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REVIEW PAPER

Contemporary Radiation Countermeasures

Vivek N. Patel, Seema Gupta, Mohammed M. Shareef, and Mansoor M. Ahmed

Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL 33136
E-mail: amansoor@med.miami.edu

ABSTRACT

Radiation countermeasures have been investigated for decades, but the search for ideal protective agents for use prior to or after irradiation still continues. This review focuses on agents that have demonstrated as potential as *in vivo* countermeasure agents and may subsequently be effectively used in human beings. Such agents are categorised as radioprotectors, radiation mitigators, or therapeutic agents dependening upon their time of administration. These protective or mitigating agents are designed to reduce inadvertent damage to normal tissue caused by radiation. These interventions function via various mechanisms of action ranging from modulating signalling pathways to inhibiting cell death, cytokines, and growth factor. Many agents demonstrated promising results in murine models and are being tested in human beings. Amifostine, and curcumin have shown radioprotection, while genistein, palifermin, and halofuginone have been shown to alleviate the side effects in patients undergoing radiotherapy. Though these compounds show some promise as radiation countermeasure agents, there are several associated limitations and the search for perfect agents still continues.

Keywords: Radioprotectors, radiation counter measures, therapeutic agents, radiation mitigators, radiotherapy

1. INTRODUCTION

In contemporary times, the possibility of a terrorist threat, nuclear industry disaster, or medical accident directs for an urgent need to develop appropriate and functional radiation countermeasure agents. Globally, there have been initiatives to find such efficient instruments to combat the deleterious effects of ionising radiation (IR). This entity is defined as subatomic particles or electromagnetic waves that have enough energy to detach electrons from atoms or molecules and hence ionise them. Thus, ionising radiation may interact directly with cells or with water molecules and oxygen to produce free radicals, and in turn, damage bio-macromolecules like DNA, protein, etc. Ionising radiation can be used to critically damage and kill rapidly proliferating cells. This principle is utilised during targeted radiotherapy of the diseased site. Unfortunately, during radiotherapy, normal cells may inadvertently be exposed to radiation, leading to severe side effects[1,2]. Normal cells may also be exposed to ionising radiation by other means such as occupational, environmental, or even nuclear accident or terrorist attack so the identification of agents to combat irradiation effects are imperative[3,4]. This article reviews various countermeasures that have shown efficacy in pre-clinical models and that can be used efficiently in human beings.

2. EFFECTS OF RADIATION

Ionising radiation-induced DNA damage is associated with increased frequency of chromosomal aberrations and induction of cell death[5,6]. Overt doses of radiation can cause both immediate and delayed effects. The effect of ionising radiation on the whole-body system may result in acute radiation syndrome (ARS)[7,8]. This syndrome encompasses dose-dependent damages that affect the hematopoietic, gastrointestinal, cerebrovascular, pulmonary, and cutaneous systems in the body[9]. The onset of symptoms may begin anywhere from a few hours to days, dependent upon the severity of the dose[10].

The hematopoetic syndrome is observed with doses as low as 1 Gy in which inhibition of mitotically active hematopoetic progenitors prevents the regeneration of blood and the lymphoid system[11]. This directly leads to immunosuppression and anemia. These symptoms invariably lead to sepsis, shock, and multiple organ failure.

At levels above 10 Gy, destructive changes occur in the gastrointestinal tract, leading to cell death in the intestinal epithelium, intestinal crypts, and endothelial cells[12]. Symptomatically, this may lead to pain, nausea, vomiting, diarrhea, infection, and to eventual dehydration and electrolyte imbalance.

Doses above 20 Gy lead to cerebrovascular injury, pulmonary, as well as cutaneous damage. Cerebrovascular injury is described as collapse of the circulatory system *via* cardiovascular damage along with increased fluid pressure in the brain[13,14]. There may be signs of brain swelling such as nausea, vomiting, headache, hypotension, and impaired cognitive function that may lead to death as no known medical interventions are known to combat this state of damage.

Pulmonary injury involves reactive oxygen species (ROS) toxicity to parenchymal cells which leads to a cycle

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of chronic oxidative stress and inflammation[15]. The initial insult builds up until lung tissue becomes fibrotic, leading to pulmonary fibrosis and pneumonitis. High doses have the capacity to cause cutaneous injury by damaging basal cells of the epidermis and dermis, leading to ulceration and necrosis[16,17].

