Protection Against Ionizing Radiation-Induced Normal Tissue Damage by Resveratrol: A Systematic Review

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ABSTRACT

The use of some agents as radioprotectors has been evaluated for protection against normal tissue toxicity following exposure to ionizing radiation. Resveratrol, a natural flavonoid, with antioxidant and anti-inflammatory properties has attracted research interests for its radioprotective potential. This study systematically evaluates existing studies to examine the radioprotective effectiveness of resveratrol. A literature search of the electronic databases, including PubMed, Scopus, and Embase was conducted to retrieve articles investigating the protective effect of resveratrol against ionizing radiation-induced damage to normal tissues. The search timeframe ranged from the inception of each database to January 2020. From an initial search of 231 articles, and after the removal of duplicates as well as applying the predetermined inclusion and exclusion criteria, 33 articles were finally included for this systematic review. Results showed promising protective effect of resveratrol against ionizing radiation-induced damage to normal tissues. Furthermore, no adverse effect was observed after administering resveratrol. Resveratrol showed the potential to protect against ionizing radiation-induced damage to normal tissue cells via notable mechanisms, including anti-apoptotic and anti-inflammatory effects. However, further studies on the efficacy of clinical translation of resveratrol would open up more insights, while other gray areas such as the optimal radioprotective dosage of resveratrol requires further investigation. Overall, resveratrol is a potential double-edged sword in cancer therapy while protecting healthy tissues.

Keywords: Resveratrol, ionizing radiation, radiation protection, DNA damage

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Introduction

The use of ionizing radiation (IR) has been on the increase since its inception in the early 1900s. Its use ranges from one sector to another vis-à-vis industrial and agricultural sectors. The medical applications of IR include diagnosis and therapy (especially in the treatment of cancers). However, exposure to IR could lead to normal tissue damage. During radiotherapy, normal tissues could be affected, thereby leading to a reduction in the therapeutic efficiency of radiotherapy as well as a reduced quality of life of cancer patients. Normal tissue damage from exposure to IR can also be via radiation accidents and disasters. For instance, during the Hiroshima and Nagasaki events, exposure to sub-lethal IR doses led to over 150,000 deaths [1]. Similar mortalities were also recorded following the Chernobyl nuclear plant catastrophe [2].

Following exposure, the DNA is the major target of IR via direct interaction. However, most radiation-induced damages are via indirect interaction (production of free radicals following the interaction of IR with water molecules in living tissues) [3]. These free radicals include reactive oxygen species (ROS) and reactive nitrogen species (RNS). They are highly reactive with the ability to attack DNA and other vital organelles in the body. Cell death or neoplasm may occur if the DNA damage overcomes DNA damage responses [4]. The mechanism of radiation-induced cell death include necrosis, necroptosis, mitotic catastrophe, apoptosis, autophagy, and senescence, [5] and the inability of normal cells to repair complex DNA damage may lead to any of these effects. It is also very important to know that the degree of cell death varies with cell type [6] as well as the IR dose received [7].

Overcoming normal tissue damage from IR has been attracting numerous researches for many years. Several strategies have been proposed such as the use of natural radioprotectors (radioprotective agents). Natural radioprotectors are notable for minimal toxicity [8] and are easily accessible and affordable [9]. Natural radioprotectors such as melatonin, resveratrol, curcumin, hesperidin, metformin, rutin, selenium, caffeic acid polyphenol ester (CAPE), alpha lipoic acid, co-enzyme Q10, etc., have been investigated for their radioprotective potential [10].

Resveratrol (3,5,4′-trihydroxy-trans-stilbene: formula $C_{14}H_{12}O_3$) (Figure 1) is a well-known polyphenol which is found in some fruits and vegetables. The main sources of resveratrol are soy, grapes, red wine, and peanuts. Generally, resveratrol naturally protects herbs against fungi, ultra-violet rays, and other stresses [11]. In recent time, resveratrol has been shown to possess potent antioxidant and anti-clastogenic properties that aid in protecting against chromosomal instability and the initiation of cancers. As a radioprotector, resveratrol has been shown to possess properties such as stimulation of inherent antioxidant system, suppression of inflammation, and redox interaction [12, 13]. In addition to its radioprotective effect, resveratrol also exhibits anti-cancer effects [14-16], potentially making it a useful radioprotector for clinical aims without significant concerns related to tumor protection. Several studies have been conducted investigating resveratrol's radioprotective effect. Thus, the aim of this study was to systematically evaluate existing literature on the radioprotective effect of resveratrol against ionizing radiation-induced damage to normal tissues.

