World Journal of Medical Sciences 10 (2): 191-197, 2014
ISSN 1817-3055

DOI: 10.5829/idosi.wjms.2014.10.2.823

Radioprotective Effect of Watermelon Juice Against Low Dose Ionizing Radiation-Induced Inflammatory Response in Mice

[1]Ainul Mardhiyah Zakaria, [1]Nurhanisa Ghazali, [1]Mohd Khairul Amran Mohammad,
[1]Muhamad Idham Mohamed, [1]Mazriazie Mohamed Isa,
[2]Hairil Rashmizal Abdul Razak and [1]Wan Mazlina Md. Saad

[1]Department of Medical Laboratory Technology, Faculty Of Health Sciences,
Universiti Teknologi Mara, Puncak Alam Campus,
42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia
[2]Department of Medical Imaging, Faculty Of Health Sciences,
Universiti Teknologi Mara, Puncak Alam Campus, 42300 Bandar Puncak Alam,
Selangor Darul Ehsan, Malaysia

Abstract: Exposure to ionizing radiation (IR) may increase tumor formation risk and has been linked to inflammatory response. It is known that IR can cause direct tissue damage, with activation of pro-inflammatory mediators released by macrophages, epithelial cells and fibroblasts. Production of pro-inflammatory cytokines induced by radiation may be overcomed by lycopene, a naturally occurring antioxidant in watermelon. Watermelon is known to have about 40% higher lycopene than raw tomatoes. Lycopene has the ability in down regulation of inflammatory response that includes inhibiting the pro-inflammatory cytokines. The present study was designed to evaluate the radioprotective effect of watermelon juice [*Citrullus lanatus* (Thunb.) Matsum. and Nakai] on low dose ionizing radiation induced inflammation in mice. Fifteen mice were divided randomly into 3 groups: negative control (normal diet), positive control (normal diet + low dose IR) and supplementation (50% watermelon juice + low dose IR). Supplementation group was given 50% watermelon juice (v/v) for 28 consecutive day *ad libitum* and low dose IR was given on day 29 with single dose 100μGy. In lung, TNF-α and IL-6 levels showed significant differences (p =0.05, p=0.01) respectively between supplementation and positive control groups. There were significant differences in lung IL-6 levels between negative and positive control groups (p=0.01). Significant differences were also observed in liver TNF-α levels between negative control and supplementation groups (p=0.02). In conclusion, the study demonstrated that watermelon juice has a protective effect against low dose IR – induced inflammatory response.

Key words: Inflammatory Response · Ionizing Radiation · Tumor Necrosis Factor-Alpha · Interleukin-6 · Watermelon

INTRODUCTION

Inflammation is a complex mechanism [1] related to reactive oxygen species (ROS) when produced redundantly [1-3]. Radiation may cause ROS production to elevate [4]. Radiation induces ROS production and leads to inflammatory response as indicated by the production of inflammatory cytokines. Pro-inflammatory mediators are released through local and systemic reaction simultaneously when triggered by insults [5]. Three major pro-inflammatory cytokines that participate in acute phase response are Interleukin 1 (IL-1), Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) [6].

Ionizing radiation (IR) exerts its biological effects when ROS is yielded [4]. Since cell is constituted mainly by water (~80%), the energy from IR is absorbed largely by water that in turn leads to production of free-radicals when the cell is excited and ionized [7]. High ionizing

Corresponding Author: Wan Mazlina Md. Saad, Department of Medical Laboratory Technology, Faculty Of Health Sciences, Universiti Teknologi Mara, Puncak Alam Campus, 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia. Tel: 03-32584429; Fax: 03-32584599.

radiation (IR) [8] and ROS [2] will damages cell and results in chemical and biological changes [7]. When cells exposed to IR, energy from the radiation will transfer to the cells causing the cell to lose its atoms and become excited. As a result, the cell will release free-radicals and structurally damaged when vital process of DNA, RNA and proteins formation are interfered. IR damages DNA and organs differently depending on cells vulnerability towards radiation effects [9]. Understanding of various organs sensitivity towards radiations is caused by many late expressed effects of IR exposure when basis of direct DNA damage cannot necessitate the explanation of such process [9]. The situation remains uncertain about the risk of low dose IR as this issue has been much debated [8-11].

