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RESVERATROL, A POTENTIAL RADIOPROTECTIVE AGENT: A MINI REVIEW

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ABSTRACT: It is well known ionizing radiations produce deleterious effects on humans. In spite of research efforts for the past several years, today we do not have a radio protective agent that meets all the prerequisites like produces no cumulative and irreversible toxicity, offers effective long term protection, possess a shelf life of 2-5 years and can be easily administered. In recent years, attention has been turned to phytochemicals due to their antioxidant properties. This review focuses on the radio protective potential of resveratrol [trans-3, 5, 4'- trihydroxystilbene], a phytoconstituent, mainly found in *Vitis vinifera*. In particular, it aims to highlight the detailed studies, both *in vitro* and *in vivo*, that have been carried out on the radio protective capability of resveratrol. It also focuses on the different possible mechanisms through which resveratrol acts in response to ionizing radiations. Previous studies show both positive and negative aspects of resveratrol on radioprotection. But a thorough analysis including earlier studies and our own preliminary studies clearly support that resveratrol is an attractive and potential candidate and can be developed into radio protective agent.

INTRODUCTION: After a cell is exposed to ionizing radiations, the exact molecular events happening in the cell and the consequential changes are still not clearly understood. However, receptor tyrosine kinase signalling [1], NF-kappa B pathway [2, 3], sphingomyelinase pathway [4], DNA damage signalling [5], redox signalling and apoptosis signalling [6] are some of the major signalling cascades which are known to be activated in response to cellular stress including ionizing radiations. These signalling cascades are involved in major cellular events governing cell growth, proliferation and apoptosis. The activation or inhibition of these cascades in response to radiation governs its ultimate effect on the cell.

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It is well known that free radicals like superoxide ($O.^{2-}$), hydrogen peroxide (H_2O_2), hydroxyl radical (HO.) peroxyl (ROO.) and alkoxyl (RO.), reactive nitrogen species (RNS) and toxic substances generated during radiation, act as secondary messengers and cause damage to genomic integrity of the cell [7 - 9]. Several agents have been investigated in the past for their capability to protect against ionizing radiations. Sulfhydryl compounds and antioxidants were the first to be studied with the goal of obtaining the highest dose reduction factor (DRF) achievable for protection against radiation exposure [10]. During 1949, cysteine, a sulphur containing amino acid was reported for its radio protective activity [11]. Followed by this, N-acetyl cysteine and cysteamine, thiol protectors, were studied in detail for their radioprotection [12]. Detailed studies of radioprotection have also been carried out on antioxidant nutrients like Vitamin E, selenium, selenium and Vitamin E combinations, Vitamin A, beta carotenoids and Vitamin C [13].

In 1995 FDA approved Amifostine, a phosphorylated aminothiol prodrug, as a potent radioprotective agent [14]. When repeatedly administrated in patients undergoing postoperative radiation treatment for head and neck cancer it reduces the incidence of moderate to severe xerostomia [15]. This agent, however, has several side effects and hence is not suitable for prophylactic use during radiation emergencies [16].

In recent years, several naturally occurring and low toxicity phytochemicals have been investigated for radioprotection. These phytochemicals include flavonoids, methylxanthines and melatonin and plant phenols. They generally show a larger window of protection (**Table 1**). The flavonoids, orientin and vicenin, obtained from *Ocimum sanctum*, possess dose-modifying factor (DMF) of 1.3 and 1.37, respectively in 30 days survival assay [47]. Methyl xanthines such as caffine can protect intestinal cells from radiation injury at 40 mg/kg dose in mice [48]. Melatonin pre-treatment can reduce chromosomal aberrations and micronuclei in human lymphocytes caused by radiations [49].

Plants containing polyphenolic compounds have been shown to exhibit anti-oxidative activities and maintain genomic stability after exposure to ionizing radiations [50, 51]. Public preference for complementary and alternative medicine, especially antioxidant to improve their quality of life after chemotherapy or radiotherapy is well known. Several clinical trials are being conducted today to find out the beneficial effect of combinations of dietary antioxidants after chemotherapy or radiation therapy [52].