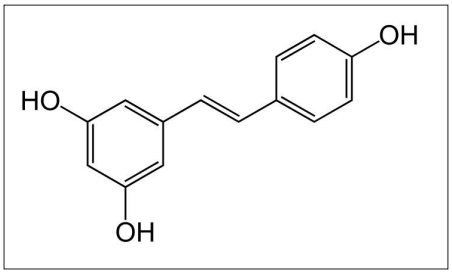

Figure 1. Chemical structure of resveratrol

Main Points

- Resveratrol showed potential to protect against ionizing radiation-induced damage to normal tissues.
- Anti-apoptotic and anti-inflammatory effects of resveratrol are its most notable mechanisms of radioprotection.
- So far, there has been no side effect from the administration of resveratrol.

Materials and Methods

Search Strategy

The reporting of this systematic review was done in line with the statement of preferred reporting items for systematic reviews and meta-analyses (PRISMA) [17]. An electronic literature search was conducted in January 2020 using the following databases; PubMed, Scopus, and Embase for articles published in the English language investigating the radioprotective effect of resveratrol against ionizing radiation-induced damage to normal tissues, without restriction on the year of publication. The search keywords were as follows: "resveratrol" and "radiation". Manual screening of references of retrieved studies was conducted to obtain relevant studies.

Inclusion Criteria

The retrieved articles were included based on the following criteria:

- Studies that were conducted to determine the radioprotective effects of resveratrol, which were published in the English language;
- Studies that used ionizing radiation;
- Experimental and clinical studies with full texts.

Exclusion Criteria

Studies were excluded based on the following criteria:

- Studies in which resveratrol was not used;
- Studies in which resveratrol was used in combination with other agents;
- Studies that made use of other forms of radiation such as ultraviolet (UV) rays, etc.;
- Studies that evaluated the effect of resveratrol with chemotherapy instead of radiation therapy; and
- Conference abstracts, case reports, simulation studies, letters, review articles, editorials, unpublished data, articles without full texts, and non-English articles.

Study Selection

All articles retrieved from the electronic databases as well as manual searches were entered into endnote software (EndNote version X6, Thomson Reuters, New York, NY, USA) for removal of duplicates. Thereafter, two authors independently reviewed the titles and abstracts of the retrieved studies for eligibility. Studies were then selected based on the predetermined inclusion and exclusion criteria. For any disagreements concerning the inclusion of studies, all authors agreed on a consensus based on factual evidence.

Data Extraction

The data from each eligible study were extracted and checked by the authors. The following information were carefully obtained from each included study: first author's name, subject, organ (or tissue) studied, radiation type and dose, resveratrol dose, time for outcome assessment as well as findings. Furthermore, these data were summarized and presented in a tabular form.

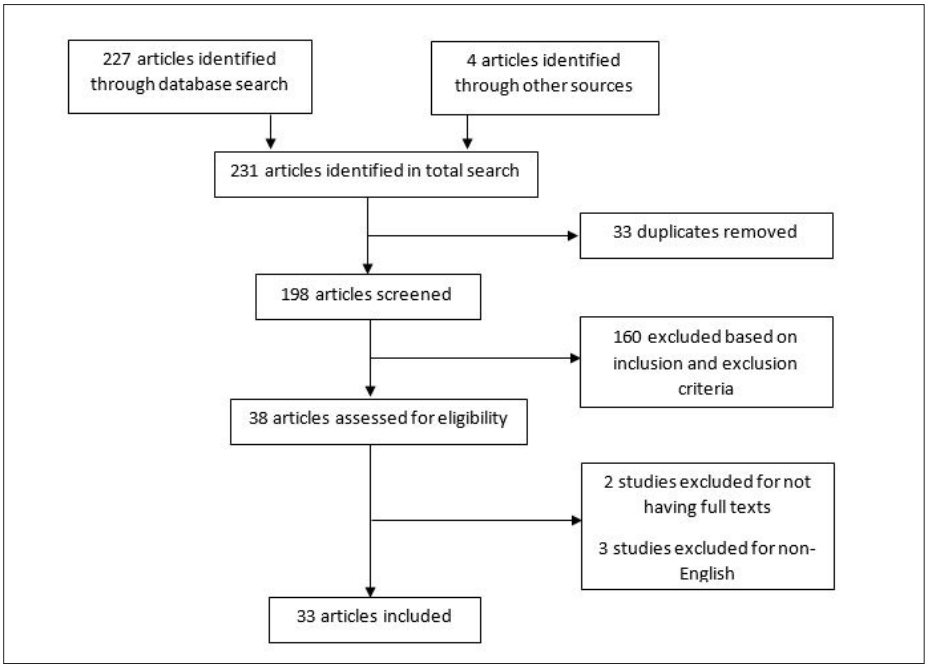

Figure 2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the selection of included articles

