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REVIEW PAPER

Chemical Radioprotectors

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ABSTRACT

Protection of biological systems against radiation damage is of paramount importance during accidental and unavoidable exposure to radiation. Several physico-chemical and biological factors collectively contribute to the damage caused by radiation and are, therefore, targets for developing radioprotectors. Work on the development of chemicals capable of protecting biological systems from radiation damage was initiated nearly six decades ago with cysteine being the first molecule to be reported. Chemicals capable of scavenging free radicals, inducing oxygen depletion, antioxidants and modulators of immune response have been some of the radioprotectors extensively investigated with limited success. Mechanism of action of some chemical radioprotectors and their combinations have been elucidated, while further understanding is required in many instances. The present review elaborates on structure-activity relationship of some of the chemical radioprotectors, their evaluation, and assessment, limitation, and future prospects.

Keywords: Radioprotectors, radiation damage, chemical radioprotectors, herbal radioprotectors, radiation injury, WR-2721, bisbenzimidazole, Hoechst-33258, analogue Hoechst-33342

NOMENCLATURE

LET	Linear energy transfer
DNA	Deoxyribonucleic acid
AET	β-Aminoethylisothiouronium bromide hydrobromide
MPG	β-Mercaptopropyonylglycine
MEA	Mercaptoethylamine
5-HTP	5-Hydroxy-L-tryptophan
5-HT	5-Hydroxytryptamine
H-342	Hoechst-33342
H-258	Hoechst-33258
2-DG	2-Deoxy-D-glucose
EAT	Ehrlich ascites tumor
BMG	Brain malignant glioma
Gy	Gray
cGy	Centi gray

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LD_{50} (30)	Lethal dose of radiation at which 50 per cent of the animals die within an observation period of 30 days
LD_{100} (30)	Lethal dose of radiation at which 100 per cent of the animals die within an observation period of 30 days
DRF	Dose-reduction factor
DMF	Dose-modifying factor
CFU	Colony formation unit
CSF	Colony-stimulating factor
L	Leavo
ILS	Interleukins
NPSH	Non-protein sulphydryl
LD_{50}	Lethal dose at which 50 per cent of the animals die within an observation period of 30 days. This is expressed in milligram per kilogram bodyweight of experimental animal
ED_{50}	Effective radiation dose at which 50 per cent of the animals show emesis
DMA	5-(4-Methylpiperazin-1-yl)-2-[2′-3, 4-dimethoxyphenyl)-5′-benzimidazolyl] benzimidazole
TBZ	5-(4-Methylpiperazin-1-yl)-2-[2′{2″-(4-hydroxy-3-methoxyphenyl)-5″-benzimidazolyl} -5′-benzimidazolyl] benzimidazole
MEG	Mercaptoethylguanidine
GSH	Glutathione
a-TMG	Tocopherol monoglucoside

1. INTRODUCTION

Development of novel and effective approaches using non-toxic radioprotectors is of considerable interest for defence (nuclear wars), nuclear industries, radiation accidents, space flight, etc, besides playing important role in the protection of normal tissues during radiotherapy of tumors.

Deleterious effects of radiation on biological systems develop in a temporal sequence across various levels of organisation, starting from the induction of primary lesions in the biomolecules and structures, eliciting repair processes, leading to the cell death or transformation responsible for morbidity, genetic disorder, and cancer. Therefore, various strategies have been developed to protect biological systems by interfering in the development of radiation damage (Fig. 1).

Ionising radiation [particularly, the low linear energy transfer (LET) radiation] exerts its effect through the generation of free radicals that destroy the vital macromolecule (eg, DNA) and structures such as membranes of the target cell. Following wholebody exposure to moderate doses (2-5 Gy), damage to the heamapoetic cells is the major cause of morbidity, while at higher doses (5- 10 Gy), damage to the gastrointestinal tract also contributes to the total effect. Therefore, development of agents, which reduce the free radical-mediated damage, acts as enhancers of repair and recovery process, as well as modifiers of immune system (biological-response modifiers) has been investigated to rescue the organism from radiation injury. An ideal radioprotector should have the following abilities functionally:

(a) Free radical scavenging

(b) Reduce oxidative damage

(c) Facilitate DNA and cellular repair

(d) Immuno-modulation, and

(e) Facilitate repopulation of damaged/affected organs.

From the viewpoint of practical application, the radioprotector is expected to have the following capabilities:

(a) It should offer good protection against both acute and chronic radiation damage.

(b) It should be suitable for oral administration and be rapidly absorbed and distributed throughout the body.

(c) It should not show any significant toxicity, including those on behaviour.

