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Protective Effects of Apricot Feeding in the Pulmonary Tissues of Rats Exposed to Low Dose X-Ray Radiation

KEYWORDS

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ABSTRACT *Radiation has potentially irreversible detrimental effects. Prevention with antioxidants may be possible. We hypothesized that, apricot may be preventive or ameliorating against the radiation effects on the rat lungs exposed to low dose X-ray radiation. Sixty rats were placed into 6 groups for 28 weeks. Group1: regular diet; group 2: regular diet and X-ray exposure; group 3: apricot diet; group 4: apricot diet and X-ray exposure; group 5: apricot diet for 20 weeks, regular diet for 8 weeks; group 6: apricot diet for 20 weeks, regular diet for 8 weeks and X-ray exposure. There were severe peribronchial, paranchimal and alveolar changes in group 2. In group 4 lung histology was mostly normal, with some mild changes. The findings were also mild in group 6; although worse than group 4. Our results suggested that, dietary intake of apricot is beneficiary against undesired effects of radiation in the lungs.*

INTRODUCTION

Although radiation is commonly utilized for medical care and potential hazards associated with exposure are well known, even developed countries are poorly equipped to protect their citizens in case of fallout as seen in the post-earth quake era in Japan.[1,2] Either caused by disasters such as recent Japanese earthquake, or accidents such as Chernobyl in 1986 and even terrorist threats, we must be aware of the danger and build some protective measures.[3]

As imaging technology has become more portable, use of portable radiographs has increased and unfortunately most areas of the emergency departments (ED) are not lead shielded.[4] ED workers do not tend to wear lead shield vests each time a portable radiograph is being taken. The exposed dose and the expected effects vary widely with respect to used imaging modality, the total dose of the radiation, and repetition/fraction of the dose.[5] The National Council on Radiation Protection (NCRP) limits health care–associated occupational exposures to radiation to 5000 mrem/y.[6,7] However, several studies have demonstrated that chronic and acute exposures to doses even in the 10–50 mGy range (50 mGy=5000 mrem) are also mutagenic and carcinogenic and may induce a genomic instability and may also increase the risk for the development of cancer via non-targeted effects in cells which are not even directly irradiated.[8-11]

We know that radiosensitivity of a tissue is directly related to its mitotic activity and inversely related to the degree of differentiation of its cells.[5] Radiation-induced functional damage to the lung occurs in two phases; the acute radiation pneumonitis phase occurring 4-30 weeks after exposure to radiation, and the fibrosis phase.[12] After irradiation of the lung, early release of surfactant and the immediate injury to the alveolar type II cells detected by electron microscopy are the first pathophysiological effects.[13,14] It is already known that, the late occurring lung fibrosis due to radiation is refractory to treatment. Reducing the odds to develop lung injury and using preventive measures are, therefore, most important parts of the approach.[15,16]

Pretreatment with several substances have been studied for prevention from radiation effects on lungs, including Amifostine, vitamin A and ACE inhibitors.[16] Another effective antioxidant which may be protective against radiation effects is Prunus armeniaca L. (apricot) with a rich content of vitamin A, vitamin C, polyphenols and carotenoids.[17-19] The total free radical scavenging activity of apricot seems to be the cumulative effect of its ingredients, which each are already effective antioxidants.[20]

Our hypothesis was that the antioxidant effects of Prunus armeniaca L. may be preventive or ameliorating against the radiation related effects on the lungs of the rats exposed to low dose X-ray radiation.

METHODS

All experiments in this study were performed in accordance with guidelines for animal research from the National Institutes of Health and were approved by the University Ethics Committee on Animal Research (approval no: 2011/A-33).

