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REVIEW PAPER

Radiation Countermeasures: Current Status

Teena Haritwal, Noopur Gupta, Mrinalini Tiwari, Sarvesh Surve, and Paban K. Agrawala*

Department of Radiation Genetics and Epigenetics,
Institute of Nuclear Medicine and Allied Sciences, Delhi - 110 054, India
**E-mail: paban@inmas.drdo.in*

ABSTRACT

Deleterious effects of ionising radiation leading to significant morbidity and mortality have been studied elaborately. A range of synthetic, semisynthetic and herbal compounds have been screened as radiation countermeasure agents and a number of promising radiation countermeasure agents are under development. Amifostin is the only drug which has been approved by the United State Food and Drug Administration (US-FDA), but that too for use in a defined population under strict medical supervision. Granulocyte Colony Stimulating Factor/filgrastim, γ-tocotrienol, genistein are at an advanced stage of development and are tested on higher animal models as per required norms of FDA. Herbal compounds are also considered very safe and of high value as radiation countermeasure agents owing to various properties like antioxidant, immunomodulation activity etc. Histone deacetylase inhibitors such as Trichostatin A, Diallyl sulphide, Sulforaphane are being viewed as very promising radiomitigating agents by our laboratory and active research in the same direction is going on. Infusion of hematopoietic stem cells and growth factors are in practice as potent therapeutics. This review gives an overview on various radioprotectors, radiomitigators and therapeutic agents either available or under development currently.

Keywords: Ionising radiation; Protectors; Mitigators; Therapeutics; Herbal; HDAC inhibitors

1. INTRODUCTION

There is an urgent need for the development of radiation countermeasure agents to ameliorate or reduce the morbidity and mortality caused due to radiation over exposures in planned and unplanned activities[1]. Protection of biological systems against ionising radiation is of paramount importance during planned exposure to radiation. Despite the great efforts and investment, we are far away from a potent radio protector suitable for human application. Radioprotectors are agents which need to be present in the body during the time of irradiation, in order to protect the exposed individual. They need to have antioxidant activity predominantly so that free radicals generated from interaction of biological system which is rich in water with irradiation are scavenged and cells are protected.

Agents used to modify radiation induced alterations are classified into three broad categories based on their time of delivery and mode of action as protectors, mitigators and therapeutics. Radioprotectors are given prior to radiation exposure; hence they are helpful in planned radiation exposure like as in radiotherapy and first responder applications. This group includes a wide range of herbal and synthetic compounds different mechanism of action and structure of the active constituent(s). The aminothiol amifostin is the only radioprotectant approved for human application in clinical scenarios[2]. Amifostin detoxifies the reactive metabolites of alkylating agents as well as scavenges free radicals so as to render radioprotective action, other possible mechanisms of its radioprotective action include DNA repair, inhibition of apoptosis, alteration in gene expression and modification of various enzyme activity[3,4], etc. Despite being a potent radioprotector, its application is limited due to toxicity concerns as it has potential to cause hypotension, neurotoxicity, etc. There are many herbal compounds which have shown antioxidant activity and can prove to be a radioprotector with no apparent toxicity. They can scavenge reactive oxygen and nitrogen species (ROS and RNS) from the cells and protect them from adverse effects of ionising radiation. Plant metabolites like: alkaloids, flavonoids lycopene, peptides, polysaccharides, phytohormones extracted from herbs like *Allium sativum, Camellia sinensis, Hippophae rhamnoides, Tinospora cordifolia, Ocimum sanctum*, *Emblica officinalis* are some of the examples.

Mitigators are the radiation countermeasure agents that are administered shortly after or during radiation exposure but prior to the manifestation of symptoms of radiation exposure. They act predominantly through the repair of the damages and inflammation caused due to radiation exposure. Therefore being antioxidant or free radical scavenger is not a prerequisite for such agents unlike radioprotectors. Many cytokines and growth factors have been reported as radiomitigator. These agents stimulate differentiation of various stem cells in bone marrow and intestine thereby mitigates death by hematopoietic syndrome and GI syndrome by replenishing the damaged cells with new and healthy ones.