Table 1. Summary of articles included in the systematic review

First author	Subject	Organ (or tissue) studied	Radiation type and dose (Gy)	Resveratrol dose/ concentration	Time for outcome assessment	Findings
Radwan et al. [20]	Rats	Intestine	Y-ray, 5	20 mg/kg	3 weeks	Attenuated intestinal inflammation following irradiation via modulating PI3K/Akt/mTOR pathway.
Yahyapour et al. [22]	Mice	Lung	Y-ray, 18	200 mg/kg	80 days	Reduced pneumonitis and protected against radiation-induced fibrosis.
Ocolotobiche et al. [33]	Human peripheral blood lymphocytes	Lymphocytes	X-ray, 4	50 mg/day	15 days	Ameliorated radiation-induced damage index.
Najafil et al. [47]	Mice	Testis	Y-ray, 2	100 mg/kg	37 days	Reduced basal lamina, epididymis and sperm density.
Gao et al. [32]	Human embryonic kidney cell lines	Kidney	Y-ray, 4	5 μM	24 hours	Reduced apoptosis and DNA damage via targeting TyrRS acetylation.
Farhood et al. [31]	Mice	Intestine	Y-ray, 7	100 mg/kg	4 weeks	Resveratrol is an effective radiomitigator compared to alpha-lipoic acid.
Azmoonfar et al. [48]	Mice	Lung	Y-ray, 18	100 mg/kg	100 days	Resveratrol mitigated radiation-induced lung injury.
Zhang et al. [49]	Mice	Lymphocytes	Y-ray, 6	20 mg/kg	30 days	Ameliorated radiation-induced long term immune malfunction at least partly via modulation of plasma cytokine.
Banegas et al. [29]	Human peripheral blood lymphocytes	Lymphocytes	X-ray, 4 and 16	15 and 60 μM	1 – 6 days	Resveratrol showed a radio-protective effect at the lowest dose (15 μM).
Zhang et al. [50]	Mice	Bone marrow	Y-ray, 4	20 mg/kg	30 days	Treatment with resveratrol alone was more effective compared to its cells combination with diphenyleneiodonium in protecting against radiation-induced hematopoietic system injury.
Zhang et al. [35]	Mice	Intestine	Y-ray, 7	40 mg/kg	6 days	Resveratrol decreased the effects of radiation on intestinal injury via activation of Sirt1.
Koohian et al. [51]	Mice	Lymphocytes	Y-ray, 2	50 and 100 mg/kg	2 hours	Inhibited radiation-induced DNA damage
Said et al. [34]	Rats	Ovary	Y-ray, 3.2	25 mg/kg.	15 days	Prevented radiation-induced damages to ovary via NF-κB inhibition.
Prager et al. [52]	Mice	Hippocampal cultures	X-ray, 4.5, 8, 12 and 16	15 μM	42 days	Reversed radiation-induced decline in neural stem cells.
Basso et al. [53]	Human peripheral blood lymphocytes	Lymphocytes	X-ray, 0.5 and 1	20 and 40 μM	72 hours	Resveratrol promoted the manifestation of DNA damage.
Barbosa et al. [21]	Rats	Mandible	X-ray, 15	100 mg/kg	30 days	No effective radioprotective impact on dental tissues.
Wang et al. [54]	Mice	Bone marrow cells	Y-ray, 1 - 4	0.01-100 μM	7 days	Resveratrol had less radioprotective effect on hematopoietic cells compared to its analogue (heyneanol-A).
Li et al. [55]	Rats	Brain	Y-ray, 4	5 and 10 mg/kg	21 days	Resveratrol reduced radiation-induced apoptosis via activation of Sirt1.
Kim et al. [56]	Rats	Bone marrow	X-ray, 17.5	2 mg/kg	30 days	Resveratrol supplementation could aid recovery from radiation-induced inflammation by modulating immune cell percentages and cytokine production.
Kim et al. [57]	Rats	Lymphocytes	X-ray, 17.5	2 mg/kg	10 days	Reduced radiation-induced damage to lipid metabolism and immune responses.
Zhang et al. [38]	Mice	Bone marrow	Y-ray, 6 -7.2	20 mg/kg	30 days	Resveratrol protected hematopoietic stem cells from radiation in part via activation of Sirt1.
Xu et al. [19]	Mice	Saliva and submandibular gland	X-ray, 15	20 mg/kg	30 days	Resveratrol protected salivary glands against the negative effects of irradiation.
Sebastia et al. [24]	Human peripheral blood lymphocytes	Lymphocytes	Y-ray, 2	2.19-219 μM	-	Reduced radiation-induced chromosomal damage.
Simsek et al. [28]	Rats	Ovary	X-ray, 7.2	10 and 100 mg/kg	24 hours	Effectively reduced the follicle loss induced by ionizing radiation.
Di Franco et al. [30]	Breast cancer patients	skin	X-ray, 50 (whole breast) 10 (tumour)	2 tablets/day	20 days	Ameliorated radiation-induced skin toxicity, an effect which was more pronounced in patients with PTV < 500 ml.
Denissova et al. [27]	Mouse	Embryonic stem cells	X-ray, 5	10-30 μM	48 hours	Resveratrol improved viability in embryonic stem cells after DNA damage without compromising genomic integrity.
Velioğlu-Öğünç et al. [36]	Rats	Ileum, liver	X-ray, 8	10 mg/kg	20 days	Supplementing cancer patients with adjuvant therapy of resveratrol may have some benefit for a more successful radiotherapy.
Carsten et al. [26]	Mouse	Bone marrow	Y-ray, 3	100 mg/kg	30 days	Reduced the mean total frequency of chromosomal aberration in bone marrow cells.