Animals

Sixty adult male Sprague-Dawley rats weighing between 300 and 345 g were enrolled in the study; they were kept at 22°C ± 2°C (room temperature) and 50% ± 10% humidity with a 12-hour light/12-hour dark cycle and were fed freely. For the 7-day acclimation period, rats were fed with regular rodent pellet diets and drinking water ad libitum. They were then divided into 6 groups (10 rats each) as follows:

Group 1: Rats on a regular diet (control diet) for 28 weeks.
Group 2: Rats on a regular diet for 28 weeks, X-ray exposure in the last 8 weeks.
Group 3: Rats on an apricot diet for 28 weeks.
Group 4: Rats on an apricot diet for 28 weeks, X-ray exposure in the last 8 weeks.
Group 5: Rats on an apricot diet for 20 weeks, regular diet for 8 weeks.
Group 6: Rats on an apricot diet for 20 weeks, regular diet for 8 weeks, X-ray exposure in the last 8 weeks.

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All rats had free access to tap water during the study. Body weights were recorded initially and at the end of the study period. The animals were killed by cervical dislocation at the end of the study period. Lungs were harvested by an immediate thoracotomy, and tissue weights were recorded immediately.

The diets

Standard (regular) rat diet

In the control groups, a commercially available standard rat chow diet (Korkutelim Yem, Antalya, Turkey) was used. The ingredients are given in Table 1. For wheat, whole wheat, and crushed wheat was fed. The diet contained vitamins A, D, and E; calcium, phosphorus, and trace amounts of iron, manganese, copper, zinc, and cobalt.

Apricot diet

Organic sun-dried apricots of the Kabaasi variety, harvested from the Malatya region were used in this study. This variety was chosen because of its higher radical scavenging power and total phenolic content.[19] After harvesting, the apricots were sun-dried for 14 days without any additives, and then minced to 1 to 2-mm pieces for the study. A mixture of 20% apricots was prepared, and the diets were maintained to be isoenergetic with the regular rodent pellet diet. The amounts of wheat, bran, and soya-48 in the apricot diet were adjusted to ensure adequate food supply for rat growth while providing the isoenergetic status with the standard diet. Both diets had a metabolic energy of 11095 J/kg.

Determination of antioxidant capacity of diets

Extract preparation

Ten grams of regular and apricot diet samples were mixed with 90 mL of ethanol (70%) and were homogenized (Ultra-Turrax, Model T25; IKA-Works, Inc, Cincinnati, Ohio) at 20 000 rpm. After incubating at +4°C for 48 hours, the liquid was filtered using a Whatman no. 1 filter paper. Extracts were used in 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging tests and total phenolic content analyses.

Determination of radical scavenging power

The radical scavenging power (RSP) of the diets was determined by the method described by Shimada et al, with modifications.[21] Two milliliters of the reaction mixture contained 2.9 mmol of DPPH (1.8 mL of 1 × 10−4 DPPH) and 0.2 mL of extracts. As a control, ethanol (70%) replaced the sample. After resting for 10 minutes in the dark, a spectrophotometric evaluation was performed at 520 nm. A decreased intensity of purple color was related to a higher RSP percentage, which was calculated using the following equation: RSP = [1 – ($A_{S:10}$ / $A_{B:10}$)] × 100 where $A_{S:10}$ is the absorbance of samples and $A_{B:10}$ is the blank absorbance at the 10th minute of the reaction period.

Determination of total phenolic content

The total phenolic content (TPC) of the diets was determined by the Folin and Ciocalteu's reagent method; 0.1 mL of extracts was diluted to 1 mL with ethanol (70%), to which 1 mL of Folin and Ciocalteu's reagent was added.[22] After incubation for 3 minutes, 1 mL of 2% sodium carbonate was added. The mixtures were incubated for 5 minutes with shaking, after which the absorbance was measured at 760 nm. The calibration curve was performed with gallic acid. The results were expressed as l g of gallic acid equivalents (mg/g gallic acid equivalent).

