Radioprotection 2018, 53(4), 293–298

https://doi.org/10.1051/radiopro/2018034

Available online at:
www.radioprotection.org

ARTICLE

Protective effects of resveratrol against X-ray irradiation by regulating antioxidant defense system

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Received: 2 May 2018 / Accepted: 1 October 2018

Abstract – Ionizing radiation interacts with biomolecules to produce free radicals, which can damage all components of the cell. The aim of this study was to evaluate the protective effects of different doses of resveratrol against X-ray-induced damage in male rat. The animals were divided into five groups, each composed of six rats: two groups as control groups received saline or ethanol (ethanol in saline, 25%, V/V as a vehicle). Two groups received resveratrol (5 and 10 mg/kg.bwt) for 30 days before X-ray exposure. One group received X-ray. The rats were sacrificed 24 h after the last exposure, blood samples were collected and serum level of malondialdehyde (MDA), total antioxidant capacity (TAC), and the activities of superoxide dismutase (SOD) and catalase (CAT) were measured by spectrophotometric method. X-ray irradiation significantly increased the levels of MDA and decreased TAC as well as SOD activity as compared with control groups. Furthermore, resveratrol pretreatment led to remarkable decrease in MDA concentration and increase in the activities of SOD and CAT as well as TAC compared to those of controls. Our results revealed antioxidant properties of resveratrol and suggest it as a potent radioprotector to ameliorate X-irradiation induced damage in the body.

Keywords: X-ray irradiation / resveratrol / total antioxidant capacity / malondialdehyde / antioxidant enzymes

1 Introduction

X-ray irradiation therapy is one of the most common and effective form of radiotherapeutic modalities for the cure of cancer (Baskar *et al.*, 2014). Apart from inducing anti-proliferative and cell-killing effects on tumor tissue, ionizing radiation like X-rays and gamma rays as well as industrial chemicals or air pollutants are the major exogenous sources of reactive oxygen species (ROS) such as superoxide anion radical, hydrogen peroxide, hydroxyl radical in mammalian cells (Azzam *et al.*, 2012; Poljšak and Fink, 2014). An increased level of ROS production induces oxidative stress and plays a critical role in cellular damage by causing lipid peroxidation, oxidative modification of proteins and DNA damage (Barrera, 2012; Møller *et al.*, 2014). Oxidative stress is now thought to make a significant contribution to many diseases such as cancer, neurological disorder, diabetes mellitus and age-related eye disease (Donohue, 2006; Prasad *et al.*, 2016; Sharifi-Rad *et al.*, 2017; Tramutola *et al.*, 2017). Accordingly, oxidative stress and its correlation with disease progression can be monitored by assessment of reaction products of oxidative damage in plasma and/or tissues. Malondialdehyde (MDA) is a lipid peroxidation marker and it is widely used to assess cell injury (Frijhoff *et al.*, 2015). Total antioxidant status (TAS) or total antioxidant capacity (TAC) is another marker of interest in evaluation of oxidative stress (Wu *et al.*, 2017).

Mammalian cells are equipped with several major protective systems, including neutralization of the deleterious effect of ROS (Birben *et al.*, 2012). Superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GR) and glutathione peroxidases (GPx) are considered as major antioxidant enzymes that scavenge the ROS and avert cellular damage. Non-enzymatic antioxidants, including the glutathione (GSH), vitamins C, E, A, transferrin, and ceruloplasmin as well as enzymatic antioxidants are known to quench ROS and disrupt chain propagation reaction (Birben *et al.*, 2012). SOD

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and CAT are the first-line antioxidants, which are scavengers of superoxide and hydrogen peroxide, respectively. To our knowledge, measurement of SOD and CAT activity has been widely used as oxidative stress markers (Ighodaro and Akinloye, 2017).

Several investigations have reported the protective effects of flavonoids as dietary antioxidants against oxidative damage induced by ROS (Procházková *et al.*, 2011). Epidemiological studies revealed that long-term consumption of diets rich in polyphenols could lead to protection against development of cancers, cardiovascular diseases, diabetes, and neurodegenerative diseases (Amararathna *et al.*, 2016). Resveratrol (trans-3, 40, 5-tri-hydroxystilbene) is a member of the flavonoid family that generally found in various plant species such as mulberries, peanuts and red grapes (Abbasi *et al.*, 2017). Resveratrol have attracted intense interest for its positive effects in biological systems which include antioxidant activity, anti-inflammatory action and cancer chemoprevention (Bo *et al.*, 2013; Varoni *et al.*, 2016).