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Therapeutic drugs are those given after the appearance of symptoms of radiation exposure and they act to ameliorate tissue toxicity and enhance tissue repair. Figure 1 gives a diagrammatic presentation of different classes of radiation countermeasure agents and their properties. Examples of currently available agents in each class are depicted in Table 1.

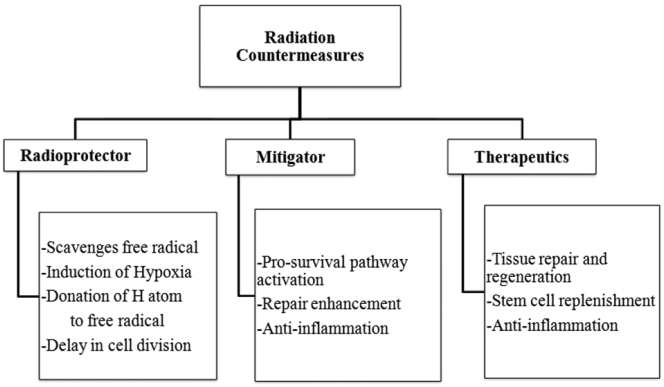

Figure 1. Chart showing different radiation countermeasure classification and their properties.

Acute radiation syndrome (ARS) occurs in human following exposure to higher than 1 Gy of whole body radiation or relatively significant dose of partial body irradiation delivered at a high dose rate. Hematopoietic ARS occurs at a dose range of 2 Gy - 6 Gy, Gastrointestinal (GI) at 6Gy - 8 Gy and Cerebrovascular at still higher dose >8 Gy[5]. Cerebrovascular syndrome is almost irremediable since it leads to death almost immediately. Thus hematopoietic and GI syndromes are specific targets for the development of radiation countermeasure agents. The hematopoietic syndrome is characterised by an immense loss of hematopoietic stem cells (HSCs) which are highly radiosensitive primarily owing to their active proliferation. The GI syndrome is characterised by massive cell death or apoptosis in epithelial cells followed by disruption of intestinal crypt cells. Diminished food intake and water absorption, electrolyte imbalance, intestinal bleeding and sepsis as a result of exposure to GI doses lead to death eventually[6].

2. RADIOPROTECTORS

Many synthetic, semisynthetic and natural compounds have been evaluated on different biological system as radioprotectors. Free radical scavengers, compounds capable of inducing delay in cell division, induction of hypoxia, and donation of hydrogen atom to the radical are some important properties of those compounds investigated as radioprotectors. Various plant extracts with above properties have been evaluated for their radioprotection ability but none of them have reached clinics so far despite having low toxicity[7].

2.1 Amifostin

Amifostin (WR 2721), a thiol, is a potent radioprotector that has been approved by USFDA for human application but only under strict medical supervision. It can scavenge oxygen derived free radicals and is applied in the head and neck cancer patients undergoing radiotherapy to protect the non tumor tissues[8]. Amifostin is a pro-drug that is inactive until conversion to WR 1065 by dephosphorylation via cellular alkaline phospahatase[9]. The selective protection of normal tissue is the result of greater accumulation of WR 1065 in the non tumor cells than in tumor cells. Tumors are relatively hypovascular thus resulting in relative hypoxia and a low interstitial pH. Moreover, alkaline phospahatase expression is reduced in malignant tissues. So the combination of hypoxia, acidic pH and low expression of alkaline phospahatase results in less accumulation of active compound in the tissue[10]. WR 2721 shows many adverse effects such as nausea, vomiting, hypotension, sneezing, somnolence, a metallic taste during infusion and occasionally allergic reaction that may include rash, fever and anaphylactic shock[11,12] limiting its application. Administration of amifostin shows protection to normal cells in the head and neck cancer, ovarian carcinoma, myeloid leukemia when it is dependent on p53 patients against oral mucositis, pneumonitis, esophagitis, and dermatitis[13,14].