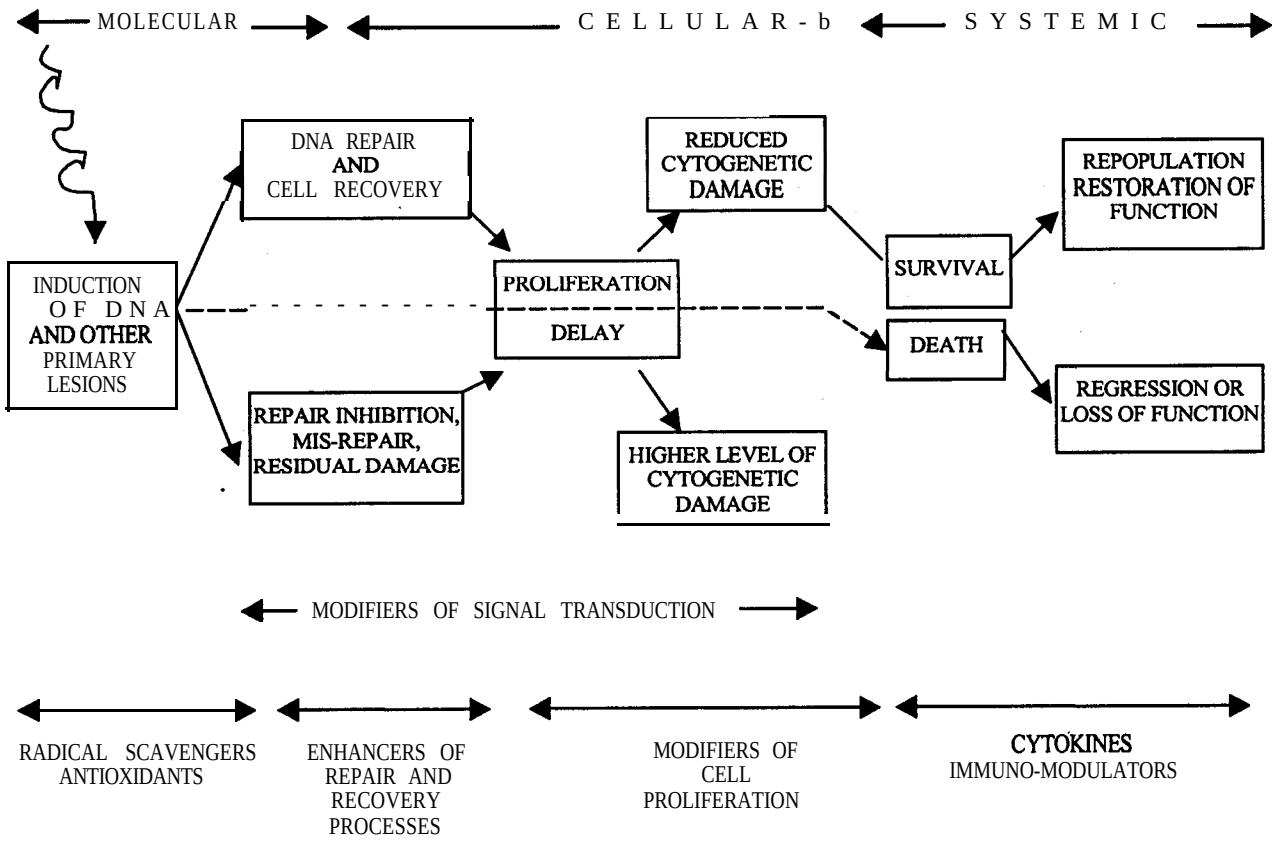


Figure 1. Biological response to radiation damage and strategies for protection

(d) Shelf-life should be long, easy handling and storage.

(e) It should be readily available and inexpensive.

The initial stages of radioprotector development, mostly aminothiol compounds like AET, MPG, MEA, L-cysteine, glutathione, cysteamine, etc emphasised on the physico-chemical and radiobiological parameters (Table 1). Table 2 shows radioprotectors currently under experimental and clinical investigations.

The efforts, development, and contemporary status of radioprotectors have been reviewed on a number of occasions in the past, which have focused on the nature of compounds, mode of action, efficacy, and toxicity'". This paper gives an overview of the various processes involved in the temporal and functional development of radiation injury in biological systems, the models and approaches currently employed in evaluation. Current status of some of the chemical radioprotectors with an emphasis on structure-function relationship has also been highlighted.

2. RADIATION INJURY & PROTECTION

Injury resulting from the penetration of biological tissue by ionising radiation is brought about by the transfer of radiation energy to critical biological macromolecules (eg, DNA, proteins, membrane, lipids, etc). The initial chemical injury can occur in two ways, either directly from the absorption of radiation energy by the target macromolecules themselves or indirectly from diffusible ions and free radicals[6] produced by radiolytic products of water. A cellular water molecule on irradiation produces hydroxyl radicals ($OH^{\bullet}$), hydrated electrons, hydrogen radicals, hydroperoxy radicals ($HO_2^{\bullet}$), etc. Of these, OH and solvated electrons are produced in the highest concentration and $OH^{\bullet}$ is considered to be the most damaging[6,7]. When target macromolecules

Table 1. Physico-chemical and radiobiological properties of some well-known chemical radioprotectors

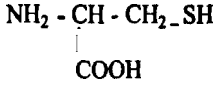
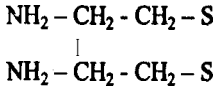
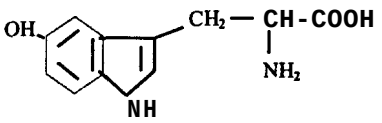
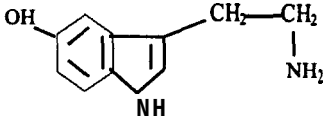
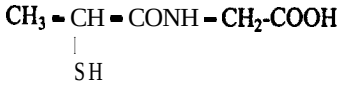
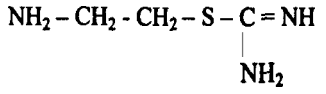
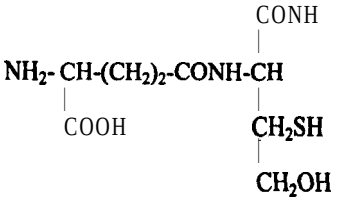
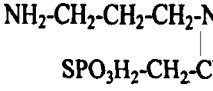
Radioprotector	Structure	Molecular weight	Dose	Biological material	DRF	Effect	Type of radiation & dose rate	Ref. No.
Cysteine		121.20	40 mg/day	Male mice	1.19	Survival	^{60}Co-γ; 0.35 Gy/s	104
Cystamine		153.33	50 mg/kg	Wister rats	1.79	Survival	^{60}Co-γ; 0.063 Gy/s	105
Cysteamine		77.20	150 mg/kg	Rat cerebral cortex	1.30	Degeneration	^{60}Co-γ; 0.05 Gy/s	106
5-Hydroxy-L-tryptophan (5-HTP)		220.20	200 mg/kg	Male mice	1.20	Survival	^{60}Co-γ; 10.5 Gy	107
5-Hydroxytryptamine (5-HT)		175.20	3 mg/ 0.5 ml	Female mice		Survival	x-ray; 6.75 Gy	108
β-Mercaptopropionyl-glycine (MPG)		163.20	20 mg/kg	Male mice		Survival	^{60}Co-γ; 15 Gy	109, 110
β-Aminoethyl-isolhiouroniumbromide hydro-bromide (AET)		281.04	0.45 mM/kg	Mouse cells	1 20 to 1.34	Reduced frequency of polychromatic erythrocytes	^{60}Co-γ; 0.24 Gy/s	111
Glutathione		307.33		Ehrlich ascites tumor cell lines		Average DNA content per cell	x-ray; 20 Gy	112
WR-272 1		232.25	400 mg/kg	Male mice	1.75	Survival	^{137}Cs-γ; 0.0195 Gy/s	113