The use of low-dose ionizing radiation in medical line has been debatable concerning biological effects and threshold dose attributed from the so-called low-dose ionizing radiation [8-11]. The degree of low-dose radiation risk has become profoundly questionable in radiological application especially in justification and optimization of diagnostic medical exposures [12]. Debate on low-dose radiation arise from the fact that International Commission on Radiological Protection (ICRP) advocated that there is no safe level of ionizing radiation by establishing linear no threshold (LNT) model [10]. LNT model hypothesized radiation risk as analogous to the dose received [11]. Therefore, the principles of Justification and Optimization to the very low doses have been problematic in diagnostic radiology application [10, 12]. ICRP's LNT is opposed by radiation hormesis that suggest low dose radiation as beneficial when balance between damage and protection is achieved [13]. Feindendegen [13] in his study deduced that low dose cause reduction in damage as equal or outweigh radiogenic damage induction itself.

In view of natural foods that possess radioprotective effect, lycopene is known as good anti-oxidant, anti-tumor and anti-inflammatory [4]. The ability of lycopene to impressively scavenge free radicals and singlet oxygen may reflect its ability to reduce ROS and hence, decrease inflammation [1, 4]. Along lycopene, flavonoid and phenolic may acts as anti-inflammatory, anti-bacterial, anti-allergic, anti-mutagenic and anti-neoplastic [14]. Over the last ten years, studies on lycopene have been done in large-scale [15]. Previously, most clinical research on lycopene used tomatoes as the subject [16].With growing evidences of lycopene benefits towards human health, watermelon (*Citrullus lanatus*) has become another subject of interest for that it has about 40% higher percentage of lycopene than raw tomatoes [16, 17]. Watermelon has lycopene with year-round mean of 4868µg/100g whereas tomato has 3025 µg/100g lycopene concentration [17]. The intake of watermelon as daily supplement can prevent certain types of cancers [17]. Therefore, watermelon's potential benefit against inflammation is highly attentive. The present study was designed to measure inflammatory response in low dose ionizing radiation-induced mice following supplementation with 50% watermelon juice.

MATERIALS AND METHODS

Study Design and Animals Handling: Fifteen (n=15), four-week-old male ICR mice, weighed around 25 grams (g) were used as models. Mice were obtained from Laboratory Animals and Facility (LAFAM), Faculty of Pharmacy of UiTM Puncak Alam. Mice were allowed to acclimatize to constant room temperature (RT) of 22 $\pm$ 2°C during adjustment period, exposed to 12-hours (h) light and 12-h dark cycle and kept at mean relative humidity in the animal house of Faculty of Health Science (FSK) at FSK1, 5. Each mouse was weighed using PW124 analytical balance (Adam Equipment Co. Ltd., Kingston, Milton Keynes, UK) and given identification number prior to supplementation. The body weights were measured once a week during supplementation period. Five mice (n=5) from supplement group were housed in separate cages. Mice were grouped into three experimental groups with different criteria (Table 1). The experiments were approved and conducted in compliance with the rules of Animal Research and Ethics Committee of UiTM Puncak Alam.

Animals Diet: All mice had free access to food pellet and filter-tap water throughout three weeks adjustment period. During supplementation period, five mice of the supplement group were given watermelon juice for 28 consecutive days while negative and positive control groups were given normal diet *ad libitum* (Table 1).

Table 1: The experimental groups and their respective criteria

Group	Criteria
Negative Control (n=5)	Filter-tap water and food pellet
Positive Control (n=5)	Filter-tap water and food pellet
	Low-dose IR of 100 µGy
Supplement Group (n=5)	Watermelon juice and food pellet
	Low-dose IR of 100 µGy

Mice were divided into three groups (n=5). For 28 consecutive days, supplement group was given watermelon juice while negative and positive control groups were given normal diet *ad libitum*. On day 29th, positive control and supplement groups were given x-ray exposure of 100 µGy.

Supplementation with 50% Watermelon Juice: Watermelon was bought from local Federal Agriculture Marketing Authority (FAMA) stall that was directly supplied with watermelon from Selangor Fruit Valley, Rawang. Watermelon juice was prepared freshly twice a day. Watermelon juice was prepared 12 hourly at 8 AM and 8 PM. Watermelon was peeled and the seeds were removed. Watermelon flesh was chopped into small pieces. Five pieces were blended smoothly into juice by using PJ-67S Juice Extractor (Pensonic Holdings Bhd., Perai, Pulau Pinang, MY). Water was added to prepare watermelon juice with 50% concentration juice at 1:1 (v/v). 100mL 50% watermelon juice was placed in the water-bottle inside the cages. After 12h, the remaining volume of watermelon juice was measured. Measurement of the remaining watermelon juice was taken in every preparation of fresh watermelon juice.