2.2 G-CSF/Neupogen/Filgrastim

Other than amifostin a number of compounds are at different stages of development as radioprotectors. Granulocyte-Colony Stimulating Factor (G-CSF) and Granulocyte-Monocyte-Colony Stimulating Factor (GM-CSF) are likely to receive FDA approval[15] in near future. G-CSF provides protection against radiation induced hematopoietic as well as gastrointestinal injuries and testicular dysfunction[16-17]. G-CSF is a cytokine produced by monocyte, fibroblast and endothelial cells which stimulates the proliferation, differentiation and enhances phagocytic activity of neutrophils in the bone marrow and protect against radiation induced neutropenia[18]. It acts by binding to its transmembrane receptor Granulocyte Colony Stimulating Factor Receptor (GCSF-R) which is a class-1 cytokine receptor family member present on various hematopoietic cells such as multipotent stem cells, Granulocyte-Monocyte progenitor cells and lymphoid progenitor cells. G-CSF with its receptor forms homo-oligomeric receptor complex. A signal cascade is activated by phosphorylating JAK-2 leading to JAK-STAT pathway activation, ras/raf/erk pathway activation, and anti-apoptotic pathway activation. G-CSF stimulate different progenitor cells such as lymphoid progenitor, erythroid progenitor, basophil progenitor and eosinophil progenitors which further give rise to lymphocyte, erythrocyte, basophils, respectively[18]. The efficacy of G-CSF has been evaluated in mice, canines (beagle), NHPs and mini pigs[15]. Survivability and radioprotection has been improved by G-CSF across species[18,19].

Neupogen (recombinant methonyl human G-CSF) is a recombinant derivatives of G-CSF produced in *E. coli* expression system. It differs from G-CSF in having an N-terminal methionine tail for the expression in a prokaryotic system furthermore it is non-glycosylated. Neulasta is a pegylated version of G-CSF. It is a covalent conjugate of human G-CSF. Administration of only two doses of Neulasta has been shown to be more effective against radiation induced neutropenia compared to daily dose of neupogen.

GM-CSF is also a colony stimulating factor and has been evaluated across species (mice, canine and NHPs). Unlike G-CSF, it is species specific and survival benefits are also

Table 1. Current status of various radiation countermeasure agents

	S. No	Name	Test system	Uses	Optimum Doses	DRF	Ref.
RADIOPROTECTORS	1	WR2721	Sprague-Dawley (SD) rats	Scavenge oxygen derived free radicals to protect non-tumor tissues	200 mg/kg	NA	8 - 14
	2	Filgrastim	BALB/c, C3H/ HeNCr mice	Protection against radiation induced hematopoietic as well as gastrointestinal injuries and testicular dysfunction	NIH BALB/c: 2,000 ug/ kg; CR BALB/c: 1 ug/kg; C3H mice: 200 ug/kg.	NA	15, 16, 18-19,
	3	γ-tocotrienol	Nonhuman Primates, CD2F1 strain mice	To reduce the mortality rate caused due to radiation induced hematopoietic syndrome	75 mg/kg	1.29	21-27
	4	Genistein	BALB/c mice	Scavenge free radicals and reduce the oxidative stress generated by radiation ultimately ameliorating DNA damage	200 mg/kg	NA	28-31, 33
	5	Herbal Radioprotectors					
	i	*Podophyllum hexandrum*	Strain 'A' Swiss Albino mice	Precursor of topoisomerase inhibitor	200 mg/Kg	1.33	35
	ii	*Hippophae rhamnoides*	Strain 'A' Swiss Albino mice	Diminish damage in DNA, scavenge free radicals, ameliorate chromosomal aberration in bone marrow cells and protection against hematopoietic syndrome	30 mg/kg	NA	36, 37
	iii	*Ocimum sanctum*	B16F1 melanoma and Fibrosarcoma bearing mice	Antioxidant activity, protect against lipid peroxidation in liver, ability to scavenge the free radicals, metal chelating and anti-inflammatory activity which provide protection to normal tissue against radiation	10 mg/kg/day for five consecutive days	1.28	40
RADIOMITIGATORS	1	5-androstenediol	CD2F1 mice, C3H/HeN mice, C3H/FeJ	Recovery of various bone marrow lineages against radiation induced myelosuppression	10 mg/kg, 30 mg/kg, and 100 mg/kg	1.25	47 - 49
	2	Histone Deacetylase inhibitors	BALB/c mice	Increase histone acetylation thus increasing the accessibility of repair proteins to DNA and enhancing DNA repair	0 h (TSA 0.5 mg/kg; VPA 600 mg/kg); 5 h (TSA, 0.5 mg/kg; VPA, 300 mg/kg)	NA	52, 53
	3	Sulforaphane	Whole blood culture	Ameliorate radiation induced micronuclei frequency in human lymphocytes	400 nM	NA	52,54
	4	Diallyl Sulphide	Rats, C57 Bl/6 mice	Enhances the bone marrow cellularity and spleen colony forming unit which further enhances the lymphocyte count	200 mg/kg	NA	55,56
	5	Epigallocatechin-3-gallate	C57 Bl/6 mice	Protection against radiation induced DNA break, DNA damage and lipid peroxidation and membrane fluidity and reduction in frequency of apoptosis in crypt cells	0.1833 mg/kg	NA	46