3. RADIATION COUNTERMEASURES

3.1 Classification of Radiation Countermeasures

To protect, counteract and compensate the damage caused by ionising radiation, various types of countermeasure agents have been developed in the past. These agents can be divided into radioprotectants, radiation mitigators, and therapeutic agents[9,18]. The nomenclature is based on the timing of administration.

- Radioprotectants are given prior to irradiation and their properties prevent injury from ionising radiation-induced free radicals. Such interventions may also increase radiation tolerance of critical tissues and production of protective mediators.
- Radiation mitigators are given after irradiation, though before the onset of tissue damage. Their properties allow them to reduce the severity of ionising radiation injury and aid in expediting the recovery and repair process of injured tissue.
- Therapeutic agents are given after irradiation and the appearance of overt symptoms of IR injury. These agents are characterised more as supportive and palliative in nature as they aid in decreasing ionising radiation-induced injury by reducing inflammation and oxidative stress.

3.1.1 Types of Radiation Countermeasures

All three of the above-mentioned classifications can be further differentiated into various types based upon an agent's modulating molecular function. The agents described here are characterised as agents that alter the: (i) oxidative process, (ii) cell-death signalling, (iii) cell-cycle phases, (iv) activators of NF-κB, (v) cytokines and (vi) growth factors (Fig. 1).

3.1.2 Agents Modulate the Oxidative Process

Ionising radiation has the ability to initiate the formation of reactive oxygen species *via* the radiolysis of water[6]. These deleterious products are superoxide, hydrogen peroxide, and hydroxyl radicals[5] which have the ability to cause direct oxidative injury as well as activate cytoplasmic signalling pathways *via* the mitochondria. The mitochondria, when triggered, release cytochrome c which leads to apoptosis[19]. Apoptosis is defined as programmed cell death in which biochemical events lead to characteristic changes in morphology, resulting in controlled cellular death[20]. The human body naturally has many antioxidants such as superoxide dismutase, catalase, peroxiredoxins, thioredoxin, and glutathione to combat the effects of reactive oxygen species [21]. Other antioxidant metabolites such as ascorbic acid, glutathione, lipoic acid, uric acid, carotenes, and ubiquinol are found in foods and can be found throughout the body for example in human serum and as detoxification agents in the liver[22] (Figs 2 and 3).

Thiol groups are reducing agents and are defined by their ability to donate reducing equivalents (hydrogen or e-) to unstable molecules such as reactive oxygen species (Fig. 2). A thiol is an organosulphur group that contains a sulphur-hydrogen bond, and hence is important biologically for the formation of sulphur-based bonds. Agents exploiting the beneficial properties of thiol groups have been used in the past with a fair degree of value[23-25]. An effective thiol radioprotector is a phosphorothioate known as WR-2721 that is known to protect against radiation-induced malignancies in mice if administered prior to radiation. This agent was injected in mice at a dose of 300 mg/kg and found to have a dose-reduction factor of 2.7 with protection offered when the agent was given 2 h prior to irradiation[26]. Amifostine is a cytoprotective adjuvant used in patients undergoing chemotherapy and radiotherapy for certain types of cancers[18]. It is marketed by MedImmune under the trade name Ethyol and is commonly known as WR-1065 in its active form. WR-1065 protects cells from cytotoxic damage by scavenging oxygen-free radicals generated by radiation by binding to highly reactive nucleophiles and subsequently preventing these nucleophiles from reacting with DNA[27]. Further, since amifostine is an organic thiophosphate that is hydrolysed *in vivo* by alkaline phosphatase to an active cytoprotective thiol metabolite, it is selective for non-malignant tissues that have higher levels of this enzyme. However, intervention is not perfectly discerning and causes serious side effects such as

