the capacity to divide (Cheng and Leblond 1974). Mucus constitutes a protective barrier against microorganisms, physical and chemical attacks, and has the role of lubrication of the digestive tract (Forstner and Forstner 1994). Previous acute radiation studies indicate that the goblet cell response is complex. Some reports describe decreases or no change in cell number, while others demonstrate increases,
Detrimental effect of ionizing radiation on the living systems occurs mainly due to its indirect effects. On exposure to radiation, free radicals are generated from the radiolysis of water molecules. These free radicals interact with various biomolecules and bring about the changes in their structure and function (Jagetia and Reddy 2005).

Biologic modifiers targeting oxidative damage for radio-protection have been studied for decades with limited success. Hence, there is a need for better and more potent compounds, especially on herbal origin to boost antioxidant defence.

Curcumin is a dietary antioxidant derived from turmeric (Curcuma longa, Zingiberaceae) and has been known since ancient times to possess therapeutic properties. It has been reported to scavenge oxygen free radicals and to inhibit lipid peroxidation and protect the cellular macromolecules, including DNA from oxidative damage (Kalpana and Menon 2004; Polasa et al. 2004).

Meanwhile, administration of curcumin in cancer patients is claimed to kill the tumor cells effectively by enhancing the effect of radiation and, at the same time, protect normal cells against the harmful effects of radiation. The available information on curcumin suggests that the radioprotective effect might be mainly due to its ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammatory responses, whereas the radiosensitive activity might be due the upregulation of genes responsible for cell death (Jagetia 2007).

Most of the reports on the radioprotective role of curcumin have been restricted to animal studies, yet no reports are available on its role as a radioprotector in ileum goblet cells. Thus the aim of the present study was to evaluate the radioprotective effect of curcumin on γ-radiation-induced ileum goblet cells damage.

**Experimental**

**Materials and methods**

**Animals**

A total of 30 12–14 weeks old Male Wistar albino rats weighing between 250 and 300 g (Trakya University Animal Care and Research Unit, Edirne, Turkey) were housed under constant temperature (21°C) and photoperiod (12 h light/dark cycle). They had free access to standard rat chow diet. All animals received human care according to the criteria outlined in the “Guide for the Care and Use of Laboratory Animals” prepared by the National Academy of Sciences and published by the National Institutes of Health. The study was approved by the Institutional Animal Ethical Committee of the Trakya University, Edirne, Turkey.

**Experimental design**

The rats were randomly allotted into one of five experimental groups: A (control), B (single dose radiation treated), C (two dose radiation treated), D (single dose radiation treated with curcumin) and E (two dose radiation treated with curcumin); each group contain six animals (Table 1).

**Irradiation**

Irradiation was delivered by a 60Co teletherapy unit (Cirus, cis-Bio Int., Gif Sur Yvette, France) at a source-skin distance of 100 cm. Five Gy radiation were given at a depth of 1.5 cm (half thickness) with a dose rate of 62.41 cGy/min to the whole abdominal area in supine position. Correct positioning of the fields was controlled for each individual rat using a therapy simulator (Mecaserto-Simics, Paris, France). The 60Co unit was calibrated with an Exradin Farmer type ionization chamber (Keithley 35040 radiation dosimeter, Cleveland, Ohio, USA). A ±3% uncertainty in absorbed dose was estimated.

The rats were anesthetized by i.p. administration of 90 mg/kg ketamine and 10 mg/kg xylazine. Animals in single dose radiation treated groups B and D, and two dose radiation treated groups C and E (on the 4th day following the first dose) were exposed to 5 Gy γ-radiation. The control rats (group A) were treated similarly and taken to the theater, but they were not irradiated. The initial and final body weight changes of the various groups were recorded.

| Table 1 Experimental design |
|-----------------------------|
| **Day** | **Randomization** |
| 1 | Administration of physiologic saline to the rats in groups A, B and C by gavage |
| 10 | First irradiation of the rats in groups B, C, D and E |
| 14 | Second irradiation of the rats in groups C and E |
| 18 | Killing of the rats in groups A, B and D |
| | Administration of curcumin to the rats in group E by gavage |
| | Group A control; group B single dose radiation treated; group C two dose radiation treated; group D single dose radiation treated with curcumin; group E two dose radiation treated with curcumin group |
Drug preparation and sample collection

Groups A, B and C received 1 ml serum physiologic, and group D for 14 days (10 days before and 4 days after irradiation) and group E for 18 days (14 days before and 4 days after the 2nd dose irradiation) were given curcumin (in a dose of 100 mg/kg body weight) once a day orally by using intra gastric intubation. Irradiation and curcumin-treated groups were decapitated on the 4th day exposure to single or two dose irradiation and ileum tissues were removed for light and electron microscopic investigation.