NA=not available

inconsistent. Like G-CSF, GM-CSF also recovers the total blood count, neutrophil count and leukocyte count decreased due to radiation. Compared to GM-CSF, G-CSF shows more protection from hematopoietic injuries and it is more effective[20].

2.3 γ-tocotrienol

After promising radioprotective activity of GT3 (member of vitamin E family) in the rodents, its efficacy in non-human primates (NHP) model is under evaluation. It reduces the mortality rate caused due to radiation induced hematopoietic syndrome by recovery in neutropenia and thrombocytopenia and is also found effective against GI syndrome. Compared to multiple doses of Neupogen and neulasta, GT3 is effective in a single dose without any supportive care in NHP [21]. The precise mechanism of radioprotection by GT3 is not well known but it provides protection against radiation by up-regulating the expression of G-CSF, interleukin IL-1α, IL-1β, IL-6, IL-17, macrophage inflammatory protein within 24 h of administration of the drug[22,23]. It also shows protection by up regulation of A20, the inhibitor of NF-κB in case there is basal level of expression of NF-κB, up regulation of anti-apoptotic genes and down regulation of pro-apoptotic genes bak-1 both at the transcriptional and translational level in the intestine[24,25]. GT3 protects normal tissues from hematopoietic and GI injuries by protecting hematopoietic stem and progenitor cells and epithelial crypt cells of intestine from the DNA damage caused by ionising radiation[26,27].

2.4 Genistein

Genistein, a phytoestrogen, has antioxidant activity and it also inhibits protein tyrosine kinase that modulate signal transduction pathway. When administered before irradiation it provides protection against intestinal damage, lung injury, and acute hematopoietic syndrome[28-31]. Genistein scavenges free radicals and reduces the oxidative stress generated by radiation ultimately ameliorating DNA damage. Hematopoietic cells are recovered due to enhanced activity of IL-6 and G-CSF level and suppression of TNF-α mediated inflammation through inhibition of ROS/Akt/NF-κB pathway by administration of genistein 24 h prior to radiation exposure. Nanoparticle formulation of genistein shows protection from apoptosis in hematopoietic stem and progenitor cells against radiation and increased bone marrow cellularity that promotes hematopoiesis[32,33].

2.5 Herbal Radioprotector

Various herbal products have been evaluated as radioprotector because of their anticipated low toxicity and excellent antioxidant activity. These include medicinal plants, green vegetables, fruits, ornamental plants and spices. Plant extracts can be good radioprotector because they are rich in compounds such as alkaloids, flavonoids, peptides, polysaccharides, vitamin B, C, E and β-carotene displaying antioxidant, anti-microbial and anti-inflammatory activities. Despite having several properties of ideal radioprotectors, there are some drawbacks with development of herbal products[34] like extraction method, batch to batch variation, seasonal variation, etc.