Table 2. Radioprotectors under experimental and clinical investigations

Compound	Mode of action	Efficacy	Toxicity	Ref. No.
Alcohols	Radical scavenging	Good	High	114
Dimethyl sulphoxide	Radical scavenging	Good	High	115
AET	Radical scavenging	Good	High	61,116, 117
Mercaptoethylamine	Radical scavenging	Good	High	118
Serotonin	Local tissue anoxia	Good	High	119
WR-272 1	Radical scavenging Response modifier	Good	High/ moderate	120-124
Vitamin E	Oxidative damage	Low-moderate	Low	125-126
DNA-Hoechst	Inactivation of free and DNA radicals	Good	Low	12, 13,37,38
Diltiazem	Calcium antagonist	Moderate	High	17, 48,49
Bacterial endotoxin	Immunomodulation	Moderate	High	127
Cytokines	Modify biological response	Moderate	High	128
Prostaglandins	Modification of membrane receptors	Low	Moderate	129
Deoxyspergualin	Immunomodulation	Moderate	Low	129
Herbal extracts	Radical scavenging, antioxidant, and immunomodulation	Moderate	Low	82-90, 93-95
5-HTP	Radical scavenging	Good	Low	18, 58
S-HTP + AET	Radical scavenging, membrane receptor modulation	Good	Low	16, 50-57,60, 65, 130-135
Polysaccharides, glucan	Immunomodulation	Moderate	High	128
a-TMG	Oxidative damage	Moderate	Low	34, 35

are irradiated directly or react with high energy free radicals and their intermediates, the targets themselves become ionised or transformed into the free radicals. The end result is disruption of molecular structure and function, leading to altered cell metabolism and injury.

Radiation-induced damages in DNA in cellular milieu include damaged purine and pyrimidine bases, single-and double-strand breaks, removal of bases and cross-linking of DNA with adjacent protein molecules. These changes, depending on their type and extent, are expressed functionally in a variety of ways, including cell death. Radiation through free radicals can produce a variety of alterations in membrane lipids and associated proteins. This can also contribute significantly to altered cellular function and cell death[8-10]. Further, radiation effects that lead to incapacitation and performance decrement, appear to occur very rapidly and are not related to DNA damage. Some of these are related to radiation-induced membrane damage. Lipid peroxidation takes place after irradiation or free-radical attack[9,10]. This leads to the production of short chain fatty acyl derivatives, lipid-lipid cross-linking as well as protein-protein and lipid-protein cross-linking, oxidation of accessible amino acids, protein denaturation, and scission of disulphide bonds in proteins. Functionally, these changes can be expressed as altered membrane fluidity and permeability, which could trigger the release of potent physiological mediators.

Activity of enzymes associated with these membranes may be altered by the disruption of lipid microenvironment and protein structure.

The radiation-induced damages occur as a sequence of events traversing a time scale from a picosecond to few hours. Earliest time is that stage at which radioprotection begins to function. Radioprotecting molecules compete with free radicals so that radiation-induced damage to cellular biomacromolecules are hindered. Between 10^{-7} and 10^{-3} s, the reactions of most water-produced free radicals are essentially complete".

At this time (10^{-6} s), radioprotectors begin to repair chemical lesions in target molecules by reducing oxidative damage induced by the free radicals. Between 10^{0} s and 10^{4} s, endogenous enzyme systems come into play to remove the more slowly reacting products of water radiolysis and to repair the chemical lesions produced in cellular macromolecules[10].

3. SCREENING & ASSESSMENT OF RADIOPROTECTORS

A number of *in vitro* as well as *in vivo* systems have been extensively used for screening potential radioprotectors. While wholebody-irradiated lower mammals (mice and rats) have been the choice models for evaluating the efficacy as well as toxicity at the systemic level, studies on the mechanisms of action have been invariably carried out using established cell lines of human, murine, and rodent origin.

3.1 *In Vitro* Studies

A great deal of work on radioprotection *in vitro* has been carried out using monolayer cultures of transformed, but non-malignant cells (eg, fibroblast) as well as transformed (eg, tumor) cells. The efficacy of radiomodifiers is assessed by evaluating their ability to enhance the degree of survival[12,13] in an irradiated cell population using the macrocolony assay[14]. Effects on the proliferation of irradiated cells have also been used as assay parameters *in vitro*.

3.2 *In Vivo* Studies

Potential radioprotectors are screened for their effectiveness by studying the animal survival against lethal dose as end-point. Some of the reasons for choosing mice are:

(i) They are relatively inexpensive

(ii) They are housed with moderate space requirement

(iii) They are susceptible to radiation damage and protection

(iv) They are easy to handle

(v) They are available as standardised strains in large numbers with known radiosensitivity index for different strains[15-17].

To determine the general applicability of a particular radioprotector and to facilitate the extrapolation to human subjects, it is desirable to demonstrate protection over a range of species like murine, rodents, canine, and primates. However, tolerance, toxicity, and effectiveness vary with animal species and are influenced by the strain, sex, age, and general condition of the animal.

The routes of administration, eg, intravenous (i.v.), intraperitoneal (i.p.), intramuscular (i.m.) and oral (o), markedly affect the protective action and toxicity of the compound. Intravenous route helps in rapid distribution of drug, but toxic reactions are more common. In general, oral administration is less effective than intraperitoneal or intramuscular administration, due to poor absorption and breakdown of the drug by the acid in the stomach, digestive enzymes, intestinal flora, or metabolism in the liver.