Light and electron microscopic procedures

For light microscopic observation, ileum specimens were embedded in the paraffin blocks after they had been fixed in Bouin’s solution. Five micrometer (μm) sections were obtained and stained with hematoxylin + eosin (H + E) and periodic acid + Schiff + hemalen (PAS + HI).

For electron microscopy, ileum tissue specimens were fixed with 2.5% glutaraldehyde in 0.1 M sodium phosphate buffer (pH 7.2) for 1.5 h at 4°C, tissues were washed in same buffer overnight after primary fixation. The tissues were postfixed with 1% osmium tetraoxide in sodium phosphate buffer for 1 h at 4°C. Then the postfixed tissues were washed in same buffer and dehydrated by graded series of ethanol starting at 50% each step for 10 min and finally with propyleneoxide. The tissue specimens were embedded in araldite. Ultrathin sections were obtained by ultramicrotome (RMC-MTX Ultramicrotome-USA) and collected on copper grids for double staining (uranyl acetate and Reynold’s lead citrate). Stained sections were finally observed under a Jeol-JEM 1010 transmission electron microscope.

Histopathologic analysis

Ileum sections were stained with H + E, and mucosal injury, inflammation and hyperemia/hemorrhage were assessed and graded in a blinded manner by a histologist using the histologic injury scale previously defined by Chiu et al. (1970). Briefly, mucosal damage was graded from 0 to 5 according to the following criteria: grade 0, normal mucosal villi; grade 1, development of subepithelial Gruenhagen’s space at the apex of the villus, often with capillary congestion; grade 2, extension of the subepithelial space with moderate lifting of the epithelial layer from the lamina propria; grade 3, massive epithelial lifting down the sides of villi, possibly with a few denuded tips; grade 4, denuded villi with lamina propria and dilated capillaries exposed, possibly with increased cellularity of lamina propria; and grade 5, digestion and disintegration of the lamina propria, hemorrhage, and ulceration. The sum of the scores for the individual alterations constitutes the Radiation Injury Score (RIS).

Morphometric analysis

For morphometric analysis four whole circumference sections, 5-μm thick and 20 μm apart were cut per animal and stained with PAS + HI. Tissue sections were examined and the number of the villus goblet cells counted within random high-power fields using a Olympus Bx 51 light microscope incorporating a square graticule in the eyepiece (eyepiece ×10, objective ×40, a total side length of 25 μm). Villus goblet cell density in each site was calculated and recorded as the number of goblet cells/μm².

Statistical analysis

All statistical analyses were carried out using SPSS statistical software (SPSS for windows, version 11.0). All data were presented in mean (±) standard deviations (SD). Differences in measured parameters among the five groups were analyzed with a nonparametric test (Kruskal–Wallis). Dual comparisons between groups exhibiting significant values were evaluated with a Mann–Whitney U test. These differences were considered significant when probability was less than 0.05.

Results

Histopathologic findings

When the ileum specimens obtained from the control group were examined as light and electron microscopic, normal histologic structure of the villi intestinalis and Lieberkhün cripts were observed (Fig. 1a–c). In the single and two dose radiation treated groups, the most consistent findings occurring in the histologic tissue sections stained with H + E and PAS + HI were those indicating severe degenerative changes. Four days after irradiation, the morphological structure of the ileum changed. Concomitantly with cell depletion, additional alterations in cell morphology were observed in the epithelium. The atrophic mucosa was lined with a continuous layer of grossly abnormal epithelial cells, racket-shaped cells at the luminal side of the ileum. Ionizing radiation-induced cell loss led to reduced circumference of the crypts and shortened the length of villi. In addition to the decrease of the villus height, light microscopic investigations revealed further alterations in shape and surface of the villus (Fig. 1d–i).