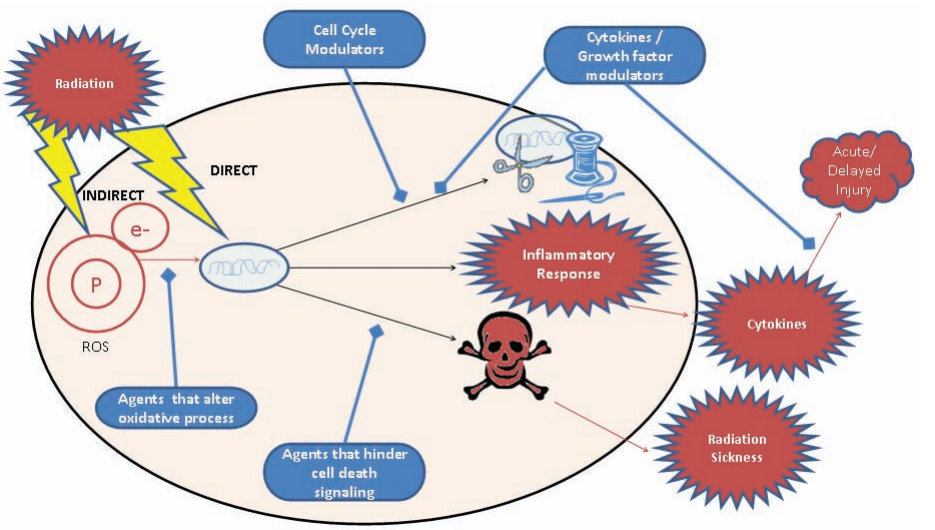

Figure 1. Ionising radiation results in both direct damage of DNA as well as indirect damage *via* reactive oxygen species.

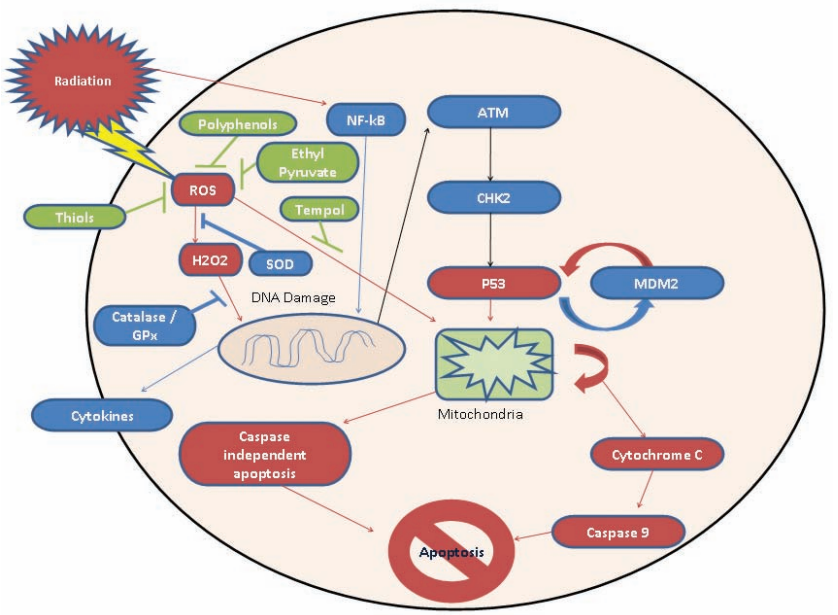

Figure 2. Radiation induces the formation of reactive oxygen species that result in products that can damage DNA as well as affect the mitochondrial permeability that can subsequently result in cell death.