The effectiveness of a potential radioprotector is always evaluated prior to its use in combination with radiation. Generally, the LD_{50} (dose that produces lethality in 50 per cent of the animals) is obtained in the animal model to be tested.

4. DOSE, DOSE RATE, QUALITY OF RADIATION & PRE-EXPOSURE TIME

The other factors that influence the observed effects are the type of radiation, absorbed dose, dose rate, and the rate of availability of radioprotectors[18].

Lethal dose varies with the strain of mice. The LD_{50} of radiation can vary from 7 Gy to 10 Gy depending on the strain. A dose of 4 Gy is generally considered sublethal. Most commonly, ***in vivo*** radioprotection studies are performed at radiation doses in the range LD_{50} (30) or LD_{100} (30). In general, radiation dose rates vary from 40-200 cGy/min. Much of the currently available information on radioprotectors has been on the low linear energy transfer (LET) radiation like x-rays or y-rays.

The time interval between radioprotector administration and maximum protection varies markedly from one compound to another. Optimum pre-exposure time must be determined for each compound. For most radioprotectors, maximum protection is achieved when administered between 15 min to 60 min before irradiation[19].

5. EVALUATION CRITERIA

The magnitude of chemical protection against radiation damage is most commonly assessed either by comparing percentage survival between the treated and the control groups at a selected lethal radiation dose, or by computing a dose-reduction factor (DRF) for the drug under study. Percentage survival requires fewer animals and is more easily determined than DRF. To determine the DRF, groups of treated and control animals are exposed to several levels of radiation and observed for survival from day 1 to day 30. The LD_{50} of radiation is determined for the control group (D_1) and the protected group (D_2). The DRF is computed[19] as D_1/D_0.

5.1 Endogenous Spleen Counts

This method is based on the observation that recovery from radiation injury is accompanied by the formation of macroscopically identifiable nodules in the spleen, the number of which is inversely related to radiation dose. Heamopoetic radiation injury is linked to blood cell development. All of the mature elements of the blood are ultimately derived from bone marrow pluripotent stem cells[20].

Following even low doses of radiation, stem cell and progenitor cell numbers are significantly reduced and the potential to generate new heamopoetic elements is compromised. Heamopoetic cell survival, proliferation, and differentiation have now clearly been demonstrated to be regulated by cytokines, specifically known as colony-stimulating factor (CSF), interleukins, and poetins. When radioprotectors are incorporated prior to radiation exposure, endogenous spleen counts have been found to increase. Different immunomodulators influence the survival-enhancing effect. That is how their protective and therapeutic effects in irradiated animals have been obtained.

6. RELEVANCE OF FUNCTIONAL GROUPS IN RADIOPROTECTION

Radioprotection under consideration can be achieved by chemical and biological means. Different theories that have been propounded are:

(a) Radical scavenging

(b) Hydrogen donation

(c) Mixed disulphide formation

(d) Release of endogenous radioprotectors

(e) Biochemical shock

(f) Hypoxia

(g) Target stabilisation.

Whether it is a chemical or a biological radioprotector, structure-activity relationship has gained importance since 1940. The general rule, that has emerged from intensive investigation of aminothiol radioprotectors, holds that the necessary requirements for radioprotectors for their activity are a two-or three-carbon backbone separating a thiol or potential thiol and a primary or secondary amino-functional group, $R\text{-}NH\text{-}C_2\text{-}C_1\text{-}SR'$. While this rule is surely an oversimplification, its precepts have generally been upheld with few exceptions.

6.1 Carbon Chain

Certain hydroxylated compounds, especially those carrying a hydroxyl group at the 2 position, were active when the amino group carried an alkyl chain. 3-Amino-propyl phosphorothioates followed this generalisation, with 2-hydroxy-3-alkyl aminopropyl phosphorothioates showing some activity[21].

Functionalisation of either *R*, or R_2 in the series $H_2NC(R_1R_2)CH_2SH$ dramatically altered the toxicity and/or radioprotective activity. Incorporation of thiol functions into these alkyl groups greatly increased the toxicity of the compounds. Hydroxylation of these alkyl groups increased the efficacy of the compound relative to the non-functionalised compound, the phosphorothioates of this series were generally highly active with relatively low toxicity[21].

6.2 Thiol Group

A thiol group or a potential thiol group is generally necessary for radioprotective activity. Blocked forms of thiols (eg, thiosulphates, phosphorothioates, disulphides or other derivatives were most promising from which free thiols may be formed metabolically) were active to varying degrees for their ability to latentiate the thiol and alter the relative potency of the parent amino-thiol. The blocked thiols have generally been considered to be prodrugs, whereas the free thiols were thought to be the active form at the site of action. The function of the blocking group was to alter the pharmacokinetics or the rates of metabolism and excretion of the drugs[21].

6.3 Amino Group

The *N'*-(*n*-alkylamino) ethanethiosulphuric acid series ($RNH\ CH_2\ CH_2\ SSO_3H$) affords an interesting pattern of activity with full activity where *R* includes a straight chain of up to three carbon atoms. Introduction of a phenyl group onto the alkyl aminoethane thiosulphuric acid (resulting in compounds of the series $C_6H_5\ (CH_2)n\ NH\ CH_2\ CH_2\ SSO_3H$ resulted in a higher degree of protection for $n = 4$ and $n = 5$. Incorporation of methoxy group on the phenyl ring of 4-phenyl-*n*-butyl aminoethane thiosulphuric acid resulted in a higher radioprotective effect. Perhaps the best known alkylamino functionalisation is the group of aminoalkylaminoethane thiols and phosphorothioates $RNH(CH_2)nNH(CH)mSR'$, represented by the prototypic compound WR-2721. Varying the length of the carbon chain between the amino groups produced a peak of activity at $n = 3$. In contrast to the thiols, phosphorothioates in this class could be hydroxylated in the aminoalkyl amino group without loss of activity. As noted above, the compounds in which $n = 2$ and $m = 3$ were of comparable activity[21] when $R' = H$ or PO_3H_2.