The epithelial cell damage in the single dose radiation treated group was not widespread as compared to two dose radiation treated group (Fig. 1d–i). In the single dose radiation with curcumin (Fig. 1j–l) and two dose radiation with curcumin-treated (Fig. 1m–o) rat ileum, the intensity of epithelial cell damages were less than in the only radiation
In the curcumin-treated groups, villi were generally normal although apical regions of some villi were thinner. On the other hand, the number of goblet cell profiles were increased significantly in both only radiation treated and radiation with curcumin-treated rats when compared to villus intestinalis areas of the control rats (Table 2). Both the decrease in enterocytes and the increase in the percentage of goblet cells led to an increase of mucin exposed to the villous surface. A few apoptotic bodies (not quantified) were seen following both irradiation regimes.

Fig. 1 Histological examination of rat small intestine taken from the segments of ileum. Photomicrographs of ileum sections stained with H + E (a, b, d, e, g, h, j, k, m, n), and PAS + HL (c, f, i, l, o). a–c Control rats ileum; showing normal morphology. d–f Single dose radiation-treated rats; shortened and thickened villi (arrowhead) and degenerative changes in the epithelial cells (arrow), lifting of epithelial layer from the lamina propria (asterisks), and increase in the goblet cells and mucins showing strongly positive to PAS staining (thick arrows). g–i Two dose radiation-treated rats; shortened and irregular villi (arrowhead) and breaking in the epithelial cells (arrow), massive subepithelial lifting and capillary congestion in the villus (asterisks), and increase in the goblet cells and mucins showing strongly positive to PAS staining (thick arrows). j–l Single dose radiation-treated with curcumin rats; villi were generally normal (Vi) although apical regions of some villi were lightly subepithelial lifting (asterisks) and thinning (arrow), normal scattered goblet cells (thick arrows). m–o Two dose radiation-treated with curcumin rats; development of subepithelial space (asterisks) and lightly capillary congestion (thick arrows) usually at the apex of the villus, occasional occurrence of thickened villi (arrowhead) along with normal villi (Vi) and breaking in the epithelial cells (arrow), goblet cells showing strongly positive to PAS staining (thick arrows) (scale bar: 50 μm).
Table 2 The numbers (number/μm²) of goblet cells in the villi intestinals of A (control), B (single dose radiation treated), C (two dose radiation treated), D (single dose radiation treated with curcumin) and E (two dose radiation treated with curcumin) groups

| Groups | Goblet cell number/0.625 μm² Mean ± SD |
|--------|---------------------------------------|
| A      | 62.75 ± 8.83                          |
| B      | 120.45 ± 12.66a                        |
| C      | 154.38 ± 17.91b                        |
| D      | 94.98 ± 9.87c                         |
| E      | 109.20 ± 11.12a                       |

a P < 0.01 compared to control group
b P < 0.001 compared to control group, P < 0.01 compared to group E
c P < 0.05 compared to control group, P < 0.05 compared to group B, P < 0.01 compared to group C

degranulation of rough endoplasmic reticulum (RER) membranes (Figs. 3b, 4b). Radiation-induced loss of mitochondrial matrix and vacuolization–disruption of outer and inner membranes of mitochondria were frequently observed in the goblet cells. Irradiation caused marginal condensation of chromatin onto the nuclear lamina, and formation of large dense chromatin clumps in the nuclear matrix (Figs. 3a, b; 4a). Enterocyte profiles in the both regimes of irradiation showed signs of greater functional capacity as indicated by increases of mitochondria and decreased in the microvillous. Microvilli of epithelial cells also showed changes in length and frequency and gradually became shorter, thus alterations were observed in bordering membrane. Decreased length and surface of villi, as well as the microvillar changes, caused a reduction of surface area of the altered ileum (Fig. 3a).

Mitotic figures were observed in the Lieberkühn crypts for both regimes of irradiation. Widening of intercellular spaces following irradiation was observed in intestinal epithelium (Fig. 4a).

Curcumin treatment was effective in preventing the dilatation of ER, mitochondrial degeneration and irregularly shaped nuclei; the irregularly shaped chromatin clumps were observed in goblet cells especially in single dose radiation treated with curcumin group (Fig. 5a, b). In the curcumin-treated groups, the severity of degenerative changes in the cytoplasm and especially in the nuclei of cells were less than that observed in the only radiation treated groups (Figs. 5, 6).