TABLE 1: PHYOCONSITUENTS AND RADIO PROTECTION

Phytoconstituent	Effect on radiation hazards
3,3'Diindolylmethane [17, 18]	Protection up to 13Gy TBI, rapid activation of ataxia telangiectasia (ATM) and NF-kB
Chlorogenic and quinic acid [19]	Chlorogenicacid ↓irradiation induced DNA damage by 4.49-48.15% and quinic acid by 5.99-53.57%
Geraniin [20, 21]	Splenocytes protects against radiation injury of 2Gy irradiation. ↓Expression level and immune-reactivity of pro-apoptotic p53, Bax and ↑ anti-apoptotic Bcl-2.↓ Single strand breaks
Beta glucan [22, 23]	80% survival rate at 30 days mortality assay
Curcumin [24, 25]	Cataractogenesis in rats fall to 40%.↑Antioxidant enzyme levels. ↓MDA levels. Protects intestinal mucosa.
Quercetin-3-o-rutinoside [26]	Protection towards gastrointestinal tract and hematopoietic system. ↑Pro-survival (ERK) and ↓ pro-apoptotic (BAX) gene expressions. Inhibition of radiation induced DNA damage
Apigenin [27]	↓ Radiation induced apoptotic incidence and modulates loss of mitochondrial membrane potential. Maintains cellular antioxidant enzymes.Protects cellular milieu from gamma radiation induced lipid peroxidation and micronuclei formation.↑ Bcl-2 and ↓ in p53, p21, Bax and NF-kB expression
Quercitrin [28]	↓ Radiation induced cell death and apoptosis in HaCaT cells. ↓ Radiation induced cell death and ROS generation in live zebra fish
Ferulic acid [29]	↑ Antioxidant status. ↓ Lipid per oxidation. ↓% tail DNA, tail length, tail movement and olive tail. Protection of gastrointestinal tract
Umbelliferone [30]	↓ Comet attributes and lipid per oxidative markers.↑ Antioxidant enzyme levels.↓ Radiation induced apoptotic incidence and modulates loss of mitochondrial membrane potential
Glyzyrrhizic acid [31]	↓ Micronuclei formation in blood reticulocytes. ↓Chromosomal aberrations in bone marrow
Alpha –asarone [32]	↓ Micronuclei formation, chromosomal aberrations in bone marrow and comet attributes.↑ Antioxidant enzyme levels.
Zingerone [33]	↑ Endogenous spleen colony formation.↓ Radiation induced mortality ↓Percentage of apoptotic cells and ROS amount. ↓DNA damage
Phloroglucinol [34]	↓ Intracellular ROS levels.↓ Apoptosis. Inhibits mitochondria mediated caspases pathway. Mitochondrial membrane potential regained.↓ Active forms of caspase 9 and 3 and Bcl_2.Inhibits mitogen-activates protein kinasekinase-4, c-Jun NH2-terminal kinase and activator protein-1 cascades. Activates glutamate cysteine ligase
Hesperidin [35]	↓ Micronuclei frequencies, dicentric aberrations and comet attributes
Epicatechin [36]	Protect radiation induced DNA strand breaks

Dehydrozingerone [37]	↑ Mean survival time. Stimulates endogenous spleen colony forming units. Protection to gastrointestinal tract.↑ Antioxidant enzyme levels.↓ Micronuclei frequencies
Vanillin[38]	↓ Comet parameters
Paeoniflorin [39]	Attenuates the activation of the mitogen-activated protein kinases. Scavenges ROS.
Naringin [40]	Protects mouse liver and intestine by ↑the antioxidant status and ↓the lipid per oxidation
Sesamol [41]	Stimulates endogenous spleen colony-forming units. Protects gastro intestinal tract.↑ Antioxidant enzyme levels. ↓ Lipid per oxidation
Vinblastine sulfate [42]	↓ Comet parameters
Orientin and Vicenin [43]	↓ Micronuclei frequencies
Geniposidic acid and Geniposide [44]	Protects hematological system
Oleanolic acid and Ursolic acid [45]	Protects hemopoietic tissue
Caffeine [46]	↓ Chromosomal aberrations

In this context, resveratrol (RSV), a polyphenolic phytoalexin found in several plant species, including grape fruits has been studied in detail [53]. The present paper reviews the available data and concludes that RSV has a very good potential to act as a radio-protector.