Table 1. Summary of articles included in the systematic review

Fiore et al. [58]	Human lymphoblastoid cells	Lymphoblastoid cells	X-ray, 5	50 and 100 µM	24 hours	Resveratrol mitigated the apoptotic clearance of irradiated cells and prevented the G2 phase cell cycle arrest induced by X-rays.
Song et al. [18]	Mice	Bone marrow	Y-ray, 6.5	20 mg/kg, 50 µM	20 days	Resveratrol increased survival time and protected against radiation-induced hematopoietic damage.
Salehi et al. [59]	Rats	Blood	X-ray, 7	5 and 10 mg/kg	30 days	Resveratrol ameliorates oxidative stress by increasing antioxidant levels.
Koohian et al. [25]	Mice	Bone marrow	X-ray, 2	50 mg/kg	24 hours	Resveratrol protects X-radiation-induced DNA damage in mice bone marrow cells.
Hedayati et al. [23]	Human lymphocytes	Lymphocytes	Y-ray, from 1311 (radiopharmaceuticals)	100 µCi/1.5 mL 50 µg/mL	2 hours	Resveratrol protected against genetic damage.

DNA: Deoxyribonucleic acid, NF-κB: Nuclear factor kappa B, Sirt1: Sirtuin 1, 1311: Iodine, G2: Gap 2 (third subphase of interphase in cell cycle), PTV: Planning target volume, TyrRS: tyrosyl-tRNA synthetase

Results

Literature Search

The PRISMA flow diagram of our search results is shown in figure 2. The initial search gave a total of 231 articles with the breakdown as follows; 227 articles were from the three electronic databases (PubMed, Scopus and Embase) and 4 articles obtained through a manual search. Our search of the online database of www.ClinicalTrials.gov showed that there were no ongoing clinical trials assessing the radioprotective effect of resveratrol against IR. From these figures, 198 articles were retained after the removal of duplicates. Thereafter, following careful examination and screening of their titles and abstracts as well as the application of the inclusion and exclusion criteria, a further 160 records were excluded. The full texts of the remaining 38 records were assessed. We excluded three articles for non-English language publication, while two more articles were removed for not having full texts. Finally, a total of 33 studies were included in this systematic review. The included studies were published between 2005 and 2020.

Study Characteristics

The summary of data showing the characteristics of included studies is presented in table 1. These articles were published between 2005 and 2020, employed an experimental design. Furthermore, they include 1 clinical, 7 *in vitro*, and 25 *in vivo* studies using rats, mouse, mice, and cultured human and animal cells. Out of the 33 included studies, gamma (γ)-radiation was utilized in 18 studies (with 1 study making use of a γ-ray from Iodine (^{131}I) radiopharmaceuticals), and X-ray radiation was used in 15 studies. The doses of the IR ranged between 0.5 to 18 Gy.

Resveratrol Dosage

Resveratrol dose of 20 mg/kg and 100 mg/kg body weight were mostly used in the included studies to assess its radioprotective effect. In addition, these doses were most effective in increasing the survival time, protected against radiation-induced normal tissue damage injury by 20 days [18] and salivary glands against the negative effects of IR in 30 days [19]. Results from another study by Radwan et al. [20] also showed that these same oral doses of resveratrol were effective in attenuating intestinal inflammation following irradiation via modulating PI3K/Akt/mTOR pathway. Contrary to the promising findings above, it was reported that 100 mg/kg resveratrol had no radioprotective effect on dental tissues [21].

Different effective doses of resveratrol have also been reported in several studies. In a study by Yahyapour et al., [22] a resveratrol dose of 200 mg/kg showed maximum reduction in pneumonitis and protected against radiation-induced fibrosis. In another study by Hedayati et al., [23] they observed that maximum radioprotective effect against genetic damage was obtained 2 hours after administering a dose of 1 µg/mL of resveratrol and 2.19 µM for lymphocytes [24]. This was similar to the studies by Koohian et al. [25] which reported that a dose of 50 mg/kg administered after 24 hours protected against x-ray induced DNA damage in mice bone marrow cells and Carsten et al. [26] who found out that a dose of 100 mg/kg of resveratrol reduced the mean total frequency of chromosomal aberration in bone marrow cells.

Denissova et al. [27] detected an improved viability in embryonic stem cells after DNA damage without compromising genomic integrity for a resveratrol concentration in a cell medium of 10 µM. In another study, resveratrol administered at a low dose (10 mg/kg) and high dose (100 mg/kg) effectively reduced the follicle loss induced by IR [28]. Furthermore, Banegas et al. [29] showed that the best radioprotective effect of resveratrol was obtained when administered at the lowest dose (15 µM).