Table 3 Mucosal histopathologic change scores of A (control), B (single dose radiation treated), C (two dose radiation treated), D (single dose radiation treated with curcumin) and E (two dose radiation treated with curcumin) groups

| Groups | Minimum | Maximum | Mean ± SD |
|--------|---------|---------|----------|
| A      | 0.00    | 0.00    | 0.00 ± 0.00 |
| B      | 2.00    | 4.00    | 3.00 ± 0.43a |
| C      | 3.00    | 4.00    | 3.50 ± 0.47b |
| D      | 1.00    | 1.00    | 1.00 ± 0.00c |
| E      | 1.00    | 2.00    | 1.50 ± 0.24d |

a P < 0.001 compared to control group
b P < 0.0001 compared to control group
c P < 0.05 compared to control group
d P < 0.01 compared to control group

Table 4 Body weight changes on the day 0 before irradiation, and on the killed day of A (control), B (single dose radiation treated), C (two dose radiation treated), D (single dose radiation treated with curcumin) and E (two dose radiation treated with curcumin) groups

| Groups | 0th day (g) | Killed day (g) |
|--------|-------------|----------------|
| A      | 257.86 ± 2.72 | 260.12 ± 3.14  |
| B      | 305.50 ± 2.34 | 284.50 ± 1.22a |
| C      | 317.16 ± 2.04 | 296.33 ± 1.86b |
| D      | 230.16 ± 2.48 | 228.50 ± 2.42  |
| E      | 206.00 ± 1.78 | 205.16 ± 1.88  |

a P < 0.05 compared to group B
b P < 0.05 compared to group C

electron microscopic findings

In the control group, the ultrastructure of epithelial cells in the ileum was normal (Fig. 2a, b). In ileal mucosa, there were ultrastructural changes in enterocytes and goblet cells following both irradiation regimes. Radiation had led to the dilatation of endoplasmic reticulum (ER) cisternae and electron microscopic findings

Table 3 shows mucosal histopathologic changes. The radiation injury score was significantly higher in the all irradiated rats when compared to the control animals. The radiation injury score reflects the global level of injury.

Table 4 shows body weight changes on the day 0 before irradiation, and on the killed day. Groups B and C rats developed diarrhea, characterized by loss of pellet formation and fecal adherence to the perianal region between day 3 and 4 after radiation. The body weight of the irradiated rats was significantly decreased on the 4th day after irradiation, and curcumin treatment normalized the body weight of groups D and E, assuring the safety of 100 mg/kg curcumin dose.

electro microscopic findings

In the control group, the ultrastructure of epithelial cells in the ileum was normal (Fig. 2a, b). In ileal mucosa, there were ultrastructural changes in enterocytes and goblet cells following both irradiation regimes. Radiation had led to the dilatation of endoplasmic reticulum (ER) cisternae and

degranulation of rough endoplasmic reticulum (RER) membranes (Figs. 3b, 4b). Radiation-induced loss of mitochondrial matrix and vacuolization–disruption of outer and inner membranes of mitochondria were frequently observed in the goblet cells. Irradiation caused marginal condensation of chromatin onto the nuclear lamina, and formation of large dense chromatin clumps in the nuclear matrix (Figs. 3a, b; 4a). Enterocyte profiles in the both regimes of irradiation showed signs of greater functional capacity as indicated by increases of mitochondria and decreased in the microvillous. Microvilli of epithelial cells also showed changes in length and frequency and gradually became shorter, thus alterations were observed in bordering membrane. Decreased length and surface of villi, as well as the microvillar changes, caused a reduction of surface area of the altered ileum (Fig. 3a).

Mitotic figures were observed in the Lieberkühn crypts for both regimes of irradiation. Widening of intercellular spaces following irradiation was observed in intestinal epithelium (Fig. 4a).

Curcumin treatment was effective in preventing the dilatation of ER, mitochondrial degeneration and irregularly shaped nuclei; the irregularly shaped chromatin clumps were observed in goblet cells especially in single dose radiation treated with curcumin group (Fig. 5a, b). In the curcumin-treated groups, the severity of degenerative changes in the cytoplasm and especially in the nuclei of cells were less than that observed in the only radiation treated groups (Figs. 5, 6).