Radiation Exposure of Animal; Mice were weighed before and after radiation exposure. The procedure of radiation exposure was done at Department of Medical Imaging, FSK, UiTM Puncak Alam. Ten mice were exposed to full-body x-ray radiation with the dose of 100 µGy using Bucky Diagnost x-ray generator (Philips Co. andover, MA, USA) (Table 1). Mice were restrained in well-ventilated transparent boxes during radiation exposure.

Euthanization of Animal and Sampling: Mice were euthanized by cervical dislocation technique within 8h post- radiation exposure and lungs and livers were collected in sterile containers. The lung tissues extraction method was conducted according to manufacturer's instruction of Cell Lysis Reagent for Mammalian Tissue (Sigma-Aldrich Co. LLC, St. Louis, MO, USA). A ratio of tissue to cell lysis reagent of 1:20 (1 g of tissue/20 mL of reagent) was based according to manufacturer's instruction. Tissue was weighed using analytical balance. Each tissue was disrupted in Cell Lysis Reagent for Mammalian Tissue (Sigma-Aldrich Co. LLC, St. Louis, MO, USA) and homogenized using mortar and pestle. Sample was centrifuged at 15,000 x g for 10 minutes (min) using K24IR refrigerated centrifuge (Centurion Scientific Ltd., Chichester, West Sussex, UK). Supernatants were removed into pre-chilled tube and kept at -70°C until ELISA testing.

Measurement of TNF-α and IL-6: The TNF-α and IL-6 concentrations were determined using commercial ELISA kits (Thermo Scientific-Pierce Biotecnology, Rockford, IL, USA). Supernatants from homogenized lung tissues and liver tissues were applied onto 96-well plates pre-coated with antibody specific for mouse TNF-α and IL-6 followed by serial incubation and wash according to manufacturer's instructions. Absorbance was measured within 30 minutes at 450 minus 550nm using POLARstar Omega micro plate reader (BMG LABTECH GmbH, Ortenberg, Germany). All samples were measured in duplicates. The concentration of TNF-α and IL-6 level in each sample was calculated based on a standard curve.

Statistical Analysis: Statistical analysis was performed using SPSS Version 18.0 for Windows (SPSS Inc., Chicago, IL, USA). One-way analysis of variance (ANOVA) followed by Tukey test was used to compare the mean between controls and supplement groups. Values were considered significantly different when $p<0.05$.

RESULTS

TNF-α Level in Lungs: Fig. 1 demonstrates the level of TNF-α in low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Values were expressed as mean ± standard errors of the mean (SEM). Based on the result, there were no significant differences ($p=0.12$) in level of TNF-α between negative and positive groups. The level of TNF-α for negative group was 716.53 ± 91.60 pg/mL and level of TNF-α for positive group was 913.87 ± 86.28 pg/mL. The positive group showed elevated level of TNF-α compared to negative group by 197.34 pg/mL (Fig. 1). There were significant differences ($p=0.05$) in TNF-α level between positive and supplement groups. The level of TNF-α for supplement group was 663.80 ± 74.67 pg/mL. The positive group showed elevated level of TNF-α compared to supplement group by 250.07 pg/mL (Fig. 1). Also, there were no significant differences ($p=0.69$) in level of TNF-α between negative and supplement groups. Supplement group showed elevated level of TNF-α compared to negative group by 52.73 pg/mL (Fig. 1).

IL-6 Level in Lungs: Fig. 2 demonstrates the level of IL-6 in low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Based on the result, there were significant differences ($p=0.01$) in level of IL-6 between positive and negative groups. The level of IL-6 for negative group was not expressed. The level of IL-6 for positive group was 24.00 ± 6.60 pg/mL. There were also significant differences ($p=0.01$) in IL-6 level between positive and supplement groups. The level of IL-6 for supplement group was 2.80 ± 2.40 pg/mL.