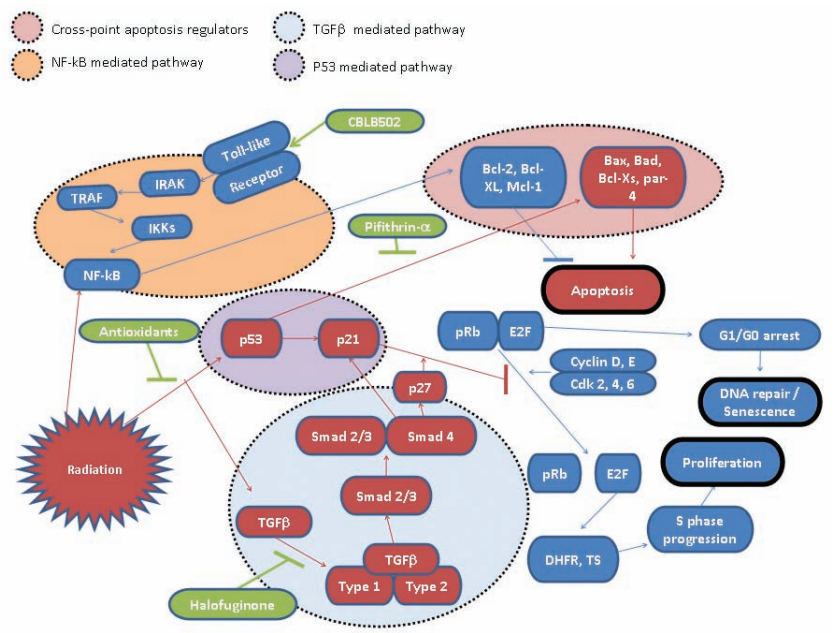

Figure 3. Radiation directly activates the NF-κB, p53, TGF-β and downstream apoptotic signalling pathways leading to either cell proliferation or cell death.

hypotension, nausea and vomiting, which greatly restricts its use[28]. Currently, another limitation with this compound is that it's recommended route of administration is intravenous although newer methods such as subcutaneous and oral routes are being explored[18].

Another effective scavenger of reactive oxygen species is ethyl pyruvate, a simple aliphatic ester of pyruvic acid. It has been shown to improve survival and recover organ damage in animal models of sepsis, ischemia, reperfusion injury, hemorrhagic shock, and after total-body irradiation (TBI)[19,29,30] (Fig. 2). Ethyl pyruvate acts as a great radioprotectant and mitigating agent for tissues that have been respectively exposed and damaged by ionising radiation. Ethyl pyruvate given to mice either 1 hour before or 5 days after 9.75 Gy dose of radiation showed a significant improvement in their survival[29]. Given the benefits of ethyl pyruvate, it may be important to further investigate this novel agent as a irradiation countermeasure tool.

Another subgroup of antioxidants of interest that has reactive oxygen species scavenging properties is polyphenols, chemical compounds found in plants (Fig. 2). Polyphenols have been shown to protect human cells against radiation-induced DNA damage[31]. In addition, polyphenols, particularly curcumin could decrease the frequency of chromatid breaks in human skin fibroblasts following irradiation[22,32]. Curcumin, diferuloyl methane, is a hydrophobic polyphenol derived from rhizome (turmeric) of the herb Curcuma longa. *In vivo* research has illustrated its activity as a novel anti-inflammatory agent, modulator of cytokine release, an immunomodulator, as well as a radioprotector and radiation mitigator[31,33]. In one of these studies, the radioprotective effects of curcumin were investigated in the lungs of mice 3 weeks post irradiation[34]. Mice that were given a 5 per cent solution of curcumin versus those that were given a controlled diet showed not only improved survival, but also decreased radiation-induced lung fibrosis. As a chemopreventive agent, curcumin has both known antioxidant and tumor cell radiosensitising properties[35]. Thus, dietary curcumin ameliorates radiation-induced pulmonary fibrosis and increases mouse survival while not impairing pulmonary tumor cell killing by radiation[34]. Mice treated with total-body irradiation of 12 Gy and given a curcumin derivative, D68, 10 min after irradiation as well as 3-5 days after irradiation showed an increase in survival compared to untreated mice. It was also observed that the gastrointestinal tract showed enhancement of crypt proliferation and preservation of intestinal villi length[9]. Although curcumin may have low bioavailability, the levels in the intestine may be sufficient for exerting pharmacological effects[33]. The inherent properties of curcumin make it an ideal candidate as a countermeasure agent for continued research and development.

Vitamin E compounds, composed of various tocopherols and tocotrienols also act as free radical scavengers[24,19]. There are eight analogs of vitamin E as α, β ,γ, δ tocopherol and α, β, γ, δ tocotrienol. Vitamin E compounds could alleviate brain and serum oxidative stress during irradiation

in mice[36]. During the last decade, tocotrienol research has gained momentum within the Vitamin E family. This subdivision has neuroprotective, anti-cancer, anti-oxidative, and cholesterol-decreasing properties that tocopherols lack[37]. Delta-tocotrienol (DT3), one of the isomers of vitamin E has demonstrated significant radioprotective effects in total-body irradiated mice as measured by 30-day post-irradiation survival, possibly through the involvement of ERK kinase activation-associated mTOR survival pathways[38]. Further, gamma-tocotrienol (GT3) also acts as a radioprotector for hematopoietic stem cells and progenitor cells in sub-lethally irradiated mice[37].