Determination of ferric-reducing power

The ferric-reducing power of the diets was determined using the Oyaizu procedure.[23] A 0.2-mL aliquot of extract was adjusted to 1 mL with ethanol (70%); 2.5 mL of 0.2 mol/L phosphate buffer (pH 6.6) and 2.5 mL of 1% potassium ferricyanide were then added and mixed gently. The mixtures were incubated at 50°C in a water bath for 20 minutes. Then, 2.5 mL of 10% trichloroacetic acid was added, and the mixtures were centrifuged at 6000 rpm for 10 minutes. From the top layer of supernatant, 2.5 mL were mixed with 2.5 mL of distilled water and 0.5 mL of 0.1% ferric chloride. After incubation for 5 minutes, the color intensity was determined at 700 nm against sample blanks. A higher absorbance corresponded to a better reducing power of the sample.

Radiation exposure

A conventional 200-kilovolt (peak), 20-ampere x-ray machine (Shimadzu, Kyoto, Japan) was used as the x-ray generator. Rats were irradiated at a distance of 80 cm with a dose rate of 0.5 Gy/min, delivering 0.2 Gy of whole body x-ray irradiation. Animals were immobilized in cages of adjustable length that accommodated the rat but prevented movement. Rats were not medicated during X-Ray exposure.

Histological evaluation of the lungs

The lung tissue was evaluated following staining with hemotoxylene and eosine (H&E), PAS ve Masson's Trichrom dyes. Histopathological evaluation of the sections was performed as follows; 6 random areas from each of the 5 sections for each subject were evaluated with Olympus BH2 light microscopy under 100x magnification. After recording the alterations within the 30 fields for each subject, histopathological damage was defined as mild for alterations in 1 to 10 fields, moderate for 11 to 20 fields and severe for 21 to 30 fields. Then, the alterations were graded as shown in Table 2.

Statistical analyses

Statistical analyses were performed using a computer software program (SPSS v12.0; SPSS Inc, Chicago, Ill). Based on a power analysis, the number of subjects studied (10 rats per group) and cell cultures used (100 slides per group) was 0.8 for each. All values were given as means ± SD. Normality for continued variables in groups was determined by the Shapiro-Wilk test. Because the variables did not reveal normal distribution ($p>0.05$), comparisons among groups were performed by Mann-Whitney test. A $p< 0.05$ was considered significant.

RESULTS

No rats had any signs or symptoms of radiation (ie, loss of appetite, molting, diarrhea, respiratory distress) or apricot (i.e., diarrhea) related side effects. The mean body and lung weights were not significantly different between groups (data not shown).

Histopathological examination results are presented in Table 3.

The control group had normal lung histology as expected.
In group 2, there was mild to moderate peribronchial and perivascular cell infiltration by mononuclear cells such as lymphocytes, plasmocytes and macrophages along with severe alveolar congestion and edema, mild to moderate pranchimal fibrosis, and mild to moderate alveolar wall thickening due to increased connective tissue in the interalveolar septum. Type II alveolar cells were highly vacuolated. Also epithelial spillage, hemosiderin loaded macrophages and serious bleedings sites were observed in some sections (Figure 1).

Normal lung histology was determined in group 3. The pseudostratified columnar bronchial epithelium with goblet cells and kinocillium and the thin interrupted muscle layer was observed to be regular in these slides. There were Clara cells both in terminal and respiratory bronchioles with their apical cytoplasm protruding thru the bronchial lumen. The simple squamous epithelium and the alveoli were protected and the interalveolar septum thickness was normal (Figure 2 b).

In group 4 lung histology was mostly evaluated as normal, except for minor changes in 2 subjects, which were mild congestion and edema accompanied by mild fibrosis in only one and mild wall thickening in two subjects (Table 3). There were no infiltrative changes with regard to group 2 (Figure 2 c1,

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c2).

The evaluation of group 5 showed similar results with groups 1 and 3 with no alterations in lung histology.

The histopathological findings were also mild in group 6 with a vast amount of normal areas; however the samples were in a worse condition compared to group 4. There were more areas of congestion, edema, infiltration, fibrosis and wall thickening when compared with group 4, but the changes were still in the range to be classified as mild (Figure 3).