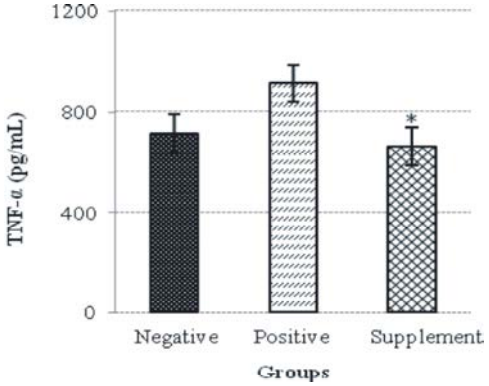

Fig. 1: Level of TNF-α in lung tissue of low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Values are expressed as mean ± SEM (n=5).
*Significantly different from positive group (p=0.05).

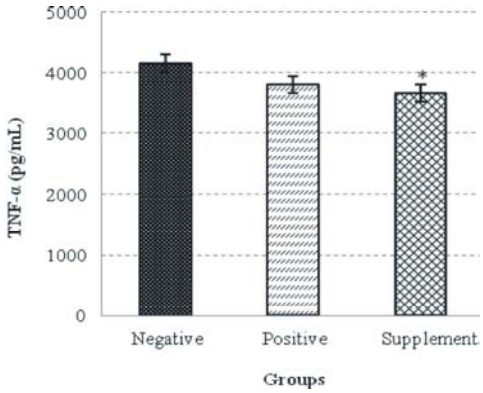

Fig. 3: Level of TNF-α in liver tissue of low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Values are expressed as mean ± SEM (n=5).
* Significantly different from negative group (p=0.02).

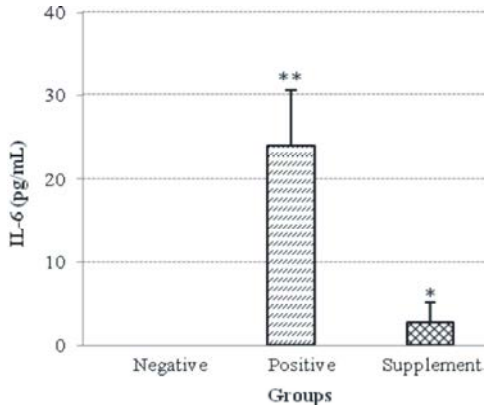

Fig. 2: Level of IL-6 in lung tissue of low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Values are expressed as mean ± SEM (n=5).
**Significantly different from negative group (p=0.01).
*Significantly different from positive group (p=0.01).

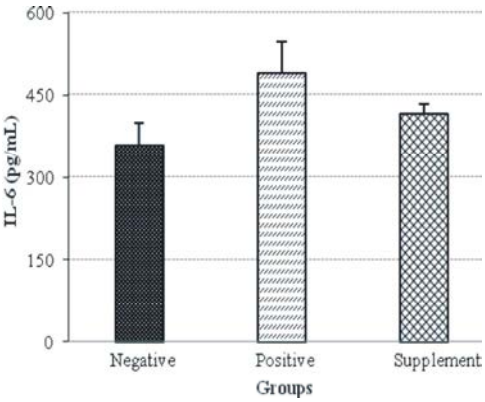

Fig. 4: Level of IL-6 in liver tissue of low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Values are expressed as mean ± SEM (n=5).

The positive group showed elevated level of IL-6 compared to supplement group by 21.20 pg/mL (Fig. 2). However, there were no significant differences (p=0.87) in level of IL-6 between negative and supplement groups.

TNF-α Level in Liver: Fig. 3 demonstrates the level of TNF-α in low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Based on the result, there were no significant differences (p=0.11) in level of TNF-α between negative and positive groups. The level of TNF-α for negative group was 4162.87 ± 178.89 pg/mL and level of TNF-α for positive group was 3804.20 ± 113.93 pg/mL. The negative group showed elevated level of TNF-α compared to positive group by 358.67 pg/mL (Fig. 3). Also, there were no significant differences (p=0.51) in TNF-α level between positive and supplement groups. The level of TNF-α for supplement group was 3663.53 ± 108.78 pg/mL. The positive group showed decreased level of TNF-α compared to supplement group by 140.67 pg/mL (Fig. 3). However, there were significant differences (p=0.02) in level of TNF-α between negative and supplement groups. Supplement group showed decreased level of TNF-α compared to negative group by 499.34 pg/mL (Fig. 3).