There have been few studies on the protective effects of resveratrol against X-ray irradiation induced damage, and the underlying mechanisms of these effects are still unknown (Carsten *et al.*, 2008). Accordingly, this study was designed to evaluate the possible role of resveratrol, when given as a supplement diet, in protecting from oxidative stress induced by X-ray irradiation exposure. To address this hypothesis, we measured the serum levels of TAC, MDA, and antioxidant defense systems such as SOD and CAT in male rats exposed to X-ray irradiation following resveratrol treatment.

2 Materials and methods

2.1 Animals

Thirty male Wistar rats weighing 230–250 g were provided by the animal breeding center of Arak University of Medical Sciences (Arak, Iran). All rats were maintained on a 12 h light/dark schedule and fed *ad libitum*. All experiments were performed according to the approved protocol by Arak University of Medical Sciences and Islamic Azad University of Tehran.

2.2 Drug and treatments

Resveratrol was purchased from Amazon Company (98% Transmax^{TM} resveratrol, Biotivia, USA). Resveratrol was first dissolved in a small amount of absolute ethanol and then diluted with saline in final 25% ethanol concentration. The rats were randomly divided into five groups of six rats each. Groups 1 and 2 (as control groups) were injected with isotonic saline (sham group) and 25% ethanol (as vehicle) alone, respectively. Group 3 (G3) received isotonic saline plus X-ray irradiation, group 4 (G4) received resveratrol 5 mg/kg plus X-ray irradiation and group 5 (G5) received resveratrol 10 mg/kg plus X-ray irradiation. In all groups, treatments were performed by intraperitoneal injections once daily for 30 days. After resveratrol and vehicle treatments, the rats in G3, G4 and G5 were exposed to whole body X-irradiation with a dose of 7 Gy at a dose rate 200 cGy/Mu (Elekta Compact Linac). Animals were sacrificed at 24 h after X-irradiation exposure under anesthesia. The blood was taken directly from the heart, centrifuged at 3 000 rpm at 4 °C for 10 min to separate the serum, and stored at −80 °C until further analysis.

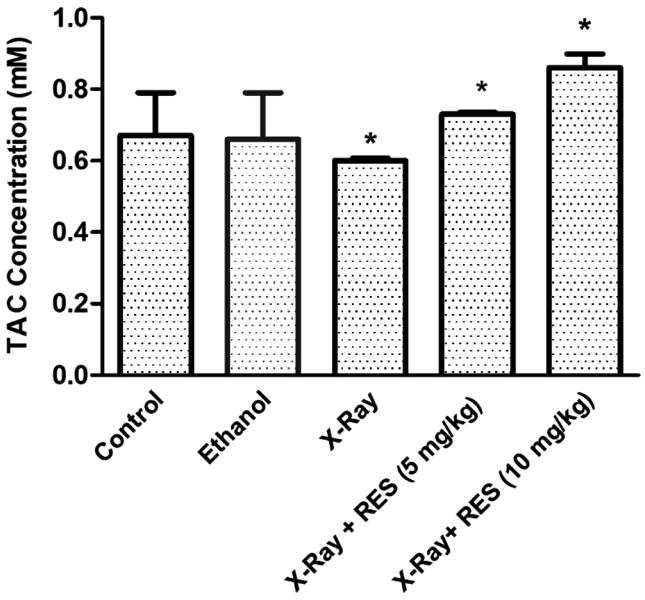

Fig. 1. Comparison of TAC concentrations between the control and treatment groups. Resveratrol pre-treatment significantly increased TAC concentrations compared to the X-ray radiated group. Values are means ± SEM for each group ($n = 6$); significant differences were observed *: $p < 0.001$. (Dunnett's *post hoc* tests). RES = Resveratrol.

2.3 Analysis of the biochemical parameters

The level of TAC and MDA and the SOD and CAT activities were assayed using spectrophotometric commercial kits according to manufacturer's instructions in the serum samples (Zell bio, Germany). The SOD and CAT activities are expressed in U/ml. MDA and TAC concentrations are expressed in μM and mM, respectively.

2.4 Statistical analysis

Data are presented as mean ± SD and are considered to be statistically significant at $p < 0.05$. Statistical analyses were conducted using one-way analysis of variance (ANOVA) with either Tukey's or Dunnett's *post hoc* tests where appropriate. SPSS 20 analytic software (SPSS, Inc., Chicago) was used for data analysis.

3 Results

To obtain more information about protective mechanisms of resveratrol against X-ray radiation, we investigated the effects of two doses (5 and 10 mg/kg bwt) of this compound on oxidative stress markers.