The differences between control group 1 and the irradiated group 2, which was irradiated with no apricot diet, was statistically significant by means of all histopathological endpoints (alveolar congestion, p=0.00; edema, p=0.00; perivascular infiltration, p=0.00; peribronchial infiltration, p=0.00; paranchimal fibrosis, p=0.00; and alveolar wall thickening, p=0.00).

There were no statistically significant differences between control group 3 and the irradiated group 4 which received apricot diet during the whole 28 weeks study period (p >0,05).

The differences between the control group 5, and the irradiated group 6, which received apricot diet only before the irradiation period were also statistically significant in some pathological aspects, while not as pronounced as the differences between groups 1 and 2 (alveolar congestion, p=0.022; edema, p=0.067; perivascular infiltration, p=0.029; peribronchial infiltration, p=0.012; paranchimal fibrosis, p=0.067; and alveolar wall thickening, p=0.029).

There were also statistically significant differences between group 2 and the other 2 irradiated groups (groups 4 and 6) by means of all pathological endpoints (alveolar congestion, p= 0.000 and p=0.000; edema, p=0.000 and p=0.000; perivascular infiltration, p=0.000 and p=0.000; peribronchial infiltration, p=0.000 and p=0.000; paranchimal fibrosis, p=0.000 and p=0.000; and alveolar wall thickening, p=0.000 and p=0.000, respectively). The differences between group 4 and group 6 were not statistically significant (p >0.05) for all pathological aspects, but peribronchial and perivascular infiltrations (p=0.012 and p=0.029, respectively).

DISCUSSION

Ionizing radiation is known to be a strong DNA damaging agent and carcinogen.[1,24] It has both beneficial and harmful effects, and the mechanism is responsible for the both is same; it readily damages DNA. Although undesired and unplanned for, same side effects occur during radiologic studies too, exposures to even low doses have mutagenic and carcinogenic effects.[1,11] These effects of radiation, naturally, targets the cells with rapid proliferation rates first, such as microvascular endothelium.[25] The genomic instability caused by irradiation is most likely due to an increased apoptotic index, which triggers phagocytic activity, neutrophil infiltration and inflammatory mediators to bring up an oxidative stress status.[26]

Swelling of the cell is the first of all derangements in all types of cellular damage and stress.[27] Disorders of cellular energy and metabolism balance causes fluid and electrolyte disorders on cellular basis via failures of energy dependent cellular pumps.[28] This type of non-lethal injury is sometimes called hydropic degeneration.[27] Our subjects showed marked cellular swelling.

On the other hand, acute inflammation, which is a self-protective reaction of the cells following the injury, goes along with edema and neutrophil migration, and may end up with tissue necrosis.[28] Leucocytes cause tissue damage by inflammation due to chemical mediators and toxic oxygen radicals. Lipid peroxidation in the cell membrane, caused by radiation injury, leads to oxidative stress related cellular damage; which may, in theory, be prevented by anti-oxidants, such as apricot. The increase in the matrix metalloproteinase activity causes an increase in the fibroblast migration, and fibronectin and collagen synthesis.[27] Our analyses showed serious signs of leucocyte infiltration and an increase in connective tissue resulting in cellular injury and parenchymal fibrosis with alveolar wall thickening in the group with no protective apricot diet, whereas these effects were obviously less significant in the two groups that received apricot diet.

The effects of radiation to the lung are complex. Since lung has a limited regenerative capacity, is prone to radiation injury.[5] Acute radiation injury to lungs may include epithelial and endothelial cell damage, edema of the air spaces and alveolar septa, desquamative changes, and mononuclear cell infiltration.[5] Early radiation related pulmonary injury is defined as changes occurring 0 to 8 weeks after radiation contact, and is characterized by injury to small capillaries causing vascular congestion and increase in capillary permeability.[13] Our results, consistent with the literature, also showed that rats exposed to radiation under normal diet had severe alveolar congestion and edema due to inflammation; massive lung injury with peribronchial and perivascular cell infiltration with mononuclear cells; paranchimal fibrosis and mild to moderate alveolar wall thickening. Also there was a large amount of epithelial desquamation in the bronchioles, hemosiderin loaded macrophages and bleeding sites, as proof of cellular reaction to stress.