6.4 WR-2721

In 1959, the US Army initiated a programme to develop radioprotecting drugs at the Walter Reed Army Research Institute and tested approximately 4400 compounds until 1973. WR-272 1 or amifostine, ie, S-2 (3-aminopropylamino) ethyl phosphorothioic acid. The SPO_3H group upon hydrolysis gets converted into -*SH* group. It has been found to be accepted globally after undergoing preclinical and clinical studies. It is used in cancer patients to reduce the toxicity of radiotherapy and chemotherapy (systemic toxicity). The phosphorylated aminothiols presented a major improvement over the earlier compounds wrt activity, tolerance, and duration of action, but still had undesirable side effects such as nausea, vomiting, and hypotension. It has been used successfully in protecting bone marrow[22], head and neck radiotherapy combined with chemotherapy[23], in protecting gastrointestinal tract[24], etc. A critical consideration in the implementation of protective strategies is that the tumor must not be protected. There has not been any evidence of tumor protection in clinical trials with WR-2721 in short and medium term follow up studies.

A large number of studies have been carried out by Yuhas[25-27] on WR-2721 in understanding different pharmacological and toxicity aspects in radioprotection. Different biological factors which affect radioprotective efficacy and how differential chemoprotection is offered by WR-2721 to the normal and malignant tissues, have been elaborated.

6.5 Vitamins as Radioprotectors

In recent years, there has been an increasing interest in the effect of micronutrients (ie, vitamin E, vitamin C, retinoic acid, selenium, and zinc) on cancer[28] based on the theory that free radicals play a role in carcinogenesis[29]. Vitamin E (a-tocopherol) is known as a micromembrane stabiliser[30]. It protects against cell membrane damage from lipid peroxidation by scavenging free radicals[31]. Clinical use of vitamin E has been found to be safe even at an oral dose[32] as high as 3200 mg/day. Vitamin C and vitamin E along with butylated hydroxytoluene have been demonstrated to be effective in not only inducing glutathione S-transferase activity, but also protecting against chemical carcinogenesis in rats[33].

More recently, tocopherol monoglucoside (a-TMG) has been found to afford protection against radiation damage when administered after irradiation. Protection against lethal irradiation doses as well as against sublethal irradiation doses has been reported. A variable DMF value was however observed for the protection of bone marrow cells from radiation-induced cytogenetic damage, viz., chromosome aberrations and micronuclei[34]. Interestingly, in tumor-bearing mice, administration of TMG does not appear to protect tumor cells against radiation-induced DNA damage, while protecting the normal cells[35]. Protection afforded by TMG when administered post-irradiation suggests its possible utility for protection against accidental radiation exposures.

6.6 Bisbenzimidazole-based DNA Ligands

The clear role of DNA as the critical molecular target of radiation action has prompted the development of radioprotective agents that directly interact with DNA. The DNA ligands, bisbenzimidazole Hoechst-33258 (H-258) and its analogue Hoechst-33342 (H-342), which binds selectively in AT-rich regions of the DNA, minor groove have been shown to protect DNA against radiation damage in aqueous solutions and cells. Studies with plasmid DNA on strand break formation and DNA sequencing gel analysis have indicated the reduction in overall level of strand breaks as well as pronounced inhibition of breakage in regions that coincide with known binding sites of the ligand[36].

The mechanisms of radiomodification by Hoechst compounds are not yet clear, although their ability to scavenge OH radicals as well as quench DNA radicals has been demonstrated in aqueous solution[37]. Recently it has been shown that non-toxic doses of both H-342 and H-258 can provide significant protection against wholebody irradiation in mice[38]. Considerable reduction of cytogenetic damage in the bone marrow cells and longer animal survival have been observed. Intravenously administered H-342 binds largely to the nuclear DNA in euoxic cells but less to the hypoxic tumor cells, and therefore, may not protect hypoxic tumor cells to a significant extent[39]. Therefore, the radiosensitising effects of H-342 have also been investigated in human and murine tumor cells *in vitro* as well as *in vivo*.

Available evidences show that addition of H-342 one hour before irradiation can protect cells [human glioma brain malignant glioma (BMG -1) and ehrlich ascites tumor (EAT)] against DNA and cytogenetic damage as well as cell death. Addition of H-342 immediately following irradiation sensitises cells[40].

In the ehrlich ascites tumor-bearing mice, intravenous administration of H-342 one hour before focal irradiation of the tumor enhanced radiation-induced growth delay in a dose-dependent manner and resulted in complete regression of the tumor in more than 50 per cent of the animals at a dose of 10 mg/kg body weight. At this dose, a cure rate (tumor-free survival for more than 100 days) of 55 per cent was observed. Taken together, these results clearly indicate that the DNA ligand H-342 can be a useful radiomodifier in tumor radiotherapy as it can protect the normal cells while sensitising the tumor cells[41].

Recently, two more analogues of Hoechst-33258, namely 5-(4-methylpiperazin-1-yl)-2-[2′-3,4 dimethoxyphenyl)-5′-benzimidazolyl] benzimidazole (DMA) and 5-(4-methylpiperazin- 1 -yl)-2-[2′{ 2″(4-hydroxy-3 methoxyphenyl)-5”-benzimidazolyl)-5’-benzimidazolyl] benzimidazole (TBZ) have been synthesised, which demonstrate radioprotective effects similar to the parental *in vitro* compound, but with minimum toxicity[42].

6.7 Non-protein Sulphydryl Release

One of the effects of at least some exogenously administered thiol or disulphide radioprotectors is to displace endogenous radioprotectant compounds that are contained in natural nonprotective mixed sulphide forms within the cell.