In a clinical study by Franco et al. [30], 30 patients with breast cancer received 2 tablets of resveratrol per day (10 days before irradiation and 10 days after irradiation). Compared with the control group (without resveratrol treatment), their results showed that this dose was effective in reducing the incidence of radiation-induced skin toxicity, and this effect was more potent in patients whose planning target volume (PTV) was less than 500 ml.

Toxicity of Resveratrol

In most of the included studies, there was no reported case of toxicity or side effects following the administration of resveratrol. However, in some studies, minimal toxicities were reported. Farhood et al. [31] reported mild increase in blood vessel congestion for a resveratrol dose of 100 mg/kg. Moreover, 10 µM resveratrol administered for 7 days showed slight toxicity on 293T cells compared to control [32]. Similar findings were also reported by Sebastia et al. [24]

Chemical agents can induce genotoxicity, leading to a possible incidence of cancer. However, resveratrol has been shown to have no genotoxic effect. This effect has been confirmed for several doses of resveratrol such as 15 µM [29], 50 µg/mL [23], and 50 mg/kg [25, 33].

IR can also reduce the quality of life of exposed patients. In the reviewed studies, resveratrol showed the potential to preserve the quality of life after irradiation. In a study by Radwan et al. [20], a dose of 20 mg/kg resveratrol showed no negative effects on the intestinal structure of rats. Furthermore, a dose of 25 mg/kg resveratrol did not induce loss of body weight following its administration [34]. Zhang et al. [35] also reported no weight loss as well as no negative effects on diet and skin luster. Finally, tissue collagen levels were not affected following resveratrol administration [36].

Discussion

Undoubtedly, IR has been of immense value to human life in several ways including medical, agricultural, and industrial. However, in order to maximize the beneficial effects of IR, it is imperative that the side effects are effectively prevented or reduced to the barest minimum. It has been shown that even sub-lethal doses of IR such as 1–4 Gy can induce short-term as well as long-term effects on healthy tissues [37]. Furthermore, during radiotherapy, the surrounding healthy tissues are at risk of being exposed which could lead to future risk of secondary cancers.

In a bid to prevent or mitigate the deleterious effects arising from IR, resveratrol, a natural flavonoid, has been explored. This study systematically reviewed existing studies on the radioprotective effect of resveratrol, with findings from the included studies showing that resveratrol has ability to protect as well as mitigate radiation-induced side effects. In most of the studies, resveratrol showed no toxicity while minimal toxicities were reported in a few. The studies also highlighted various mechanisms of radioprotection by resveratrol. A study by Zhang et al. [35] demonstrated the anti-apoptotic effect of resveratrol as it ameliorated radiation-induced intestinal injury by elevating superoxide dismutase 2 (SOD2) as well as stimulating p53 expression. It was also reported that resveratrol administration before and after radiation exposure led to protection against hematopoietic injury via down regulating the production of ROS and NOX4. The anti-inflammatory effect of resveratrol has been shown to be associated to inhibition of NF-κB and cyclooxygenase-2 (COX-2) [38].

In addition to normal tissue protection, resveratrol has been reported to induce cell death through apoptosis, senescence, or autophagy in some cancer cells [39]. Resveratrol has also shown the ability to improve the effectiveness of various anti-cancer therapies including chemotherapy, radiotherapy, immunotherapy, and targeted cancer therapy [40]. One of the major mechanisms of cancer cell resistance to radiotherapy is autophagy [41]. Via inhibition of mTOR, resveratrol has been shown to counter autophagy in MCF-7 breast cancer cells [42]. The radiosensitive effect of resveratrol has also been observed for prostate cancer cells [43], with further studies associating this effect to enhancement of p21, p27, and p53 expressions leading to an increase in cell cycle arrest [44].

By protecting normal tissues as well as potentiating the killing of tumor cells, resveratrol could potentially be a double-edged sword in cancer therapy. However, in order to maximize these potentials of resveratrol, some areas would need to be addressed in future studies. In the reviewed studies, several doses of resveratrol were administered with protective effects reported. Nevertheless, it is imperative that further investigations be carried out to examine the optimal dose of resveratrol. Till date, clinical trials on resveratrol are still very limited as our study only reported one clinical study [30]. While resveratrol protected against radiotherapy-induced skin toxicity in patients with breast cancer, very few patients were enrolled in that trial. Thus, it is important that further clinical studies involve a large number of patients as well as study the radioprotective effect of resveratrol on other normal tissues. Although, several barriers to its clinical translation have been reported including low bioavailability (since resveratrol comes in powdered form) as well as weak ability to penetrate cells and cross into blood vessels [45]. However, it has been suggested that the development of nano-carriers, liposomal encapsulation and some other nano-formulations such as nano-lipids and micelles could help resolve these challenges [46].