Alveolar type II cells are cuboidal cells located in the alveoli. They secrete surfactant, absorb fluid and ions from the alveolar space, and terminally mature to differentiate to type I cells.[29,30] Type II pneumocyte proliferation is expected to occur during normal fetal and neonatal lung development, following penumonectomy and diffuse lung injury.[31] Alveolar type II cell hypertrophy and hyperplasia have been proposed to be critical in the structural and functional restoration of the lung after alveolar epithelial injury.[30] Our samples also showed hypertrophy in type II alveolar cells and a high amount of vacuolization as well, especially in group 2, which did not receive apricot diet.

Following the systemic exposure to radiation, local or systemic measures shall be taken, such as providing potassium iodide like in Fukushima incident in Japan.[1] However, since ionizing radiation affects the whole body and causes widespread DNA damage, local or organ targeted preventive features are far from optimal to protect individuals, especially those less than 20 years of age.[32] Although amifostine is another well-known radioprotective agent, being only administrable intravenously makes it unsuitable in many cases.[33,34] Since it is hard to predict the radiation exposure in many cases, and even harder to treat the damage once it occurred, prevention and minimizing the likelihood of development shall be the main target.[16] Apricot, a natural antioxidant that is easily consumable thru daily diet, is proven to be an effective antioxidant and a successful preventive agent against the destructive effects of radiation.[17,19,20,22] In our study, three groups were exposed to radiation. Two of these groups received apricot diet, group 4 for the whole study period (28 weeks) and group 6 had only for 20 weeks prior to irradiation. Our results suggest that, a constant apricot diet, started weeks before and continued during the exposure is much effective by means of prevention of radiation injury.

Radiation exposure in the ED is an underestimated casualty. The increase in the use of portable radiographs and the fact that most areas of the ED are not lead shielded, make ED staff and patient vulnerable against the effects of low dose radiation.[4] Other radiological imaging techniques such as CT scans should also be considered. Analyses of Biswas et al showed that, the radiation delivered by CT scan of the body ranged between 4.95 and 19.15 mSv.[10] Given that Lee et al reported a total of 27,631 individual patients receiving

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34,671 CT scans in an urban hospital ED, cumulative doses for patients and healthcare providers should not be under estimated.[35] Our results suggest that doses as low as 0.2 Gy may cause massive tissue damage if protective measures are not taken, such as antioxidants like apricot which showed a great deal of success in preventing radiation injury to the lungs in our study.

Conclusion

Our results suggested that, regular dietary intake of, L. Prunus armenica (apricot), which has established antioxidant potency, is beneficiary against undesired effects of radiation in the lungs. These benefits became more evident in the group having apricot diet both prior to and during the radiation exposure. Therefore we believe that apricot shall be routinely consumed as a part daily diet, not only for prevention of possible radiation related, but also for all types of oxidative stress related hazards.

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Table 1: Ingredient composition (gram per kilogram) of the standard diet and 20% apricot diet

Ingredient	Standard diet	20% apricot diet
Corn	300	287.44
Wheat	154.81	–
Bran	149.87	69.3
Soya-48*	260.38	380.85
Fish flour	80	80
Molasses	30	32.54
Marble	10.64	10.88
Salt	9.95	10
V-221†	2.5	2.5
Syn-Met‡	1.77	2.48
Apricot	–	200

The metabolic energy provided by both diets was 11095 J/kg; 20% apricot diet ingredients were adjusted to provide an iso-energetic diet similar to the standard diet. Wheat was removed from and bran reduced in the apricot diet, whereas Soya-48 was increased to achieve this goal, resulting in a balanced apricot diet that is adequate for rat growth.