This non-protein sulphydryl (NPSH) release hypothesis[43-46] suggests that radioprotection results from the released endogenous sulphydryl compounds (mainly glutathione), which function, in turn, to prevent radiation damage by radical scavenging and hydrogen donation. This hypothesis is based on the observation that the ability of sulphydryl compounds to increase cellular levels of NPSH correlates well with their radioprotective effectiveness[44-47]

Glutathione may exert protective activity in ways that may not be mimicked by other thiol-containing radioprotectors[47]. However, recent research on the nature of those thiols present in naturally occurring protein-thiol mixed disulphides tends not to support the theory, because only a small fraction of the low molecular weight thiols bound to protein have been identified as glutathione.

Diltiazem is a benzothiazepine and calcium antagonist used in the treatment of cardiovascular diseases. It has been observed to protect against bone marrow damage and mortality in wholebody irradiated mice (10 Gy).

Endogenous colony formation unit (CFU) counts in spleen of mice administered 110 mg/kg body weight of diltiazem before 10 Gy wholebody irradiation have been found to be 6-times more than in the irradiated animals. Pretreatment with diltiazem abolishes radiation-induced lifespan shortening and post-irradiation (10 Gy) administration of diltiazem marginally (- 15 %) enhances the survival.

Although the mechanism involved in the radioprotection by diltiazem is unknown, possible free radical scavenging, prevention of calcium influx, and reduction of ATP levels resulting in reduced enzyme-mediated cell death, have been proposed[17,48,49].

7. RADIOPROTECTION BY COMBINED AGENT REGIMENS

The basic reason for combination of radioprotectors is to obtain a reduced toxicity with greater protective efficacy and therapeutic potential. By using a single radioprotector, this is most often not achievable. Search for more active and less toxic than MEA, AET, 5-HT, or WR-2721 against acute radiation-induced death in mammals has necessitated the use of most active mixtures of chemical protectors. The most effective radioprotective agents exhibit toxicities that can limit their usefulness. It may be possible to use a combination of agents with different radioprotective mechanisms of action at less toxic doses, or to reduce the toxicity of the major protective compounds by adding another reagent. The known mechanisms of action of potential radioprotective agents and varying effects of different doses and times of administration in relation to radiation exposure must be considered when using combined agent regimens. The combined radioprotector regimen namely 5-HTP + AET has been investigated extensively.

7.1 Combination of 5-HTP & AET

The combination of 5-HTP and AET (5:1 by weight ratio) has been proved to be much better for radioprotective purposes than 5-HTP alone against a lethal 'y-ray dose of 10.5 Gy and 12.5 Gy, without any significant toxicity to any other tissue or organ except kidney and testis. Further, it has been observed that kidney damage in 50 per cent of the animals and testis damage in all animals are completely reversed at some stage [16]. A complex is formed between 5-HTP and AET and radiation-induced changes in the complex have also been noted[50].

7.2 Combination of 5-HTP & MPG

A combination of 5-HTP and MPG protects the wholebody of mice up to a dose of 10.5 Gy, but the effect was significantly reduced at 12.5 Gy. Similarly, a combination of 5-HTP + cysteamine has been found to provide protection against 10.5 Gy, which is marginally higher than 5-HTP alone[16]. In all these studies with the combinations, the thiol drugs (eg, MPG, MEA, etc) were ineffective in rendering protection after wholebody y-irradiation.

7.2.1 Mechanism of Radioprotection by 5-HTP+AET in Different Biological Systems

It has been found that 5-HTP + AET in the weight ratio of 5:1 (ie, 100 mg; 20 mg) provides protection to mice jejunum[51], blood[52], and urine[53], kidney, sperm cells[54], sialic acids in testis and plasma cells[55], bone marrow[56], splenic cells[57], etc in the range 4 Gy to 12 Gy. Normalcy appeared in these different cells at different time intervals after different doses of irradiation. The working hypothesis proposed is that since S-HTP or AET alone does not provide protection against lethal dose, the possibility of formation of a complex between 5-HTP and the thiol drug cannot be ruled out. It might be that the thiol drugs help S-HTP at the receptor sites by some unknown mechanism and enhance the radioprotective action of 5-HTP.

The different radiolytic products that are formed from 5-hydroxy-L-tryptophan and 5-hydroxy tryptamine have been indicated[58]. Binding of 5-HTP with AET is in the form of a secondary amide. The complex is stable for 6 days at room temperature. With y-radiation, there is a consistent decrease in p*H* for 5-HTP and AET, but for 5-HTP + AET combination the change in p*H* is biphasic[34]. The changes that occur in 5-HTP upon y-irradiation are deamination from the side chain, decarboxylation from the side chain, intermolecular hydrogen bonding through 5-hydroxyl group, which gets deformed upon irradiation, and cleavage of the double bond in the β carbon atom in 5-HTP takes place upon irradiation[59,60].

The AET gets converted to MEG and this conversion is facilitated in alkaline p*H*. Auxochromes like

$$SH,\text{-}S\text{-}C{=}NH,\ NH_3^+ \text{ and } H_3N^+\text{–}C{=}NH \quad (NH_2)$$

are responsible for increased absorption and fluorescence with increase in alkalinity. IR studies indicate that C-S-C linkage of AET gets distorted as a result of γ-irradiation[61]. Perturbation and stretching of $=NH$, $-NH_2$ and $H_2N\text{-}C{=}NH$ takes place as a result of y-irradiation. Protection mechanism of AET is by its conversion to MEG and scavenging of OH° radicals up to 2.5 Gy as evidenced by analytical techniques[61,62]. 5-HTP + AET complex does bind to DNA of different types of cells mentioned earlier where they contained DNA. Binding the complex provides protection by not allowing the free radicals to interact with DNA directly.

The molecular weights of 5-HTP and AET are low and even after complex formation, when it is incorporated intraperitoneally, it is possible that either the complex binds to the cell membrane and alters its functional aspect, or it penetrates the cell membrane and interacts with cytoplasmic and nuclear structures.