2.5.1 Podophyllum Hexandrum

The herbal extract of *P. haxandrum* shows 80 per cent of radioprotection. It contains podophyllotoxin and other bioactive constituents which is a cure for many inflammatory and allergic conditions of the skin, cold, constipation, skin, bladder, lungs and brain cancer. In the treatment of leukemia, lung and testicular cancer, psoriasis, malaria, rheumatoid arthritis podophyllotoxin has been used as a precursor of topoisomerase inhibitor. In the last couple of decades many radioprotective studies using *P. hexandrum* has been performed such as survival studies, gastroprotection, neuroprotection, hepatoprotection, hematopoietic system protection in different strain of mice against gamma radiation[35].

2.5.2 Hippophae Rhamnoides

It belongs to the *Elaegnaceae* family and it has been reported that its alcohol and aqueous extracts render increased survivability (up to 82 per cent). Both the extracts of *H. rhamnoides* diminish damage in DNA, scavenge free radicals, ameliorate chromosomal aberration in bone marrow cells and thus provide protection against hematopoietic syndrome. On the parameters of toxicity study the leaf extract of *H. rhamnoides* was found less toxic than the berry extract. Both the extracts are promising radioprotector *in vivo* but further studies are required before it can reach clinical set up[36,37].

2.5.3 Ocimum Sanctum

It belongs to the *lamiaceae* family containing two flavonoids orientin (Ot) and vicenin (Vc) in the leaves. Both flavonoids have been evaluated against radiation induced chromosomal aberration in mice. They have been observed to reduce micronuclei frequency in bone marrow and peripheral blood cells as well. Both compound show antioxidant activity against radiation and protect against radiation induced lipid peroxidation in liver. Both compounds have the ability to scavenge the radiation induced free radicals[38,39]. They also show metal chelating and anti-inflammatory activity by that they can provide protection to normal tissue against radiation[40].

Tinospora cordifolia, *Emblica officinalis*, *Centella asiatica*, *Curcuma longa*, *Allium sativum*, *Piper longum*, *Mentha piperita*, *Aegle marmelos* and *Zingiber officinalis* extracts also have been evaluated in different biological systems or animal models. They can be used as promising radioprotector either in their crude extract form or in the form of certain formulations[41,42] but further studies are necessary.

3. RADIOMITIGATORS

Development of radiomitigator is also as important as radioprotector because it is required during unplanned and accidental radiation exposure. Radiomitigators are agents which are administered after radiation exposure to mitigate the effect of radiation[43]. Sulforaphane, Trichostatin A, Diallyl sulphide and epigallocatechin-3-gallate and other histone deacetylase inhibitors have shown effective radiomitigating activity[44-46]. 5-androstenediol (5-AED), entolimod and recombinant human IL-12 are well known radioprotector at very advance stage of development but these all have also been evaluated as radiomitigator in mice and NHPs[47,48].

3.1 5-androstenediol

It is a naturally occurring adrenal steroid hormone holding promise against hematological acute radiation syndrome as protector as well as mitigator. It stimulates recovery of various bone marrow lineages against radiation induced myelosuppression[49]. Neumune is an injectable suspension formulation of 5-AED and it has been tested on NHPs where it has been shown to mitigate hematopoietic effect induced by radiation and increase survivability[50]. It elevated the expression of NF-κB dependent granulocyte colony stimulating factor, induced the expression of bcl-2 and also decreased the persistence of DNA double strand breaks. 5-AED is suggested to mitigate radiation injuries by enhancing the level of expression of anti-apoptotic genes and growth factors[50].

3.2 Histone Deacetylase Inhibitors

Histone Deacetylase inhibitors (HDACi) are epigenetic modifiers involved in regulation of gene expression, differentiation, proliferation and apoptosis of cells. Some HDAC inhibitors have been approved by FDA for the treatment of various types of cancer like as vorinostat or SAHA. Moreover, HDAC inhibitors show effect in non-oncologic diseases like asthma, arthritis, diabetes and muscular dystrophy. Some HDAC inhibitor has shown radiomitigation activity against radiation injury[51]. HDAC inhibitor increases histone acetylation thus increasing the accessibility of repair proteins to DNA and thereby enhancing DNA repair. HDAC

inhibitors were found to mitigate radiation induced lethality by stimulation of bone marrow stem cells[52].