Discussion

This study aims to evaluate the radioprotective effect of curcumin on γ-radiation-induced small intestinal damage. The efficacy of anticancer treatment increases the number of long-term survivors and thus the probability of late severe side effects. Therefore, a new challenge for physicians is to ensure patient quality of life by protecting normal tissue from radiation injury while enhancing anticancer
Small intestine is one of the most radiosensitive organs (Smith and De Cosse 1986). Intestinal toxicity is a major type of complication. Whole abdominal irradiation causes inflammation in small intestine with submucosal edema, hyperemia and infiltration of lamina propria with activated inflammatory cells, such as macrophages and neutrophils (Guzman-Stein et al. 1989; Klimberg et al. 1990).

Recently, curcumin has been evaluated for its radio-protective and radiosensitizing activities. Curcumin, a

efficacy (Weichselbaum 2005). Small intestine is one of the most radiosensitive organs (Smith and De Cosse 1986). Intestinal toxicity is a major type of complication. Whole abdominal irradiation causes inflammation in small intestine with submucosal edema, hyperemia and infiltration of lamina propria with activated inflammatory cells, such as macrophages and neutrophils (Guzman-Stein et al. 1989; Klimberg et al. 1990).

Recently, curcumin has been evaluated for its radio-protective and radiosensitizing activities. Curcumin, a
polyphenol confers radiosensitizing effects in prostate cancer cell line by inhibiting the growth of human prostate PC-3 cancer cells and down regulating radiation-induced prosurvival factors (Chendil et al. 2004). Moreover, curcumin has also been shown to inhibit growth of myeloid leukemia cells, epidermoid carcinoma cells, HT29 colon cancer cells and human colon epithelial cells. It was suggested that arrest at the S/G2M phases of the cell cycle may have had a radioprotection action (Kha\textit{\textsuperscript{f}} et al. 2005; Shimizu and Weinstein 2005). This indicates that curcumin is probably a potent antitumor agent for some cancer cells. Pretreatment of mice with a single curcumin dose of 100 mg/kg body weight before exposure to different doses (2, 4, 6 or 8 Gy) of whole body irradiation resulted in an enhancement of wound healing, as evidenced by increased wound contraction and reduced wound healing time (Jagetia and Rajanikant 2004).

Several investigators have demonstrated natural antioxidants scavenge the free radicals and protect the cellular DNA against indirect effects of ionizing radiation (Sasaki and Matsubara 1977). Importantly, Zhao et al. (1989) have shown removal of free radicals by curcumin using spin traps. Being a known antioxidant, it was quite possible that curcumin might have intercepted these various free radicals and inactivated them by electron donation/hydrogen transfer. On scavenging by curcumin, the availability of free radicals would decrease considerably resulting into lowering of damage and in turn the extent of regeneration in the liver and spleen. The health benefits of curcumin include many pharmacological activities such as cholesterol-reducing, antiinflammatory, antiplatelet, anticancer, antimutagenic, antiHIV, etc. (Sharma et al. 2005).

After ionizing irradiation, epithelial cells frequently loose their contact to each other and possess many lateral and basal projections (Carr 1981; Fatemi et al. 1985; Wartiovaara and Terpila 1977). The altered interactions between epithelial cells and their micro-environment may be critical for the maintenance of normal, balanced homeostasis. Experimental evidence shows that disrupting this balance can induce aberrant cell proliferation, adhesion, function
and migration reviewed by Barcellos-Hoff (1998). In Porvaznik’s (1979) early freeze-fracture studies, a significant shift was mentioned in the mean depth of the tight junction zonule on the 3rd day after 3 and 5 Gy γ-irradiation in ileal epithelium. Our results indicate γ-irradiation-induced disorganization of the adherent junctions.

In the present study, radiation exposure caused severe degenerative changes, such as dilation of ER cisternae and degranulation of RER membranes, degeneration cristae of mitochondria, marginal condensation of chromatin onto the nuclear lamina and formation of large dense chromatin clumps in the nuclear matrix of epithelial cells. Microvilli of epithelial cells also showed changes in length and frequency and alteration of bordering membrane. These data are corroborated by previous studies reported by other investigators on radiation-induced intestinal injury in animals (Carr 1981; Carr et al. 1992a; Fatemi et al. 1985; Somosy 2000). Given the documented pharmacological safety of curcumin and scarcity of adverse side effects that typically accompany traditional chemotherapy, curcumin may represent an alternative therapeutic with potent and selective induction of tumor regression, while providing cytoprotection in normal cells. In our study, in the curcumin-treated rat ileum, the severity of degenerative changes in the cell organelles, especially in the ER cisternae and in nucleus of cells was less than that observed in the only radiation treated groups. The dilated ER cisternae and the distorted goblet cells were mainly absent in the curcumin-treated rats.