IL-6 Level in Liver: Fig. 4 demonstrates the level of IL-6 in low-dose ionizing radiation-induced mice following supplementation with 50% watermelon juice. Based on the result, there were no significant differences (p=0.11) in level of IL-6 between negative and positive groups. The level of IL-6 for negative group was 359.40 ± 39.03 pg/mL and level of IL-6 for positive group was 489.80 ± 57.79 pg/mL. The positive group showed elevated level of IL-6 compared to negative and supplement group by 130.40 pg/mL and 73.20 pg/mL respectively (Fig. 4). Based on the result, there were no significant differences (p=0.45) in level of IL-6 between positive and supplement groups. There were also no significant differences (p=0.60) in level of IL-6 between negative and supplement groups. The level of IL-6 for supplement group was 416.60 ± 15.68 pg/mL. Supplement group showed elevated level of IL-6 compared to negative group by 57.2 pg/mL (Fig. 4).

DISCUSSION

For more than a century until recently, the biological effects of low dose IR has been debated and investigated [8, 11]. While the risk of low dose IR remains unclear, high dose IR clearly produce deleterious outcome in humans including generation of cancer [8]. Studies on low dose IR is essential concerning its societal importance on varied issues including screening tests for cancer, future of nuclear power, frequent-flyer risks, occupational radiation exposure, manned space exploration and radiological terrorism [8]. Among these issues, studies on low dose IR have become necessarily important in diagnostic setting. To date, IR is assumed carcinogenic even at low doses when radiation protection is applied in health line including industry and public health [18].

Exposure to IR may lead to disturbance of normal tissue function through modification that finally causes tissue death [19]. TNF-α is one of the pro-inflammatory cytokines that promotes inflammation [20]. Based on present findings, significant difference in TNF-α level in lung of supplement group was observed when compared to positive group. The results demonstrated that supplementation of 50% watermelon juice with its natural source of lycopene and other antioxidants such as flavonoid and phenolic may help in down regulation of TNF-α level in lung. Ma and Kinneer [21] reported that phenolic has the ability to inhibit signal-induced TNF transcription, thus controlling cytokine induction through its properties as anti-inflammatory. Adding to that a study also found flavonoids may act as preventive agents in reducing lung injury induced by radiation [22].

Study findings showed that lung exposed to low dose x-radiation on positive group demonstrates a significant increase in IL-6 level compared to negative group. The outcome provides evidence that low-dose IR may induce inflammatory response by the production of IL-6 in lung. Under normal circumstances, cytokines are not detectable in body fluids or tissues [22]. This statement highly agrees with the present findings that the negative group demonstrate no expression of IL-6. IL-6 secreted by alveolar macrophages, type II pneumocytes and T-lymphocytes and are involved in immunologic responses and inflammation [1, 23]. Increased IL-6 level in lung from positive group may be caused by whole body irradiation-induced lung injury. This study outcome was supported by Ao *et al.* [23] study indicating significant increase in mice lung IL-6 level when induced by 12 Gy x-radiation. During acute lung injury, alveolar macrophages secrete pro-inflammatory cytokines IL-1, IL-6 and TNF-α that act locally to activate neutrophils and stimulate chemotaxis [24]. Influxes of macrophages and inflammatory cells into alveoli resulted from induction of pro-inflammatory cytokines IL-1, IL-6 and TNF-α [25] and elevated level of IL6 in lung after radiation exposure is possibly due to increase macrophages production into alveolar.

Based on the findings, a significant decrease in lung IL-6 level from supplement group was observed when compared to positive group. The present study showed that inflammatory response was down regulated by 50% watermelon juice and possibly by the act of the watermelon lycopene contents that demonstrates radio protective effect against IR. The findings highly agrees with a study conducted by Yaping *et al.* [1] that demonstrated significant reduction in ear inflammation when mice are supplemented with lycopene at lowest dose of 0.1 g/kg body weight. Also, decrease levels of IL-6 were observed in mice with adipose tissue inflammation when treated with lycopene [26].

Relative to the type of tissue involved, lycopene shows a prominent effect in decreasing cancer risk in lung, prostate and stomach cancers [27]. A review study by Palozza et al. [28] suggested increasing evidence advocating the preventive effect of lycopene in the formation and development of lung cancer. Mechanism of action of lycopene against tumor development is related to modulation of cytokine expression [28]. Radio protective effect of watermelon is achieved when lycopene exerts its effect by scavenging singlet oxygen due to strong affinity towards free radicals as well as preventing cells from lipid peroxidation [4].