Mitochondria-targeted antioxidants would be important molecules providing protection from reactive oxygen species as mitochondria dysfunction by excess radicals can lead to cell death[39,40]. One such approach directed at the mitochondria in protecting cells from ionising radiation damage with Tempol[41] (Fig. 2). This agent is a nitroxide that promotes metabolism of many reactive oxygen species and improves nitric oxide bioavailability. Tempol also preserves the mitochondria against oxidative damage and improves tissue oxygenation. In its active state, Tempol can quickly be bio-reduced to its non-radioprotective hydroxylamine form[18]. This makes it an ideal radioprotectant since normal tissues that are highly oxygenated, the compound would not be reduced. It can further be used in radiotherapy for tumor cells as tumors have hypoxic compartment. Currently, the only limitation to use this compound for radiation protection is the requirement of high *in vivo* concentrations[18].

3.1.3 Modifiers of Cell Signalling

Radiation damage to a cell may lead to its death *via* the activation of cytotoxic signalling processes. These varying processes will eventually lead to an apoptotic pathway. Various agents have the ability to halt these signals, prevent the unintentional death of normal cells or those accidentally exposed to irradiation. One of the important players in cell signalling is p53, a guardian of genome protein that has a key role in apoptosis, genetic stability, and also inhibition of angiogenesis. Activation of p53 has been linked to normal tissue damage after irradiation, as p53 eliminates the damaged cell by apoptosis[42]. Inhibitors of p53 like pifithrin-alpha, particularly in cells that were inadvertently exposed to radiation have the potential to salvage the tissue [43] (Fig. 3). In glioma cells, it was shown that there was an increase in survival of normal astrocytes and fibroblasts post-irradiation. It is also important to note that there were no changes in radiosensitivity of the tumor to irradiation using pifithrin-alpha[43]. Therefore, this agent may prove valuable in protecting normal tissues from the side effects of radiotherapy while maintaining treatment efficacy. These results are further corroborated in numerous studies using zebrafish where p53 inhibition improves the survival of irradiated zebrafish[44,45]. Additional studies are needed to fully utilise the possibilities that this agent offers.

Bowman-birk proteinase inhibitor (BBI) is a radioprotector that has shown to improve DNA repair mechanisms and protect against radiation-induced fibrosis[46], possibly through both epidermal growth factor receptor phosphorylation as well as nuclear transport. It was demonstrated that pre-treatment of mice with BBI significantly decreased radiation-induced leg contracture[47]. Based on the previous experiments, it was determined that this inhibitor improved DNA repair of initial damage and thus enhanced genomic integrity and prevented radiation-induced terminal differentiation of fibroblasts[46].

NF-κB (nuclear factor kappa-light-chain enhancer of activated B cells) is widely utilised within eukaryotic cells as a regulator of genes that control cell proliferation and cell survival[12,48] (Figs. 2 and 3). Activated NF-κB turns on the expression of genes for the cell proliferating and survival functions from conditions that would otherwise cause apoptosis. NF-κB also has the ability to produce cytokines and induce toll-like receptors (TLR) which subsequently have various functions—some even radioprotective[49,50].

Toll-like receptors play a role in the innate immune system in which there exists a pattern recognition receptor for pathogens. Once a pathogen is detected, NF-κB gets activated. It is believed that subsequent to activation of NF-κB signalling, cytokines are induced and these induced cytokines was found to cause a suppression of ionising radiation-induced apoptosis[50]. Of importance is a polypeptide drug derived from salmonella flagella, CBLB502, which binds to toll-like receptor 5 and subsequently activates the toll-like receptor to initiate NF-κB signalling[51] (Fig. 3). In a recent study, it was observed that a single injection of CBLB502 prior to a fatal dose of total-body irradiation protected mice from gastrointestinal and hematopoietic ARS and improved survival while it did not alter radiosensitivity of the tumor site[50]. Of note was that CBLB502 showed radioprotective activity in rhesus monkeys[50]. It was also shown in another study that activation of NF-κB *via* toll-like receptors served to protect mice from total-body irradiation[52]. The results from such studies suggest that toll-like receptor agonists as well as activators of NF-κB could serve as countermeasure agents in radiation emergencies without compromising the efficacy of radiotherapy for tumors.