Resveratrol: RSV is mainly present in the skin of grape berries and produced in response to injury as a defense mechanism such as fungal infection, UV exposure or chemical exposure. It is also present in the roots of *Veratrum grandiflorum* O. Loes and *Polygonum cuspidatum* [54]. The percentage of RSV is high in red wine as a result of the fermentation process of the skin of the red grape [55]. Chemically, RSV is 5-[(E)-2-(4-hydroxyphenyl)ethenyl] benzene-1,3-diol with the molecular formula $C_{14}H_{12}O_3$ and a molecular weight of 228.247 g/mol [56]. It exists both as Cis and Trans geometric isomeric forms. The Trans form is biologically more active than Cis form. It is reported to confer protection against cardiovascular dysfunction [57], inflammatory process [58], Alzheimer's disease [59], diabetics [60] and prevents cancer development [61, 62].

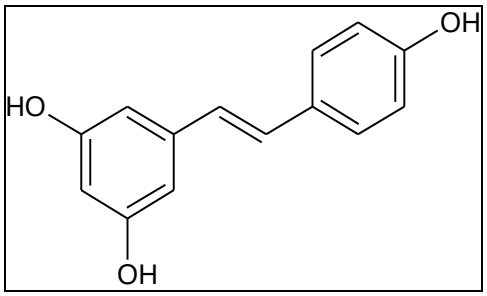

FIG. 1: RESVERATROL

RSV is both a free radical scavenger and a potent antioxidant. It also can improve the activity of endogenous antioxidant enzymes. Mitochondrial complex III is the site from where reactive oxygen species (ROS) are generated. RSV can decrease mitochondrial complex III activity by competition with coenzyme Q. It can thus oppose the production of ROS as well as scavenge those [63]. The fee radical scavenging activity of RSV has been well studied and it is an effective scavenger of hydroxyl, superoxide, and metal-induced radicals [64, 65]. RSV can restore the levels of some of the intracellular antioxidants such as glutathione reductase, glutathione peroxidase, glutathione S-transferase, dismutase and catalase, which are reduced under oxidative stress [66-68].

Several studies have shown that RSV has a key role in regulating certain signalling pathways, such as inhibit NFkB signalling through suppression of p65 and IkappaB kinase [69,70], down regulate Akt/GSK and ERK signalling [71], modulate DNA double strand break repair pathways in an ATM/ATR p53 and Nbs1 dependent manner [72] and antiapoptotic activity [73]. When damage to DNA occurs, RSV protects the genome through antioxidant activity by inhibition of inflammation, suppression of metabolic carcinogen activation, de novo expression of genes that encode detoxifying proteins. The free radical scavenging capacity of RSV also contributes to the manintance of genomic stability [74].

Being a lipophilic, phenolic compound, RSV crosses the plasma membrane and is well absorbed when given orally. But it is rapidly metabolized, *via* phase II glucocuronide or sulfate conjugations, which gives it a short half-life of ~8–14 min leading to low bioavailability [75-77]. Administrating RSV with piperine can increase the bioavailability [78]. Larger doses of RSV (2000 and 4000/3000 mg/kg in mice and 3000 mg/kg in rats) have shown

renal toxicity, while a daily dose of 20 mg/kg, 100 mg/kg in rats did not [79]. Almeida *et al.,* have clearly demonstrated the safety profile of RSV in a multiple dose study in healthy volunteers and shown that RSV is well tolerated in humans on doses up to 5g per day without toxic effects [80].

Resveratrol and Radioprotection: A relatively nontoxic compound with the above-mentioned properties, RSV is expected, therefore, to have the potential to act as a radio-protector in normal cells exposed to the damaging effects of ionizing radiation. In this context, several studies have been carried out in the past on the radio-protective capability of RSV.

Carsten *et al.,* have evaluated the radio protective effect of orally administered RSV (100 mg/kg per day), initiated 2 days prior to 3Gy whole body gamma irradiation continued up to 30 days [81]. The study revealed that the frequencies of chromosome aberrations in irradiated mouse (CBS/CaJ) bone marrow cells reduce significantly. It also showed that a daily dose of 100 mg/kg of RSV for 30 days does not produce any chromosomal aberrations in mice. The authors have thus demonstrated for the first time that RSV has radio protective effects, *in vivo*. In this study the dose of RSV was fixed as 100 mg/kg because it can produce a tissue concentrations between 10-50µm. Dumazet *et al.,* have demonstrated RSV induces of cell cycle arrest at 15-20, 30 and 100µm concentrations in normal leukemic hematopoietic cells [82, 83]. The possible mechanism for the radio protective activity of RSV can be explained by its potential to induce cell cycle arrest in s phase and/or at G2/M transition [84]. It can also provide a longer period for chromosomal repair after irradiation. The direct free radical scavenging activity of RSV or the indirect induction of antioxidants like glutathione and increase in enzymes like superoxide dismutase and catalase are also possible reasons [85, 86].