A combination of 5-HTP+ AET (5: 1 by weight ratio) has proved to be much better for radioprotective purposes than 5-HTP alone against lethal doses of 10.5 Gy and 12.5 Gy of y-irradiation. Daily administration for 15 days in normal, double, triple, and quadruple the radioprotective dose of 5-HTP + AET formulation in Wistar rat has caused no damage to any tissue or organ except kidney and testis. Routine hematological examination and biochemical estimations of blood and urine have yielded normal values. Reversal studies done after 30 days of stopping the drug administration have shown that in 50 per cent animals kidney histological damage disappeared and in all the animals, testis damage was completely cured. No neurotoxic symptom was noted at any stage[63]. 5-HTP + AET was encapsulated in RBC membrane ghost and it was found to provide radioprotection against lethal dose at about 1/200th amount needed for radioprotection compared to free 5-HTP + AET. It has been found to protect different organs against radiation damage[64,65]. It has been suggested that the combination can be made more versatile by mixing vitamin C, vitamin E, and salts[66] of manganese *(Mn)* and zinc *(Zn)*.

Most of the active sulphur-containing radioprotective chemicals are toxic to living systems. The combined regimen of sulphur-containing radioprotectors decrease DNA synthesis and prolong the cell cycle of stem cells in small intestine. But in protective dose, nucleus, mitochondria, and endoplasmic reticulum get structurally deformed[67].

It has been found that polysaccharides alone render radioprotection against 6.5 Gy x-rays. The four polysaccharides extracted from yeast ***Saccharomyces cerevisiea*** or from yeast ***Rhodotorula rubra*** displayed a significant radioprotection with a dose-reduction factor close to 2. The protection is offered to the bone marrow. The erythropoetic system does not appear to be involved in the protective action[68].

Organic zinc salts (eg, zinc aspartate, zinc histidine, zinc orotate, and zinc acetate) reduce the fall of heamatocrit, thrombocytes, erythrocytes, and leukocytes in irradiated mice. Zinc-aspartate affords synergistic heamatological protection and does not enhance the toxicity of WR-272 1. Probably, zinc aspartate stabilises exogenous and endogenous thiols by forming zinc-thiol complexes[69].

WR-2721 when mixed with MPG in the ratio of 50 mg/kg: 20 mg/kg protects bone marrow cells against radiation dose as determined by chromosomal aberration studies with increase in dose of drug administered protection increased. Administration of MPG after WR-2721 helps to maintain the higher GSH level compared to WR-272 1 alone[70].

After sublethal dose of irradiation, WR-272 1 is considered the best for radioprotecting normal tissues as DRF = 4.5 for mouse bone marrow chromosome as biological end-points. MPG showed a DRF = 2.6 for the same dose and biological end-point. By combining these two drugs, it is possible to minimise toxic effect and increase protective effect[71]. Toxicity of WR-2721 could be reduced using ***Ocimum sanctum.*** This particular combined regimen significantly enhanced bone marrow radioprotection against radiation dose. This indicates that flavanoid compounds present in ***Ocimum sanctum*** are capable of giving increased radioprotection[72].

Biological-response modifiers like glucan are potential therapeutic agents as these stimulate immune system to fight cancer. Glucan has a DRF of 1.2 to 1.3, but when it is mixed with WR-2721, the DRF increases to 1.5-l .6. Glucan appears to reduce the behavioural toxicity of WR-2721[73].

These are some of the examples that indicate the efficacy of combined agents as a promising approach for maximising radioprotection with minimal toxicity.

8. RADIOPROTECTION

8.1 Behavioural Radioprotectors

Under many circumstances, exposure to ionising radiation can impede performance significantly. After large doses, lethal or supralethal, behavioural effects are rapid (within minutes) but up to 10 Gy, performance deficits develop rather slowly and are long-lasting. All tasks are not radiosensitive equally, tasks with complex and demanding requirements may be disrupted even at low radiation doses (< 1 Gy). Combined injuries can act synergistically with radiation exposure to greatly increase behavioural deficits. Most of the radioprotectors[74] developed todate are themselves behaviourally toxic at radioprotective as well as non-radioprotective doses, and the adverse effects are further aggravated in the presence of radiation. A very limited number of radioprotectors have been found to give behavioural radioprotection at very low, almost non-toxic doses[75].

With accidental radiation dose, supralethal doses produced early transient incapacitation and early performance decrement, invariably followed by confusion, irritability, restlessness, coma, and death. Lower radiation doses may produce mild but persistant behavioural changes characterised by weakness and fatigue[76]. The different radioprotectors that have been tried on rats to observe conditioned taste aversion for a dose up to 1 Gy are diltiazem, ondansetron, Hoechst, and ginseng at dose levels of 5 mg/kg, 2 mg/kg, 2 mg/kg, and 50 mg/kg body weight. Relative saccharin consumption has come to closest value of unirradiated control for ginseng. WR-2721, an excellent radioprotectant, has been extensively evaluated for its side effects and has been found to be behaviourally toxic. In all the species tested (eg, mice, rats, and monkeys), it disrupted behaviour and performance when administered alone, and in the presence of radiation, degradation was further aggravated[77]. The compounds that have been tried are metoclopramide, dazopride, and

zacopride for monkeys after exposure to 8 Gy y-radiation. These drugs are effective anti-emetics'*.

8.1.1 Practical Application of Behavioural Radioprotectors

For the space explorers beyond earth's protective atmosphere, emesis will be a problem due to space radiation and motion sickness, ie, space adaptation syndrome. A study in monkeys to test for synergy between radiation and motion reported that the emesis ED,, was 4.5 Gy for radiation alone, and 2.6 Gy for radiation plus motion[79]. Mechanisms of emesis produced by radiation and motion are different, so combined drug regimens are needed[80].

The important point here is that performance requirements can change traditional toxicity end-points, and thus, determination of behavioural toxicity combined with lethality may be more meaningful than looking at lethality alone. Finally, since these end-points differ in terms of effect levels, it may be the reason that finding behavioural radioprotectors has not been easy and /or that the behavioural findings reported may be negative.