3.1 Total antioxidant capacity (TAC)

The effects of resveratrol on X-ray-induced TAC concentrations in the rats' serum are shown in Figure 1. Resveratrol

pretreatment prior to X-ray irradiation significantly increased the concentration of TAC in a dose-dependent manner compared to X-ray exposed group and control groups. In addition, TAC concentrations were significantly decreased in irradiated group (G3) compared with the control groups (G1 and G2) 24 h after irradiation ($p < 0.05$).

3.2 Lipid peroxidation marker level

Lipid peroxidation in the serum was quantified by measuring MDA concentrations. The effect of X-rays with or without resveratrol on the concentrations of MDA in serum after X-irradiation is shown in Figure 2. As shown in this figure, pretreatment of X-ray exposed rats with resveratrol, in a dose-dependent manner, significantly decreased the concentrations of MDA compared to irradiated and control groups ($p < 0.001$).

3.3 Catalase (CAT) activity

Serum activities of CAT in all treated groups are depicted in Figure 3. As shown in this figure, resveratrol pretreatment prior to X-ray irradiation significantly increased CAT activity in a dose-dependent manner compared to X-ray irradiation exposure group and control groups ($p < 0.001$). However, no significant difference was observed in CAT activity in the X-ray exposed group, when compared with the control groups.

3.4 Superoxidase dismutase (SOD) activity

Figure 4 shows the effects of resveratrol on the serum activities of SOD enzyme in the irradiated groups compared to the controls. As illustrated in this figure, resveratrol pretreatment prior to X-ray irradiation significantly increased SOD activity in a dose-dependent manner when compared with X-ray irradiated group and control groups ($p < 0.001$). Nonetheless, SOD activity was significantly decreased in the X-ray exposed group, as compared to the control groups.

As indicated in all figures, all data showing the levels of MDA, TAC, SOD and CAT in the serum of ethanol treated group of rats were not significantly different from those of saline treated animals. Therefore, this indicates that ethanol 25% had no remarkable interfering effect on our main results.

4 Discussion

The widespread popularity of complementary and alternative medicine (CAM) therapy has encouraged researchers to investigate different biologic effects of medicinal plants. Accordingly, we aimed to study the radioprotective potential of resveratrol regarding its antioxidant and free radical scavenging properties *in vivo*.

The data presented in the current study clearly showed that whole body X-ray (7 Gy) irradiation of rats leads to a decrease in the SOD and CAT activity and the levels of TAC as well as increase in the levels of MDA in the rat serums. There are several *in vivo* and *in vitro* studies showing the effect of irradiation on decreasing the activity of SOD and catalase as well as increasing the levels of MDA (Pence and Naylor, 1990; Lewicka *et al.*, 2015). Our data are consistent with the previous results.

Multiple modifying mechanisms, as a consequence of excessive ROS production, have been suggested to inactivate

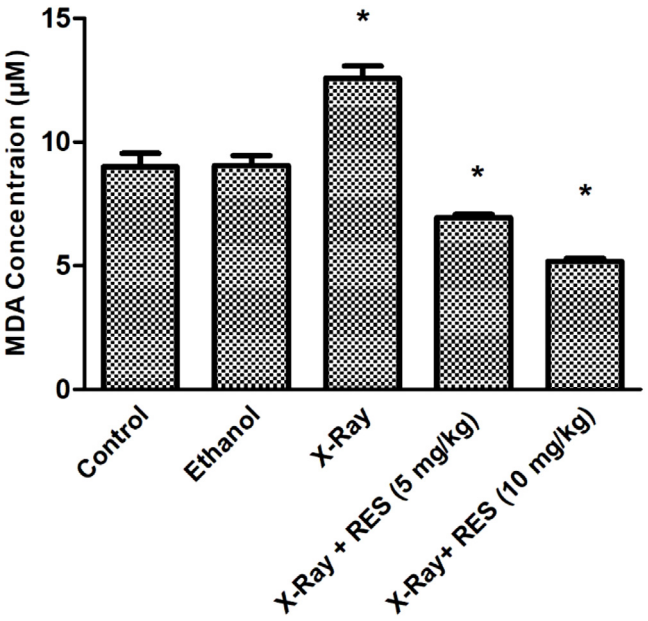

Fig. 2. Comparison the concentrations of MDA between the control and treatment groups. Resveratrol pre-treatment remarkably reduced MDA induced by X-ray irradiation. All data are means ± SEM for each group ($n = 6$); significant differences were observed *: $p < 0.001$ (Tukey's *post hoc* tests). RES = Resveratrol.