Denissova *et al.,* have shown that RSV protects mouse embryonic stem cells (mECS) from ionizing radiations by accelerating the recovery from DNA strand breakage and resuming the cell division faster [87]. They exposed mESC, 48 h pre-treated with RSV (10µM), to 5Gy. RSV treated survival of the stem cells after exposure to ionizing radiations was found to be >2. The influence of RSV on genomic stability was estimated by comparing the frequencies of ionizing radiations induced mutation at a chromosomal reporter locus with RSV treated group with control group. Here the frequencies were not increased, showing that RSV can improve viability in mESC after DNA damage induced by ionizing radiations without compromising the genomic integrity. The radio protective activity of RSV may be due to the more rapid DNA repair, rather than reduced DNA damage or delayed cell cycle progression [88, 89]. In other words, RSV can speed up DNA repair by facilitating a critical step in DNA damage sensing pathway by modulating the expression or activity of specific target enzymes like Sirt1. Sirt1 is known to modify DNA and chromatin, alter the conformation of DNA by direct physical interaction and contact by stricture responsive proteins of the DNA damaging signalling pathway. Pre-treatment with RSV 10µm for 48 hr may possibly result in pre-activation of DNA damage response at a low level, which can act positively to up-regulate DNA damage response without inducing cell cycle arrest or apoptosis.

Moreno *et al.,* have studied the radio-protective effect of RSV on mouse connective tissue (NCTC clone 929) and observed protection at 12.5µM, 25µM for 500 and 800Gy, respectively [90]. The IC_{50}, LD_{50} values were found to be 50µm and 354Gy, respectively. Their hypothesis is that RSV can be given as an adjuvant to cancer patients during radiotherapy to reduce the radiation hazards. The antioxidant property of RSV was given as the reason for its radio-protective activity. The contradiction that RSV acts as a radio senstitizer for tumour cells but as a radio-protector action for normal cells, however, was not explained.

Simsek *et al.,* have shown that RSV, at a relatively high dose (100 mg/kg), can protect sub-mandibular and parotid glands from the deleterious effects of irradiation [91]. Their studies on histopathological investigations of sub-mandibular gland showed a decrease in the scales of acinar loss, less ductal damage, vacuolization and cellular necrosis in RSV treated group compared to the unirradiated group. When human subjects were exposed to radiotherapy at 2, 5 to 10Gy to the head and neck region, a 50% reduction parotid gland was observed within a few days [91, 92].

Supplementation of RSV was thus shown as an adjuvant therapy for protecting salivary glands. But the major problem, however, is that the efficacy of radiotherapy reduces because RSV also provides antioxidant benefits to the cancer cells along with normal cells [93]. RSV thus increases the antioxidant (GSH) levels and reduces lipid per oxidation of the glands exposed to total body irradiation.

Sebastia *et al.,* have evaluated *in vitro* the radio-protective efficiency, genotoxicity and cytotoxicity of RSV [94]. Cells were pre-treated with RSV 1h before irradiation (2Gy) to human lymphocytes at concentrations from 0 to 219µm. After 1 h incubation, the chromosomal damage was analyzed. It was found that RSV reduces the radiation induced chromosomal damage. Results showed that RSV has 52% radio-protective effect corresponding to a concentration of 2.19Mµ with minor toxicity. High concentrations of RSV showed negative toxic effects whereas low concentrations show positive toxic effects. RSV can thus induce cytogenetic effect in human peripheral blood cells as acentric chromosomes and gaps. According to the authors the protective activity of RSV against ionizing radiation induced oxidative DNA damage is mainly due to its free radical scavenging activity and its property to maintain intracellular antioxidants. The opposite effects of cytotoxicity that occur at low and high doses can be explained by its hormetic response. The deleterious effect of RSV on the genomic stability may be due to its topo-isomerase poison action.

