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

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 C14H12O3) (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.

**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.

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[Figure 1. Chemical structure of resveratrol](image)

[Figure 2. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram for the selection of included articles](image)
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 | | X-ray, 4 | 50 mg/day | 15 days | Ameliorated radiation-induced damage index. |
| Najafi 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 | 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 diphenylenedione 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-kB 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 (whole breast) (tumour) | X-ray, 50 | 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. |
| Veloğlu-Oğnç 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. |
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.Clinical-Trials.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 [27], 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].

Table 1. Summary of articles included in the systematic review

| Study Characteristics | 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. |
|-----------------------|---------------------------|---------------------|---------|----------------|---------|-----------------------------------------------------------------------------------------------------------------------------------|
| 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-ray-induced DNA damage in mice bone marrow cells. |
| Hedayati et al. [23]  | Human lymphocytes         | Lymphocytes         | Y-ray, from 131I | 100 µCi/1.5 mL | 2 hours | Resveratrol protected against genetic damage. |

DNA: Deoxyribonucleic acid, NF-κB: Nuclear factor kappa B, Sirt1: Sirtuin 1, 131I: Iodine, G2: Gap 2 (third subphase of interphase in cell cycle), PTV: Planning target volume, TyrR5: tyrosyl-tRNA synthetase
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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