3.1.4 Cell-cycle Modulators

Cells are less sensitive to radiation during the G1/G0 and S phases, and hence, arrest or entry into one of those phases would be beneficial for cellular survival. Furthermore, ensuring that certain processes are completed at checkpoints is essential for the proper growth and survival of a cell. Genistein is one such isoflavone which not only act as a potent antioxidant but also a cell-cycle modulator that has shown radioprotective effects[24,25]. Genistein is noted to protect normal cells while promoting G2/M cell cycle arrest in cancer cells[53]. Genistein in non-toxic doses provides protection against acute radiation injury to animals that are exposed to a lethal dose of γ-radiation[54]. Another study utilising human eosinophils and neutrophils showed that genistein blocked the inhibition of tyrosine phosphorylation

and subsequently prevented granulocyte apoptosis[55]. In a pilot study, patients receiving genistein during chemotherapy and radiotherapy reported less pain and diarrhea[56]. Given these benefits, genistein appears to be a promising radioprotective agent that needs further clinical study.

3.1.5 Cytokines and Growth Factors

Numerous cytokines and even growth factors may be used as radiation mitigators and have been utilised in the past to enhance recovery from ARS. These agents work to accelerate the differentiation of stem cells in bone marrow as well as in the intestine to prevent gastrointestinal and hematopoietic effects of ARS after ionising irradiation exposure. Currently, granulocyte colony-stimulating factor (G-CSF) is used to assist in bone marrow recovery and to reduce lethality after total-body irradiation[18] based on the observation that administration of G-CSF 6 h after post irradiation increased hematopoietic cells and decreased aplasia in non-human primates[57].

Keratinocyte growth factor (KGF) is another potential mitigator that has recently been studied. This growth factor serves to stimulate a number of processes such as differentiation, DNA repair, as well as scavenging reactive oxygen species[58]. Given this capacity, keratinocyte growth factor has been successfully shown in the animal model to prevent xerostomia and mucositis post ionising radiation. Palifermin is a human recombinant keratinocyte growth factor that reduced the incidence of mucositis in patient receiving hyperfractionated radiotherapy in a phase II clinical trial[58]. A recombinant human fibroblast growth factor, Velafermin, has also emerged as a promising radio-mitigating agent as it reduces the severity and duration of mucositis when given on days 3 and 9 post-irradiation[59] in hamster cheeks.

Interventions involving growth factors may also serve as therapeutic agents after damage such as fibrosis. Transforming growth factor (TGF)-β is a growth factor that plays a key role in radiation-induced fibrosis[60]. Previously, it was demonstrated that inhibition of radiation-induced TGF-beta signalling *via* abrogation of the RII function enhances the radio-resistance of normal lung epithelial cells[61]. Hence, TGF-β signalling inhibition may prevent damage to normal lung tissue post ionising radiation. In fact, halofuginone, an inhibitor of TGF-β signalling has been shown to inhibit radiation-induced fibrosis[62] (Fig. 3). This agent was also used successfully to prevent esophageal and hypopharyngeal fibrosis following irradiation of head and neck in mice[63]. Though these agents are effective in preventing fibrosis further testing is necessary before their use in the clinics.

It is a well known fact that inflammatory pathways, such as increased cytokine expression, aid in prevention of radiation damage and in repair of injured cells [53]. These cytokines subsequently induce other progenitors cells, scavenging proteins, antioxidant enzymes, or may lead to prevention of apoptosis[53]. The foremost pro-inflammatory cytokine to show radioprotective potential was interleukin 1 (IL-1) in a mouse model[64]. Use of IL-1 (1000 units) resulted in 100 per cent survival of the mice that were irradiated with LD50/30 dose. IL-12, known to induce progenitor cells, has also been shown to act as a radioprotector in mice treated with IL-12, 18 to 24 h prior to irradiation[65]. IL-3 was also shown to reduce the period of thrombocytopenia and neutropenia 2 h post-radiation in non-human primates receiving 7 Gy total-body irradiation[53]. IL-11, a thrombopoietic growth factor has been shown to ameliorate early intestinal radiation injury in mice. The proposed mechanism for interleukins involves a cascade effect within the cell as well as interaction with each other. Interleukin activation has potential as a radioprotective agent, though induction of all interleukins is not ideal as IL-6 is known to radiosensitise cells[65].