In conclusion, findings from the reviewed studies showed that resveratrol has the potential to protect as well as ameliorate radiation-induced normal tissue toxicity. Resveratrol also showed potent anti-apoptotic and anti-inflammatory effects. In addition, there was no reported case of major toxicity from resveratrol administration. The optimal radioprotective dose of resveratrol still needs to be elucidated. Further studies on the efficacy of clinical translation of resveratrol would open up more insights. Overall, resveratrol is a potential double-edged sword in cancer therapy while protecting healthy tissues.

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References

1. Shimizu Y, Kodama K, Nishi N, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. BMJ 2010; 340: b5349. [Crossref]
2. Berger EM. The Chernobyl disaster, concern about the environment, and life satisfaction. Kyklos 2010; 63: 1-8. [Crossref]
3. Mozdarani H. Biological complexities in radiation carcinogenesis and cancer radiotherapy: impact of new biological paradigms. Genes 2012; 3: 90-114. [Crossref]
4. Najafi M, Cheki M, Rezapoor S, et al. Metformin: Prevention of genomic instability and cancer: A review. Mutat Res Genet Toxicol Environ Mutagen 2018; 827: 1-8. [Crossref]
5. Manda K, Glasow A, Paape D, Hildebrandt G. Effects of ionizing radiation on the immune system with special emphasis on the interaction of dendritic and T cells. Front Oncol 2012; 2: 102. [Crossref]
6. Hekim N, Cetin Z, Nikitaki Z, Cort A, Saygili EI. Radiation triggering immune response and inflammation. Cancer Lett 2015; 368: 156-63. [Crossref]
7. Rödel F, Frey B, Multhoff G, Gaipl U. Contribution of the immune system to bystander and non-targeted effects of ionizing radiation. Cancer Lett 2015; 356: 105-13. [Crossref]
8. Citrin D, Cotrim AP, Hyodo F, Baum BJ, Krishna MC, Mitchell JB. Radioprotectors and mitigators of radiation-induced normal tissue injury. Oncologist 2010; 15: 360-71. [Crossref]
9. Hosseinimehr SJ. Trends in the development of radioprotective agents. Drug Discov Today 2007; 12: 794-805. [Crossref]
10. Yahyapour R, Shabeeb D, Cheki M, et al. Radiation protection and mitigation by natural antioxidants and flavonoids: implications to radiotherapy and radiation disasters. Curr Mol Pharmacol 2018; 11: 285-304. [Crossref]
11. Ahmadi Z, Mohammadinejad R, Ashrafizadeh M. Drug delivery systems for resveratrol, a non-flavonoid polyphenol: Emerging evidence in last decades. J Drug Deliv Sci Techno 2019; 51: 591-604. [Crossref]
12. Farhood B, Goradel NH, Mortezaee K, et al. Intercellular communications-redox interactions in radiation toxicity; potential targets for radiation mitigation. J Cell Commun Signal 2019; 13: 3-16. [Crossref]
13. Farhood B, Ashrafizadeh M, Khodamoradi E, et al. Targeting of cellular redox metabolism for mitigation of radiation injury. Life Sci 2020; 250: 117570. [Crossref]
14. Mortezaee K, Najafi M, Farhood B, Ahmadi A, Shabeeb D, Musa AE. NF-κB targeting for overcoming tumor resistance and normal tissues toxicity. J Cell Physiol 2019; 234: 17187-204. [Crossref]
15. Khodamoradi E, Hoseini-Ghahfarokhi M, Amini P, et al. Targets for protection and mitigation of radiation injury. Cell Mol Life Sci 2020; 77: 3129-59. [Crossref]