*Soya-48: Soybean bagasse with 48 proteins;

†V-221 is the combined form of vitamins A, D, E, and trace elements;

‡Syn-Met is synthetic methionine.

Table 2: Staging scale for lung injury in subjects, showing the extent of the injury (by MK)

	0	1	2	3
Alveolar congestion	Normal alveoli	Mild	Moderate	Severe
Edema	Normal parenchyma and alveoli	Mild	Moderate	Severe
Perivascular / Peribronchial infiltration	None	Mild	Moderate	Severe
Parenchymal fibrosis	Normal parenchyma	Mild	Moderate	Diffuse
Alveolar wall thickening	None	Mild	Moderate	Severe

Table 3: Results of the histopathological evaluation

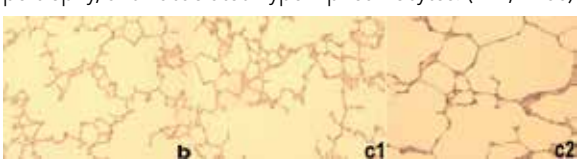
	Alveolar Congestion (n*/e†)	Edema (n/e)	Perivascular Infiltration (n/e)	Peribronchial Infiltration (n/e)	Parenchymal Fibrosis (n/e)	Alveolar Wall Thickening (n/e)
Group 1	10/0	10/0	10/0	10/0	10/0	10/0
Group 2	10/3	7/2 3/1	8/2 2/1	9/2 1/1	7/2 3/1	7/2 3/1
Group 3	10/0	10/0	10/0	10/0	10/0	10/0
Group 4	2/1 8/0	2/1 8/0	10/0	10/0	1/1 9/0	2/1 8/0
Group 5	10/0	10/0	10/0	10/0	10/0	10/0
Group 6	6/1 4/0	3/1 7/0	4/1 6/0	5/1 5/0	3/1 7/0	4/1 6/0

*n: number of subjects, †e: extent of injury

a1= Totally distorted alveolar structure due to alveolar wall thickening, with sporadically cellular infiltrations (H-E, X10)

a 2= Totally distorted alveolar structure due to alveolar wall thickening, with diffuse cellular infiltrations, alveolar congestion and edema (Mason-Trichrom, X10)

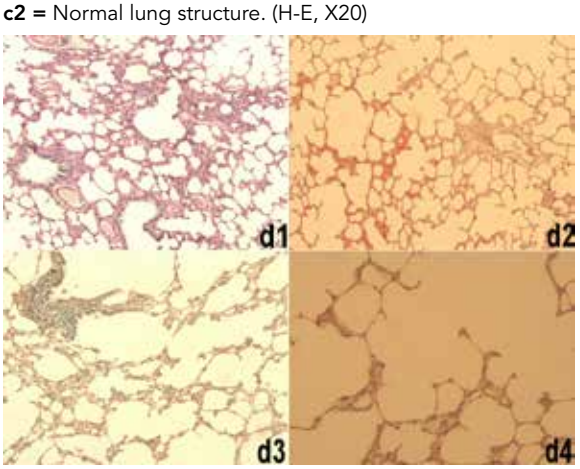
a 3= Alveolar wall thickening, alveolar congestion and hypertrophy, and vacuolated Type II pneumocytes. (H-E, X100)



b= Normal lung structure. (H-E, X20)

c1 = Normal lung structure. (H-E, X10)

c2 = Normal lung structure. (H-E, X20)



d1= Normal lung structure with occasional areas of thickened alveolar wall and cellular infiltration. (H-E, X10)

d2= Normal lung structure with occasional areas of thickened alveolar wall, congestion and edema. (H-E, X10)

d3= Areas of thickened alveolar wall and cellular infiltration. (Mason-Trichrom, X10)

d4= Normal lung structure with occasional areas of thickened alveolar wall, congestion and edema. (H-E, X20)

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