4. CONCLUSIONS

Many countermeasure agents exist in the form of antioxidants, cell-cycle modulators, agents that interfere with cell-death signalling, as well as protective cytokines that have radioprotective features as investigated in this review. This review highlights the accomplishments of several groups using *in vivo* models as those seem to be most effectively translated in clinical settings. Of these *in vivo* models, only a handful of agents such as amifostine, genistein, keratinocyte growth factors and curcumin have been explored for use in human beings and have shown enormous benefits. List of the agents is shown in Table 1.

Radiation not only causes acute and chronic effects on normal tissue functions but can also promote carcinogenesis in the damaged tissues. Several international agencies

Table 1. Clinically used countermeasure agents

Agent	Type of countermeasure	Classification	Selective for tumor versus normal tissue	Clinical uses
WR-1065[27,28] (Amifostine)	Radioprotector	Antioxidant; scavenges ROS	Selective	Cytoprotective adjuvant for chemotherapy / RT to reduce xerostomia in Head and neck cancers
Curcumin[32,35]	Radioprotector	Antioxidant; polyphenol	Selective	Phamacological effects seen in cancer patient intestines
Genistein[56,25]	Radiation mitigator	Cell cycle modulator; antioxidant	Selective	Reduced pain / diarrhea in patients undergoing chemotherapy / RT of the abdomen
Palifermin[58]	Radiation mitigator	Growth factor	N/A	Reduce mucositis in patients receiving RT
Halofuginone[62,18]	Radiation mitigator / therapeutic agent	TGF-β inhibitor	Selective	Reduce fibrosis in patients undergoing RT

and academic institutions have focused their efforts on the development of drugs or agents that can mitigate the sequential acute effects of radiation. In spite of substantial investments by these agencies in the last decade, there has not been even a single agent yet developed to mitigate the effects of irradiation. This is due to the fact that agents that are in research and development phase focus more on organ system such as protective effects on the bone marrow or gastrointestine or central nervous system rather on the whole organism itself. Approaches, that combine agents which can protect multiple organs, can potentially lead to an ideal countermeasure strategy. It is important that in this idealistic situation, the cocktail of countermeasure agents should not synergistically promote the radiation-induced carcinogenesis, rather help in abrogating carcinogenesis.

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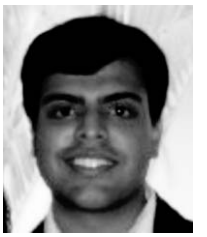
Contributors



Mr Vivek N. Patel received his Degree in Biology Honours from University of Miami, Coral Gables, FL, USA and is currently a Candidate for Doctor of Medicine at University of Miami Miller School of Medicine, Miami, FL, USA.

Dr Seema Gupta received her PhD from University of Delhi, Delhi. She worked as Post-doctoral Fellow at University of Kentucky, Lexington, Kentucky, USA and Geisinger Clinic, Danville, Pennsylvania, USA, before joining the Department of Radiation Oncology at University of Miami, Miami, FL, USA as Research Assistant Professor. Her research interest includes radiation and cancer biology with a goal to develop novel therapeutic strategies for prostate, lung, ovarian, breast and brain cancers.

Dr Mohammed M. Shareef received his PhD from National Institute of Mental Health and Neurosciences (NIMHANS), Bengaluru. He worked as Post-Doctoral Fellow at University of Kentucky, Lexington, Kentucky, USA and as Research Scientist at Geisinger Clinic, Danville, Pennsylvania, USA before joining the Department of Radiation Oncology at University of Miami, Miami, FL, USA as Research Assistant Professor. His primary area of research interest includes unraveling the regulation of signaling during radiation and hypoxia and it's modulation in several different cancers.

Dr Mansoor M. Ahmed obtained his PhD from University of Madras, India, with pre-doctoral training at Hiroshima University, Japan. Following post-doctoral tenures at Thomas Jefferson University, Philadelphia, PA, USA and University of Kentucky, Lexington, KY, USA, he worked as Assistant Professor and Associate Professor at University of Kentucky, Lexington, KY, USA and as Staff Scientist at Geisinger Clinic, Danville, PA, USA. He is currently Associate Professor of Radiation Oncology at Sylvester Comprehensive Cancer at University of Miami, Miami, FL. His current research focus is radiation-induced signal transduction and apoptosis in solid tumors.