Zhang Heng *et al.,* have demonstrated that RSV has the potential to protect hematopoietic stem cells from radiation in part via activation of Sirt1 [95]. In addition, RSV can be used to reduce total body irradiation induced long-term bone marrow injury. This study revealed that RSV can increase the survival of mice exposed to 7.5Gy lethal dose compared to control. Radiation induces the chronic oxidative stress through NADPH oxidase 4(NOX4) derived oxygen species leading to senescence in hemopoietic stem cells. RSV pre treatment helps in the down regulation of NOX 4 expression and up regulation of siritin 1/ Sirt 1 deacetylase activity and Ex 527, superoxide dismutase 2, and glutathione peroxide 1 expression resulting in bone marrow protection.

Yue fu *et al.,* have demonstrated that RSV inhibits ionizing radiation induced inflammation in mesenchymal stem cells (MSC), by activating Sirt1 and limiting NLRP-3 inflamamsome activation [96]. Pre-treating MSC with RSV 1h before irradiation inhibits the secretion of ILI beta (procytokine) by down regulating the protein and mRNA levels of ILI beta. The authors' thus demonstrated radiation induced increase in ILI beta through NLRP3 pathway. RSV was shown to inhibit the radiation induced IL-1beta expression in a concentration dependent manner, partially by inhibition of the trans-activation potential of NF-kappa B. The proposed pathway is by suppression of NFkb activity by the functional interaction between Sirt1 and p65 that involve the deacetylation of Lys310 in p65. They have thus provided a theoretical basis for radio protective effect of RSV.

Li jinanguo *et al.,* have demonstrated that RSV inhibits apoptosis induced by radiation in neuronal tissue *via* the activation of Sirt 1 [97]. RSV treatment for 21 days following irradiation thus results in an increase in Sirt 1 mRNA. As a result of this the protein activity of Sirt 1also increases resulting in radioprotection.

Though several authors have reported on the radio-protective potential of RSV, Fabre *et al.,* have, however, reported that RSV does not show any radio-protective effect [98]. We, therefore, carried some studies to check the radio-protective effect of RSV from ionizing radiations. Studies using AA8 (Chinese hamster ovary cell lines) and NIH 3T3 (Standard mouse embryo fibroblast cell line) cell lines using clonogenic survival assay were carried out by us. Initially we checked the toxicity of RSV on these cell lines to fix the nontoxic doses. The nontoxic doses were found to be 2 µM and 5 µM. Cells (300) were seeded in DMEM medium, pre-incubated for 24h with the nontoxic dose (2µM and 5 µM) of RSV and exposed to sub lethal dose of 2Gy using cobalt 60 gamma source and incubated to 1-2 weeks. Colonies obtained were fixed with glutaraldehyde (6.0%v/v), stained with crystal violet (0.5%w/v) and counted using a stereo-microscope [99]. The results obtained are shown in (**Table 2**). The data reveal significant radio protection obtained for RSV treated cell lines at 2µM and 5 µM for 2Gy. The survival fraction for treated cell lines is near to 1.

TABLE 2: CLONOGENIC SURVIVAL ASSAY

	AA8 cell line Survival fraction	NIH 3T3 cell line Survival fraction
Control	1	1
Radiation 2Gy	0.7233±0.0305	0.740 ± 0.0163
RSV 2μ+2Gy	0.9022±0.0234**	0.9226± 0.0169**
RSV 5μ+2Gy	0.8955±0.0411**	0.9066± 0.0124**

Notes: Values are mean ± SD. The difference in survival fraction is statistically significant ($p<0.01$).

CONCLUSION: Humans get exposed to ionizing radiations from several sources. To protect them from the deleterious effects of these ionizing radiations, we need radio-protective agents for prophylactic, therapeutic and mitigator purposes. The antioxidant property of phytochemicals can scavenge free radicals generated in the body and thus involve in radio-protection. RSV is a potent antioxidant and possesses a variety of biological activities that have been studied in detail. It has been shown that RSV can act as a potent radio-protector, both as a prophylactic and therapeutic agent, in radiation exposure situations. In our laboratory, we examined in two cell lines, namely AA8 and NIH_3T_3, for studying the radio-protective activity of RSV at 2Gy. We found that in both the cell lines, pre-treatment with RSV before exposure to 2Gy gamma irradiation, gives significant radio-protection. Various studies have revealed that only RSV metabolites are present in serum upto 9 h and not RSV. Further studies are, therefore, required to ascertain the protective action of RSV. The problem of its short half-life can be improved by preparing targeted mitochondrial delivery. RSVs bioavailability can be enhanced by combination with piperine. Presently studies in these directions are in progress in our laboratory.

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