Our results indicate that also abdominal exposure of rats to a single or two doses of 5 Gy γ irradiation results in a disruption in the ileum mucosa, on the 4th day following irradiation. Both radiation regimes produced an increase in the number of goblet cell profiles, resulting in increase of the total production of mucin. In the curcumin-treated groups, number of goblet cells was less than in the only radiation treated groups. Mucin is known to contain secretory immunoglobulin A and could assist in preventing the colonization of the epithelium by opportunistic pathogens, known complications of post-irradiation injury (Walker and Conklin 1987). Previous acute radiation studies indicate that the goblet cell response is complex. Some reports describe decreases or no change in cell number at 72 h after irradiation (Becciolini et al. 1985; Carr et al. 1991; Carr et al. 1992a, b; Cooper 1974), while others demonstrate increases, particularly after several weeks and months (Lewicki et al. 1975; Van Dongen et al. 1976).

In conclusion, antioxidant treatment with curcumin prior to irradiation, provides effective protection against intestinal damage, suggesting that clinical transfer is feasible. Therefore, curcumin can be very useful in cancer patients receiving radiotherapy.

Acknowledgments This study was supported as Project 633 by Trakya University Research Center, Edirne, Turkey. The authors would like to thank to M. Sc. Fadime Alkaya for irradiation studies.

Open Access This article is distributed under the terms of the Creative Commons Attribution Noncommercial License which permits any noncommercial use, distribution, and reproduction in any medium, provided the original author(s) and source are credited.

References

Barcellos-Hoff MH (1998) How the tissue respond to damage at the cellular level? The role of cytokines in irradiated tissues. Radiat Res 150:109–120
Becciolini A, Fabbrica D, Cremonini D, Balzi M (1985) Quantitative changes in the goblet cells of the rat small intestine after irradiation. Acta Radiol Oncol 24:291–299
Becciolini A, Balzi M, Fabbrica D, Potten CS (1997) The effects of irradiation at different times of the day on rat intestinal goblet cells. Cell Prolif 30(3–4):161–170
Brennan PC, Carr KE, Seed T, McCullough JS (1998) Acute and protracted radiation effects on small intestinal morphological parameters. Int J Radiat Biol 73:691–698
Carr KE (1981) Scanning electron microscopy of tissue response to irradiation. Scann Electron Microsc 4:35–46
Carr KE, McCullough JS, Nunn S, Hume SP, Nelson AC (1991) Neutron and X-ray effects on small intestine summarized by using a mathematical model or paradigm. Proc R Soc Lond B 245:187–194
Carr KE, McCullough JS, Nelson AC, Hume SP, Nunn S, Kamel HM (1992a) Relationship between villous shape and mural structure in neutron irradiated small intestine. Scanning Microsc 6:561–572
Carr KE, Nelson AC, Hume SP, McCullough JS (1992b) Characterization through a data display of the different cellular responses in X-irradiated small intestine. J Radiat Res 33:163–177
Chendil D, Ranga RS, Meigooni D, Sathish Kumar S, Ahmed MM (2004) Curcumin confers radiosensitizing effect in prostate cancer cell line PC-3. Oncogene 23:1599–1607
Cheng H, Leblond CP (1974) Origin, differentiation, and renewal of the four main epithelial cell types in the Mouse small intestine V. Unitarian theory of the origin of the four epithelial cell types. Am J Anat 141:537–562
Chiu CT, McArdle AH, Brown R, Scott H, Gurd F (1970) Intestinal mucosal lesion in low-flow states. Arch Surg 101:478–483
Dalla P (1968) Intestinal malabsorption in patients undergoing abdominal radiation therapy. In: Sullivan ME (ed) Gastrointestinal radiation injury. Richland, Washington, pp 261–275
Denham JW, Hauer-Jensen M, Peters J (2001) Is it time for a new formalism to categorise normal tissue radiation injury? Int J Radiat Oncol Biol Phys 50:1105–1106
Fatemi SH, Antosh M, Cullan GM, Sharp JG (1985) Late ultrastructural effects of heavy ions and gamma irradiation in the gastrointestinal tract of the mouse. Virchows Arch B Cell Pathol 48:325–340
Forstner JF, Forstner GG (1994) Gastrointestinal mucus. In: Johnson LR (ed) Physiology of the gastrointestinal tract. Raven Press, New York, pp 1255–1283
Grdina DJ, Murley JS, Kataoka Y (2002) Radioprotectants: current status and new directions. Oncology 63:2–10
Guzman-Stein G, Bonsack M, Liberty J (1989) Abdominal radiation causes bacterial translocation. J Surg Res 46:104–107
Jagetia GC (2007) Radioprotection and radiosensitization by curcumin. Adv Exp Med Biol 595:301–320
Jagetia GC, Rajanikant GK (2004) Role of curcumin, a naturally occurring phenolic compound of turmeric in accelerating the repair of excision wound, in mice whole body exposed to various doses of γ-radiation. J Surg Res 120:127–138