16. Amini P, Nodooshan SJ, Ashrafizadeh M, et al. Resveratrol induces apoptosis and attenuates proliferation of MCF-7 cells in combination with radiation and hyperthermia. Curr Mol Med 2020. [Crossref]
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151: 264-9. [Crossref]
18. Song XR, Cheng YQ, Su DF, Liu AJ. The Sirt1 activator resveratrol improved hematopoiesis in pancytopenia mice induced by irradiation. J. Pharmacol Sci 2019; 140: 79-85. [Crossref]
19. Xu L, Yang X, Cai J, et al. Resveratrol attenuates radiation-induced salivary gland dysfunction in mice. Laryngoscope 2013; 123: E23-9. [Crossref]
20. Radwan RR, Karam HM. Resveratrol attenuates intestinal injury in irradiated rats via PI3K/Akt/mTOR signaling pathway. Environ Toxicol 2020; 35: 223-30. [Crossref]
21. Barbosa GL, Pimenta LA, Almeida SM. Micro-CT evaluation of the radioprotective effect of resveratrol on the mandibular incisors of irradiated rats. Braz Oral Res 2016; 30: S1806-83242016000100229. [Crossref]
22. Yahyapour R, Amini P, Saffar H, et al. Protective Effect of Metformin, Resveratrol and Alpha-lipoic Acid on Radiation- Induced Pneumonitis and Fibrosis: A Histopathological Study. Curr Drug Res Rev 2019; 11: 111-7. [Crossref]
23. Hedayati M, Shafaghati N, Hosseinimehr SJ. Resveratrol mitigates genotoxicity induced by iodine-131 in primary human lymphocytes. Radiat Environ Biophys 2013; 52: 287-91. [Crossref]
24. Sebastia N, Almonacid M, Villaescusa JI, et al. Radioprotective activity and cytogenetic effect of resveratrol in human lymphocytes: an in vitro evaluation. Food Chem Toxicol 2013; 51: 391-5. [Crossref]
25. Koohian F, Shanei A, Shahbazi-Gahrouei D, Hejazi SH, Ahmadi A, Sharifi M. The effect of resveratrol administration in irradiated mice on the induction of micronuclei in bone marrow. J Radiat Oncol 2017; 6: 423-7. [Crossref]
26. Carsten RE, Bachand AM, Bailey SM, Ullrich RL. Resveratrol reduces radiation-induced chromosome aberration frequencies in mouse bone marrow cells. Rad Res 2008; 169: 633-8. [Crossref]
27. Denissova NG, Nasello CM, Yeung PL, Tischfield JA, Brenneman MA. Resveratrol protects mouse embryonic stem cells from ionizing radiation by accelerating recovery from DNA strand breakage. Carcinogenesis 2012; 33: 149-55. [Crossref]
28. Simsek Y, Gurocak S, Turkoz Y, et al. Ameliorative effects of resveratrol on acute ovarian toxicity induced by total body irradiation in young adult rats. J Pediatr Adolesc Gynecol 2012; 25: 262-6. [Crossref]
29. Banegas YC, Ocolotobiche EE, Padula G, Cordoba EE, Fernandez E, Guerci AM. Evaluation of resveratrol radiomodifying potential for radiotherapy treatment. Mutat Res Genet Toxicol Environ Mutagen 2018; 836: 79-83. [Crossref]
30. Di Franco R, Calvanese M, Murino P, et al. Skin toxicity from external beam radiation therapy in breast cancer patients: protective effects of Resveratrol, Lycopene, Vitamin C and anthocianin (IxorR). Radiat Oncol 2012; 7: 12. [Crossref]
31. Farhood B, Hassanzadeh G, Amini P, et al. Mitigation of radiation induced gastrointestinal system injury using resveratrol or alpha-lipoic acid: A pilot histopathological study. Antiinflamm Antiallergy Agents Med Chem 2020; 19: 413-24. [Crossref]
32. Gao P, Li N, Ji K, et al. Resveratrol targets TyrRS acetylation to protect against radiation-induced damage. FASEB J 2019; 33: 8083-93. [Crossref]
33. Ocolotobiche EE, Banegas YC, Guerci AM. Modulation of ionizing radiation-induced damage in human blood lymphocytes by in vivo treatment with resveratrol. Int J Radiat Biol 2019; 95: 1220-5. [Crossref]
34. Said RS, El-Demerdash E, Nada AS, Kamal MM. Resveratrol inhibits inflammatory signaling implicated in ionizing radiation-induced premature ovarian failure through antagonistic crosstalk between silencing information regulator 1 (SIRT1) and poly(ADP-ribose) polymerase 1 (PARP-1). Biochem Pharmacol 2016; 103: 140-50. [Crossref]
35. Zhang H, Yan H, Zhou X, et al. The protective effects of Resveratrol against radiation-induced intestinal injury. BMC Complement Altern Med 2017; 17: 410. [Crossref]
36. Velioglu-Ogunc A, Sehirli O, Toklu HZ, et al. Resveratrol protects against irradiation-induced hepatic and ileal damage via its anti-oxidative activity. Free Radic Res 2009; 43: 1060-71. [Crossref]
37. De Felice F, Marchetti C, Marampon F, Cascialli G, Muzii L, Tombolini V. Radiation effects on male fertility. Andrology 2019; 7: 2-7. [Crossref]