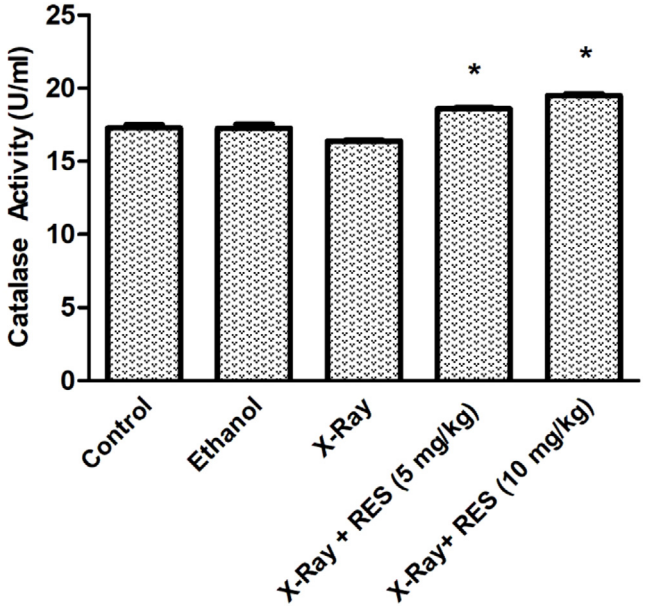

Fig. 3. Comparing the activity of catalase between the control and treatment groups. Resveratrol pre-treatment increased catalase activity compared to X-ray exposed group. The results are expressed as means ± SEM ($n = 6$); significant differences were observed. *: $p < 0.001$ (Dunnett's *post hoc* tests). RES = Resveratrol.

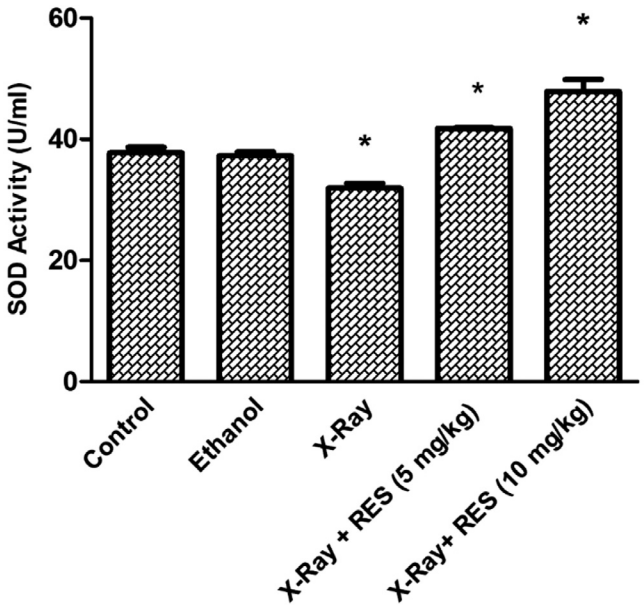

Fig. 4. Comparison of SOD activity between the control and treatment groups. Resveratrol pre-treatment considerably increased SOD activity compared to X-ray irradiated group. Values are means ± SEM ($n = 6$) for each group; significant differences were observed. *: $p < 0.001$ (Dunnett's *post hoc* tests). RES = Resveratrol.

the functional proteins. These mechanisms include site-specific amino acid modification, changed electric charge, aggregation of cross-linked reaction products, fragmentation of the peptide chain and enhanced susceptibility of proteins to degradation (Sharma *et al.*, 2012). Accordingly, it appears that these mechanisms were responsible for enzyme inactivation, leading to the decrease in SOD and CAT activity observed in our X-ray irradiated group. Furthermore, increase in MDA level and decrease in TAC level in this group may be due to high level of ROS, which results in producing lipid peroxidation products and depleting antioxidant systems. However, we found that pretreatment with resveratrol with dose of 5 and 10 mg/kg ameliorates the deleterious effects of X-ray irradiation by increasing the antioxidant enzymes activity of SOD, CAT and the levels of TAC as well as decreasing MDA concentration in the serum. Our results also showed that this effect is dose dependent with the higher dose being more effective. However, we did not analyze other oxidative stress biomarkers such as GPX, glutathione and total oxidant status as well as the effect of other doses of X-irradiation during radiotherapy. On the other hand, the protective effects of resveratrol on radiation-induced hepatotoxicity and nephrotoxicity were not evaluated in the present study. Therefore, it is suggested that in future studies, ALT, AST, gamma-GT, creatinine, and urea to be measured in the serum. In addition, oxidative stress biomarkers can be evaluated in the tissues such as liver, kidney and lymphocytes. Another limitation of our study is that we did not include a resveratrol treated control group to assess the adverse effects of this compound on our animal models. A final limitation of this research is fail in incorporation of different doses of X-ray radiation against several concentrations of resveratrol.