3.2.1 Sulforaphane

Sulforaphane (SFN) is an isothiocynate dietary supplement present in cruciferous vegetables like broccoli, cabbage and cauliflower and shows anticancer activity. SFN ameliorated radiation induced micronuclei frequency in human lymphocytes suggesting its antimutagenic effect due to enhanced repair activity. SFN acts by Nrf-2 Keap-1 pathway for its anticancer property[53,54]. SFN has been shown to inhibit histone deacetylase activity as well. SFN-cys competes for the binding site in HDAC thus it enhances histone acetylation level and increase anti apoptotic genes level[55]. Sulforaphane has the ability to mitigate the radiation induced genotoxicity and it can diminish both acute as well as late effects of radiation[55].

3.2.2 Diallyl Sulphide

Diallyl sulphide (DAS) is a naturally occurring organosulphur present in garlic. It has histone deacetylase inhibitor activity besides antimutagenic, antimicrobial, hepato and reno protective activity[51]. DAS exhibits radioprotective activity in liver, intestinal mucosa and hematopoietic injury[51, 56-57]. It enhances the bone marrow cellularity and spleen colony forming unit which further enhances the lymphocyte count. DAS has already been shown to enhance cellular antioxidant activity through Nrf-2 pathway under various stress condition.

3.2.3 Epigallocatechin-3-gallate

Green tea contains a polyphenol named as epigallocatechin-3-gallate (EGCG) which shows high anti-oxidant and anti-inflammatory activity. Administration of 100 µM concentration of EGCG shows protection against radiation induced DNA break, DNA damage and lipid peroxidation and membrane fluidity. The frequency of apoptosis in crypt cells is also reduced by the administration of EGCG. EGCG has widely studied for its anticancer activity and it can also alter the histone methylation and acetylation. EGCG is an inhibitor of DNMT1, a DNA methyl transferase enzyme and it also shows histone deacetylase inhibitor activity. EGCG enhanced the survival of mice and reduced the cytogenetic damage to bone marrow cells induced by radiation. EGCG has been shown to provide mitigation against radiation induced hematopoietic injury[47,58].

4. THERAPEUTICS

A therapeutic is an agent which is given after the appearance of physical symptoms of radiation exposure. Clinical management for hematopoietic acute radiation syndrome is limited to supportive care[59]. Few agents have been tested as therapeutics and have been shown to improve survivability after irradiation.

4.1 Infusion of Hematopoietic Stem Cells

Infusion of *ex-vivo* expanded murine hematopoietic stem (HSC) and progenitor cells (HSPC) into major histocompatibility complex (MHC) mismatched recipient mice exposed to a lethal dose of radiation led to rapid recovery of myeloid progenitor cells and resulted in improved survival. These HSCs and HSPCs are expanded in presence of notch ligand outside any biological system. Survival benefit was significant even after three days of lethal dose of irradiation.

4.2 Growth Factors

It has already been reported that hematopoietic growth factors like IL-1, tumor necrosis factor (TNF), interferon-γ (IFN), GM-CSF and G-CSF when administered prior to radiation exposure render protection against hematopoietic syndrome[60,61]. They enhance survival when administered as therapeutics after radiation exposure also. Single injection of IL-1 promotes survival in a dose dependent manner and IFN-γ exhibits same effect[62]. Moreover, combination of growth factors has also been shown to be very effective against radiation. Combined administration of IL-3 and GM-CSF is more effective than administration of alone GM-CSF or IL-3[63]. Glucan, a macrophage activator when synergised with G-CSF enhanced survival and hematopoietic regeneration and recovers from myelosuppression[64]. Co-administeration of IL-6 and IL-3 improves platelet recovery and survival[65].