38. Zhang H, Zhai Z, Wang Y, et al. Resveratrol ameliorates ionizing irradiation-induced long-term hematopoietic stem cell injury in mice. Free Radic Biol Med 2013; 54: 40-50. [Crossref]
39. Chang C-H, Lee C-Y, Lu C-C, et al. Resveratrol-induced autophagy and apoptosis in cisplatin-resistant human oral cancer CAR cells: A key role of AMPK and Akt/mTOR signaling. Int J Oncol 2017 Mar; 50: 873-82. [Crossref]
40. Mortezaee K, Najafi M, Farhood B, Ahmadi A, Shabeeb D, Musa AE. Resveratrol as an Adjuvant for Normal Tissues Protection and Tumor Sensitization. Curr. Cancer Drug Targets 2020; 20: 130-45. [Crossref]
41. Hu L, Wang H, Huang L, Zhao Y, Wang J. Crosstalk between autophagy and intracellular radiation response. Int J Oncol 2016; 49: 2217-26. [Crossref]
42. Park D, Jeong H, Lee MN, et al. Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition. Sci Rep 2016; 6: 1-11. [Crossref]
43. Benitez DA, Pozo-Guisado E, Alvarez-Barrientos A, Fernandez-Salguero PM, Castellón EA. Mechanisms Involved in Resveratrol-Induced Apoptosis and Cell Cycle Arrest in Prostate Cancer-Derived Cell Lines. J Androl 2007; 28: 282-93. [Crossref]
44. Fang Y, DeMarco VG, Nicholl MB. Resveratrol enhances radiation sensitivity in prostate cancer by inhibiting cell proliferation and promoting cell senescence and apoptosis. Cancer Sci 2012; 103: 1090-8. [Crossref]
45. Kamran MZ, Ranjan A, Kaur N, Sur S, Tandon V. Radioprotective agents: strategies and translational advances. Med Res Rev 2016; 36: 461-93. [Crossref]
46. Singh VK, Wise SY, Scott JR, Romaine PL, Newman VL, Fatanmi OO. Radioprotective efficacy of delta-tocotrienol, a vitamin E isoform, is mediated through granulocyte colony-stimulating factor. Life Sci 2014; 98: 113-22. [Crossref]
47. Najafi M, Cheki M, Amini P, Javadi A, Shabeeb D, Eleojo Musa A. Evaluating the protective effect of resveratrol, Q10, and alpha-lipoic acid on radiation-induced mice spermatogenesis injury: A histopathological study. Iran J Reprod Med 2019; 17: 907-14. [Crossref]
48. Azmoonfar R, Amini P, Yahyapour R, et al. Mitigation of radiation-induced pneumonitis and lung fibrosis using alpha-lipoic acid and resveratrol. Antiinflamm Antiallergy Agents Med Chem 2019; 18: 1-9. [Crossref]
49. Zhang H, Yan H, Ying J, et al. Resveratrol ameliorates ionizing irradiation-induced long-term immunosuppression in mice. Int J Rad Bio 2018; 94: 28-36. [Crossref]
50. Zhang J, Han X, Huang S, Lu L, Li D, Meng A. The combined effect of resveratrol and diphenyleneiodonium on irradiation-induced injury to the hematopoietic system. Int Immunopharmacol 2017; 43: 33-9. [Crossref]
51. Koohian F, Shanei A, Shahbazi-Gahrouei D, Hejazi SH, Moradi MT. The Radioprotective Effect of Resveratrol Against Genotoxicity Induced by gamma-Irradiation in Mice Blood Lymphocytes. Dose Response 2017; 15: 1559325817705699. [Crossref]
52. Prager I, Patties I, Himmelbach K, et al. Dose-dependent short- and long-term effects of ionizing irradiation on neural stem cells in murine hippocampal tissue cultures: neuroprotective potential of resveratrol. Brain Behav 2016; 6: e00548. [Crossref]
53. Basso E, Regazzo G, Fiore M, et al. Resveratrol affects DNA damage induced by ionizing radiation in human lymphocytes in vitro. Mutat Res Genet Toxicol Environ Mutagen 2016; 806: 40-6. [Crossref]
54. Wang H, Yang YL, Zhang H, Yan H, Wu XJ, Zhang CZ. Administration of the resveratrol analogues isorhapontigenin and heyneanol-A protects mice hematopoietic cells against irradiation injuries. Biomed Res Int 2014; 2014: 282657. [Crossref]
55. Li J, Feng L, Xing Y, Wang Y, Du L, Xu C, et al. Radioprotective and antioxidant effect of resveratrol in hippocampus by activating Sirt1. Int J Mol Sci 2014; 15: 5928-39. [Crossref]
56. Kim KO, Park H, Kim HS. Effects of High-Protein Diet and/or Resveratrol Supplementation on the Immune Response of Irradiated Rats. Prev Nutr Food Sci 2014; 19: 156-63. [Crossref]
57. Kim KO, Park H, Chun M, Kim HS. Immunomodulatory effects of high-protein diet with resveratrol supplementation on radiation-induced acute-phase inflammation in rats. J Med Food 2014; 17: 963-71. [Crossref]
58. Fiore M, Festa F, Cornetta T, Ricordy R, Cozzi R. Resveratrol affects X-ray induced apoptosis and cell cycle delay in human cells in vitro. Int J Mol Med 2005; 15: 1005-12. [Crossref]
59. Salehi S, Bayatiani M, Yaghmaei P, Rajabi S, Goodarzi M, Jalali Mashayekhi F. Protective effects of resveratrol against X-ray irradiation by regulating antioxidant defense system. Radioprotection 2018; 53: 293-8. [Crossref]