Radioprotective effects of resveratrol pretreatment have been also reported in several *in vivo* and *in vitro* studies. Carsten *et al.* conducted a study to investigate the radioprotection potential of orally treated resveratrol in whole body of gamma-irradiated mice (Carsten *et al.*, 2008). They found that resveratrol treatment significantly reduces the frequencies of chromosome aberrations in irradiated mouse bone marrow cells. *In vitro* studies have also shown that pretreatment of cultured cells with resveratrol could mitigate ultraviolet irradiation (UV)-induced damage (Chan *et al.*, 2015). In the Sheu *et al.* study, UV-irradiated retinal pigment epithelial (RPE) cells were treated with meclofenamic acid, paxilline and resveratrol. The results of that study indicated that resveratrol pretreatment has protective effect against damage caused by UV-radiation. However, resveratrol post-treatment seems to have no such a protective effects on these cells (Sheu and Wu 2009).

Interestingly, resveratrol appears to exert its radioprotective effects through suppressing the generation of intracellular hydrogen peroxide (H_2O_2) induced by UV-irradiation in a concentration-dependent manner (Chan *et al.*, 2015). H_2O_2 has been reported to induce cytotoxicity, DNA fragmentation, intracellular accumulation of ROS and elicit inflammatory responses by inducing nuclear factor NF-κB pathway, which are inhibited by resveratrol pretreatment (Jang and Surh, 2001). Resveratrol pretreatment has found to reduce oxidative stress induced by H_2O_2 in RPE cells, by increasing the activities of SOD, GPx and CAT and also enhancing the levels of reduced glutathione (GSH) as well as direct scavenging the ROS in RPE cells (Sheu *et al.*, 2010; Pintea *et al.*, 2011). Several lines of evidences indicate that resveratrol has a potential to switch from antioxidant to pro-oxidant behavior (Tomasello *et al.*, 2012; Dobrzynska, 2013). This polyphenol has antioxidant activity at lower doses and acts as pro-oxidant at higher doses (Murias *et al.*, 2005). Accordingly, it is noteworthy that protective effects of resveratrol on oxidative stress may appear to be dose dependent and this phytophenol may exerts its protective roles at safe and effective doses (Szende *et al.*, 2000; Pintea *et al.*, 2011). Truong *et al.* suggested two different mechanisms for describing the protective role of resveratrol against oxidative damage. They proposed that resveratrol directly scavenges ROS and organic radicals with mechanisms of hydrogen atom transfer and sequential proton loss electron transfer, and indirectly could induce the expression of diverse antioxidant enzymes such as heme oxygenase 1, CAT, GPx, and SOD as well as enhancing GSH concentrations (Truong *et al.*, 2018). Accordingly, it appears that protective effects of resveratrol that were observed in our study may be explained by these two proposed mechanisms. To our knowledge, there are no published studies investigating the possible X-irradiation-protective effects of resveratrol on serum by measuring activities of these antioxidant enzymes, at different doses after exposure of whole-body to X-irradiation. However, our study is a preliminary report and more detailed studies need to be conducted to evaluate the potential protective effects of resveratrol in reducing X-ray irradiation-induced oxidative stress.

5 Conclusion

The present study indicated that X-ray irradiation causes oxidative damage and resveratrol could act as a radioprotector, alleviating X-ray irradiation-induced oxidative damage by increasing cellular defense. Indeed, our report showed resveratrol can reduce ROS formation by increasing the activity of antioxidant enzymes such as SOD and CAT, and as a result decreasing in lipid peroxidation. Resveratrol is found in various plant species such as mulberries, peanuts and red grapes. Hence, based on our result, it is suggested that these fruits can be used to decrease the harmful effects of radiation during radiotherapy for cancer patients.

Acknowledgments. This paper has been extracted from the M.Sc. thesis of Salman Salehi. The study was conducted after approval by the Ethics Committee of Arak University of Medical Sciences and Islamic Azad University of Tehran, Science and Research Branch and receiving the ethics code number IR. NREC.007.1394.05.

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Cite this article as: Salehi S, Bayatiani M, Yaghmaei P, Rajabi S, Goodarzi M, Jalali Mashayekhi F. 2018. Protective effects of resveratrol against X-ray irradiation by regulating antioxidant defense system. *Radioprotection* 53(4): 293–298