The current study also demonstrated significant differences in liver TNF-α level between negative and supplement group. Under normal circumstances, cytokines are produced by liver cells at low levels [29]. This explains the increase level of TNF-α in negative group. Excessive amount of TNF-α level in liver may result in liver injury [29], therefore lowering the production of TNF-α induced by IR will protect liver against damage. A study conducted by Agarwal and Rao [30] indicated that lycopene is the major source of carotenoid and concentrated in adrenal gland, testes, prostate gland and mainly in liver [28, 30]. Once the liver's immune cells (kupffer cells) become activated, the production of cytokines may increase dramatically [29].

CONCLUSION

Overall, 50% watermelon juice may counterbalance the ROS production induced by low dose IR. From the study outcomes, the study proposed that supplementation of 50% watermelon juice may improve inflammatory response by decreasing the production of TNF-α and IL-6 levels following lycopene action on scavenge the singlet oxygen that caused the response.

ACKNOWLEDGEMENTS

The authors would like to thank Faculty of Health Science (FSK) and Research Management Institute (RMI), UiTM for funding the project (399/2012). Also, the authors greatly acknowledge Department of Medical Laboratory Technology, Department of Medical Imaging, Postgraduate Department, Pharmacogenomics Centre (PROMISE), UiTM and Forest Research Institute Malaysia (FRIM) for their contribution.

Author's Disclosure of Potential Conflict of Interest: The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

REFERENCES

1. Yaping, Z., Y. Wenli, H. Weile and Y. Ying, 2003. Anti-Inflammatory and Anticoagulant Activities of Lycopene in Mice. Nutrition Research, 23: 1591-1595.
2. Johar, D., J.C. Roth, G.H. Bay, J.N. Walker, T.J. Kroczak and M. Los, 2004. Inflammatory Response, Reactive Oxygen Species, Programmed (Necrotic-Like and Apoptotic) Cell Death and Cancer. Roczniki Akademii Medycznej w Białymstoku, 49: 31-39.
3. Klaunig, J.E., L.M. Kamendulis and B.A. Hocevar, 2010. Oxidative Stress and Oxidative Damage in Carcinogenesis. Toxicologic Pathology, 38: 96-109.
4. Meydan, D., B. Gursel, B. Bilgici, B. Can and N. Ozbek, 2011. Protective Effect of Lycopene against Radiation-Induced Hepatic Toxicity in Rats. Journal of International Medical Research, 39: 1239-1252.
5. Cavaillon, J.M. and D. Annane, 2006. Compartmentalization of the Inflammatory Response in Sepsis and SIRS. Journal of Endotoxin Research, 12: 151-170.
6. Playfair, J.H.L. and B.M. Chain, 2005. Immunology at a Glance. Blackwell Science, pp: 21.
7. Azzam, E.I., J.P. Jay-Gerin and D. Pain, 2012. Ionizing Radiation-Induced Metabolic Oxidative Stress and Prolonged Cell Injury. Cancer Letters, 327: 48-60.
8. Brenner, D.J., R. Doll, D.T. Goodhead, E.J. Hall, C.E. Land, J.B. Little, J.H. Lubin, D.L. Preston, R.J. Preston, J.S. Puskin, E. Ron, R.K. Sachs, J.M. Samet, R.B. Setlow and M. Zaider, 2003. Cancer Risks Attributable to Low Doses of Ionizing Radiation: Assessing What We Really Know. Proceedings of the National Academy of Sciences of the United States of America, 100: 13761-13766.
9. Mothersill, C., M.J. Moriarty and C.B. Seymour, 2005. Bystander and Other Delayed Effects and Multi-Organ Involvement and Failure Following High Dose Exposure to Ionising Radiation. British Journal of Radiology, 27: 128-131.
10. Dendy, P.P. and M.J.P. Brugmans, 2003. Low Dose Radiation Risks. British Journal of Radiology, 76: 674-677.
11. Anoopkumar-Dukie, S., A. McMahon, A. Allshire and T.J. Conere, 2005. Further Evidence for Biological Effects Resulting from Ionizing Radiation Doses in the Diagnostic X-ray Range. British Journal of Radiology, 78: 335-337.
12. Wall, B.F., G.M. Kendall, A.A. Edwards, S. Bouffler, C.R. Muirhead and J.R. Meara, 2006. What are the Risks from Medical X-rays and Other Low Dose Radiation? British Journal of Radiology, 79: 285-294.
13. Feinendegen, L.E., 2005. Evidence for Beneficial Low Level Radiation Effects and Radiation Hormesis. British Journal of Radiology, 78: 3-7.