4.3 Recombinant GCSF/ Filgrastim

Recombinant G-CSF provides protection when administered before radiation exposure but can also used as a therapeutic[16,18]. Administration of r-GCSF with supportive care as soon after radiation as possible has significant effect on lethality. It modulates the hematopoiesis and lessens the duration of neutropenia and thrombocytopenia. Thus, early and continuous administration of G-CSF with supportive care enhances recovery of myelopoiesis, neutrophil, platelets and survival[66,67]. It also recovers bone marrow, splenic and peripheral blood cellularity, splenic Granulocyte-Macrophage progenitor cells, multipotent HSCs and overall survival[62,68].

4.4 Recombinant Pegfilgrastim/Neulasta

Pegfilgrastim, a leukocyte growth factor, has been studied as radioprotector extensively. But it also has the properties to be a therapeutic agent. It has been currently approved for treatment of chemotherapy induced myelosuppression. Filgrastim is the only LGF that has gone for efficacy assessment under animal efficacy rule to treat radiological and nuclear exposure injuries. Administration of Neulasta after 24 h and 8 days has increased survival in NHPs to 91.3 per cent against 47.8 per cent in the radiation alone group. It also decreased the intermediary time of thrombocytopenia and neutropenia and improved the recovery of neutrophil number in the animal exposed to a lethal dose of radiation leading to H-ARS[69,70]. Neutrophil recovery was significantly enhanced by administration of pegfilgrastim on day 1 and day 7 after radiation exposure compared to daily or single dose administration. It also enhances survival by mitigating cytopenia, thrombopenia, erythropenia and anemia[71]. It has also been reported that patients receiving pegfilgrastim had a lower incidence of febrile neutropenia than those received filgrastim[72].

5. CONCLUSIONS

From the present review it is apparent that there is requirement of more research in the field of mitigation and

therapeutics. To date, amifostin is the only drug that has been approved by USFDA for use as a protector but only under medical supervision. However, there are several radioprotective compounds which are either sowing successful results in pre-clinical studies or are in advanced stages of drug development. This is a good sign for the world that some degree of preparedness is expected soon in the area of radiation countermeasure which will be essential in the fight against terrorist threats involving nuclear or radiological material, nuclear power sector accidents, nuclear warfare and most importantly against the complications arising following radiotherapy.

However, the process of any drug development so far is a very long, difficult, costly and low success story despite tremendous advancements in knowledge, approaches and technology. Especially, development of drugs against radiation induced morbidity and mortality becomes more complicated due to our inability to carry out human efficacy studies owing to ethical issues and hence the success rate is far low or beyond our ability to evaluate. Molecules or compounds, whether natural or synthetic, that are under investigation or development can only be expected to be useful but that cannot be ascertained. That of course poses another big issue related to post-marketing inspections and reporting of adverse reactions.

Considering all constrains it can easily be understood that the development of a radiation countermeasure agent, whether protector, mitigator or therapeutic is a very complicated task with rare success. Therefore, there is a need of constant and holistic efforts by more and more researchers with increasing will and funding from appropriate bodies.

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CONTRIBUTORS

Ms Teena Haritwal is currently working as a Senior Research Fellow at Institute of Nuclear Medicine and Allied Sciences, Delhi on development of radio-mitigator with special emphasis on murine reproductive system.
Contribution in the current work: Collection and compilation of data.

Ms Noopur Gupta did her MSc in Plant Biotechnology. Currently working as a Senior Research Fellow at Institute of Nuclear Medicine and Allied Sciences, Delhi on development of radio-mitigator targeting Gastro-Intestinal System.
Contribution in the current work: Proof reading and Editing.

Ms Mrinalini Tiwari did her MSc in Biotechnology. Currently working as a Senior Research Fellow at Institute of Nuclear Medicine and Allied Sciences, Delhi on development of radio-mitigator emphasising on DNA damage and repair.
Contribution in the current work: Proof reading and Editing.

Mr Sarvesh Surve did his MSc in Biotechnology.
He helped TH in material collection and proof reading.

Dr Paban Kumar Agrawala is a PhD in Life Sciences working on the development of radiomitigators from HDAC inhibitors.
Contribution in the current work includes : Designing, compilation, editing and final approval of the manuscript.