Jagetia GC, Reddy TK (2005) Modulation of radiation induced alteration in the antioxidant status of mice by naringin. Life Sci 77:780–794

Kalpana C, Menon VP (2004) Curcumin ameliorates oxidative stress during nicotine induced lung toxicity in Wistar rats. Ital J Biochem 53:82–86

Khafif AVI, Hurst R, Kyker K, Fliss DM, Gil Z, Medina JE (2005) Curcumin: a new radio-sensitizer of squamous cell carcinoma cells. Otolaryngol Head Neck Surg 132:317–321

Klimberg VS, Souba WW, Dolson DJ, Salloum RM, Hautamaki RD, Plumley DA, Mendenhall WR, Bova FC, Khan SR, Hackett RL, Bland KI, Copeland EM (1990) Prophylactic glutamine protects the intestinal mucosa from radiation injury. Cancer 66:62–68

Lewicki Z, Figurski R, Sulikowska A (1975) Histological studies on the regeneration of small intestinal epithelium of rats irradiated with sublethal doses of X-rays. Pol Med Sci Hist Bull 15:539–548

Polasa K, Naidu NA, Ravindranath I, Krishanaswamy K (2004) Inhibition of B(a)P induced strand breaks in presence of curcumin. Mutat Res 557:203–213

Porvaznik M (1979) Tight junction disruption and recovery after sublethal gamma irradiation. Radiat Res 78:233–250

Sasaki MS, Matsubara S (1977) Free radical scavenging in protection of human lymphocytes against chromosome aberration formation by gamma-ray irradiation. Int J Radiat Biol 32:439–445

Sharma RA, Gescher AJ, Steward WP (2005) Curcumin: the story so far. Eur J Cancer 41:1955–1968

Shimizu M, Weinstein B (2005) Modulation of signal transduction by tea catechins and related phytochemicals. Mutat Res 591:147–160

Smith DH, De Cosse JJ (1986) Radiation damage to the small intestine. World J Surg 10:189–194

Somosy Z (2000) Radiation response of cell organelles. Micron 31:165–181

Van Dongen JM, Koyman J, Visser WJ (1976) The influence of 400 R X-irradiation on the number and localization of mature and immature goblet cells and Paneth cells in intestinal crypt and villus. Cell Tissue Kinet 9:65–75

Walker RI, Conklin JJ (1987) Mechanism and management of infectious complications of combined injury. In: Conklin JJ, Walker RI (eds) Military radiobiology. Academic Press, Orlando, pp 219–230

Cooper JW (1974) Relative and absolute goblet cell numbers in intestinal crypts following irradiation or Actinomycin D. Experientia 30:549–550

Wang J, Zheng H, Kulkarni A, Ou X, Hauer-Jensen M (2006) Regulation of early and delayed radiation responses in rat small intestine by capsaicin-sensitive nerves. Int J Radiat Biol Phys 164(5):1528–1536

Wartiovaara J, Terpila S (1977) Cell contacts and polysomes in irradiated human jejunal mucosa at onset of epithelial repair. Lab Invest 36:660–665

Weichselbaum R (2005) Radiation’s outer limits. Nat Med 11:477–478

Weiss JF, Kumor KS, Walden TL (1990) Advances in radioprotection through the use of combined agent regimens. Int J Radiat Biol 57:709–722

Zhao BL, Li XJ, He RG, Cheng SJ, Xin WJ (1989) Scavenging effect of extracts of green tea and natural antioxidants on active oxygen radicals. Cell Biophys 14:175–185