14. Henriquez, C., S. Almonacid, I. Chiffelle, T. Valenzuela, M. Araya, L. Cabezas, R. Simpson and H. Speisky, 2010. Determination of Antioxidant Capacity, Total Phenolic Content and Mineral Composition of Different Fruit Tissue of Five Apple Cultivars Grown in Chile. Chilean Journal of Agricultural Research, 70:523-536.
15. Collins, J., P. Perkins-Veazie and W. Roberts, 2006. Lycopene: From Plants to Humans. HortScience, 41: 1135-1144.
16. Arnold, J., 2002. Watermelon Packs a Powerful Lycopene Punch. Agricultural Research Magazine, 50: 12-13.
17. Edwards, A.J., B.T. Vinyard, E.R. Wiley, E.D. Brown, J.K. Collins, P. Perkins-Veazie, R.A. Baker and B.A. Clevidence, 2003. Consumption of Watermelon Juice Increases Plasma Concentrations of Lycopene and β-carotene in Humans. Journal of Nutrition, 133: 1043-1050.
18. Harbron, R.W., 2012. Cancer Risks from Low Dose Exposure to Ionising Radiation - Is the Linear No-Treshold Model Still Relevant? The College of Radiographers, 18: 28-33.
19. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2000. Sources and Effects of Ionizing Radiation: Sources. United Nations Publications, pp: 1.
20. Dinarello, C.A., 2000. Proinflammatory Cytokines. Chest, 118: 503-550.
21. Ma, Q. and K. Kinneer, 2002. Chemoprotection by Phenolic Antioxidants Inhibition of Tumor Necrosis Factor Alpha Induction in Macrophages. Journal of Biological Chemistry, 277: 2477-2484.
22. Remick, D.G. and T.L. Whiteside, 2001. Cytokine assays. In cytokines reference: overview, Eds., Oppenheim, J.J. and M. Feldmann. Massachusetts, MA: Academic Press, pp: 53-76.
23. Ao, X., L. Zhao, M.A. Davis, D.M. Lubman, T.S. Lawrence and F. Kong, 2009. Radiation Produces Differential Changes in Cytokine Profiles in Radiation Lung Fibrosis Sensitive and Resistant Mice. Journal of Hematology and Oncology, 12: 1-12.
24. Cepkova, M. and M.A. Matthay, 2006. Pharmacotherapy of Acute Lung Injury and the Acute Respiratory Distress Syndrome. Journal of Intensive Care Medicine, 21: 119-143.
25. Jang, S.S., H.G. Kim, J.S. Lee, J.M. Han, H.J. Park, G.J. Huh and C.G. Son, 2013. Melatonin Reduces X-ray Radiation-Induced Lung Injury in Mice by Modulating Oxidative Stress and Cytokine Expression. International Journal of Radiation Biology, 89: 97-105.
26. Gouranton, E., C. Thabuis, C. Riollet, C. Malezet-Desmoulins, C. El Yazidi, M. J. Amiot, P. Borel and J.F. Landrier, 2011. Lycopene Inhibits Proinflammatory Cytokine and Chemokine Expression in Adipose Tissue. Journal of Nutritional Biochemistry, 22: 642-648.
27. Hwang, E.S. and P.E. Bowen, 2002. Can the Consumption of Tomatoes or Lycopene Reduce Cancer Risk? Integrative Cancer Therapies, 1: 121-132.
28. Palozza, P., R.E. Simone, A. Catalano and M.C. Mele, 2011. Tomato Lycopene and Lung Cancer Prevention: From Experimental to Human Studies. Cancers, 3: 2333-2357.
29. Neuman, M.G., 2003. Cytokines-Central Factors in Alcoholic Liver Disease. Alcohol Research and Health, 27: 307-316.
30. Agarwal, S. and A.V. Rao, 2000. Tomato Lycopene and Its Role in Human Health and Chronic Diseases. Canadian Medical Association Journal, 163: 739-744.