8.1.2 Clinical Implications of Behavioural Radioprotection

Recently, there has been considerable interest in the use of implanted radionuclide sources for the treatment of brain neoplasms, but focal irradiation injury poses the most serious problem. It has been also observed that during cranial radiation therapy, there is substantial risk of intellectual deterioration in patients, leading to significant alterations in their quality of life[81].

8.2 Herbal Radioprotectors

The rationale for using herbal preparations as radioprotectors is that these have proved to be non-toxic to human beings and are already being used for different types of ailments, readily available, inexpensive, and works upon digestive system and heamatopoetic system[82-84].

Oral administration of Liv-52 has been shown to protect mice against wholebody irradiation at moderate doses (- 3 Gy). Radioprotective activity has been attributed to the inhibition of lipid peroxidation by increasing the level of a-tocopherol and glutathione reduction in the cytogenetic damage[85,86].

Both orientin and vicenin obtained from the extract of *Ocimum sanctum* protect against death from gastrointestinal syndrome as well as from bone marrow syndrome when injected intraperitonially before wholebody exposure to lethal y-radiation (11 Gy). Though optimum dose for radioprotection was found to be 50 μg/kg body weight, 100 μg/kg body weight dose also did not have any acute toxicity. The protection by vicenin with DRF 1.37 was slightly better than orientin[84] with DRF 1.30. The protection has been ascribed to the antioxidant property to inhibit lipid peroxidation and free radical scavenging property of these compounds[83].

8.2.1 Mentha Piperita

A dose of 1 g/kg body weight per day when administered before a y-radiation dose of 8 Gy was found to protect Swiss Albino mice. The DRF value was found to be 1.78 with a biological end-point of different types of chromosomal damage (eg, dicentrics, sister chromatid exchange, acentric fragments, etc). A combination of antioxidative and antimutagenic activities via modulation of DNA repair processes may be held responsible for the radioprotective effect of *Mentha piperita*[87].

8.2.2 Ginkgo Biloba

Extract (Eglo 76 1) containing flavonoids and terpenoids at a dose of 3 x 40 mg/person for two months gave protection to persons of Chernobyl accident. The radiation exposure varied from 1 cGy to 1.95 Gy. The biological end-points were different types of chromosomal aberration (eg, ring formation, dicentrics, telomeric expulsions, chromatid breaks, etc.). Anticlastogenic effect was observed in the plasma of the persons irradiated. This anticlastogenic effect is due to oxidative stress. So, it can be influenced by antioxidant *in vivo*. Prophylactic use of antioxidants can be discontinuous, thus reducing the cost of intervention trials[88]. Superoxide anion, which is directly or indirectly implicated in cell

damage, is scavenged by ***Ginkgo biloba*** extract. Its antiradical effect was demonstrated by low-temperature electron spin resonance and in a non-enzymatic system by polarographic determination[89].

Mammary tumorigenesis was induced in female rats with a dose of ^{60}Co-γ rays for a wholebody irradiation of 1.5 Gy. From a tumor induction value of 70.3 per cent, there was a reduction of 18.5 per cent of tumor incidence when the rats were fed curcumin during initiation stage. Appearance of first palpable tumor was delayed by 6 months in the curcumin-fed group. By histological examination, the protection of adenocarcinoma (16.7 %) in total tumors in the curcumin-fed rats was found to be decreased to half that in (32.1 %) in the control group. At the time of irradiation, curcumin did not have any effect on organ weight or on the development and differentiation of mammary glands of pregnant rats. The serum concentration of fatty acids, thiobarbituric acid-reactive substances, and ovation and pituitary hormones, except LH, remained at the control level. The results suggest that curcumin does not have side effects and is an effective agent for chemoprevention acting at the radiation-induced initiation stage of mammary tumorigenesis[90].

The results seem to be promising from mice model studies. There is a scope to further explore the potentiality of these herbal drugs for higher species. In some of these extracts, the active principle of the working of these herbal extracts has been explained. As these extracts contain a large number of ingredients, the mode of action is complex. The mechanism of radioprotection might be antioxidant, radical scavenging, and immunomodulation. Accessibility of different organs by oral route, relatively easier excretion of unwanted compounds after absorption of active and effective components are some of the promising points for these herbal drugs. But to put these herbal drugs as radioprotectors, one needs to know the following:

(a) The exact composition

(b) Mechanism of action of each component

(c) Possibility of synergistic action between different components

(d) Exploration regarding mechanism of action as radioprotectors

(e) Elimination of the toxic components from the extract

(f) Pharmacokinetics of the different components in the body organs

(g) Some physico-chemical parameters like membrane permeability, interaction possibilities with cellular and nucleolar membranes, diffusion coefficient of the components, interaction possibilities with body fluids, biodistribution etc.

8.3 Prospective Aspects of Radioprotectors

Unfortunately, none of the radioprotectors available today ideally meets all the requirements of a radioprotector mentioned before. The limitations of chemical radioprotectors are:

(a) These have to be administered before irradiation.

(b) Their toxicity cannot be totally eliminated.

(c) These are not always suitable for oral administration.

(d) The metabolic products take long time for excretion.

Although combining more than one radioprotector with different mechanisms of action would be one of the approaches, attempts to use such combinations in bigger animals have met with limited success either due to poor protection or higher toxicity. However, design and identification of new chemicals with low systemic toxicity and DRF values of 1.5 or more still holds promise for the future[91]. Further, the toxicity can be brought down substantially by encapsulating the radioprotectors (singly or in combination) in erythrocyte membrane ghosts, liposomes, nanoparticle, or polystyrene microspheres. Thus, these can be targeted more easily to the organs of interest and also eliminate the requirement of large doses without compromising the efficacy. Alternatively, the use of complex natural products (herbal preparations) from plants, fru'its, leaves, etc, has received much attention in the last decade and appears to be favourable in many respects as compared to chemical radioprotectors[84,92-94]. These

include lower toxicity in human beings (as many of these are used in alternative medicine in Asian countries for centuries), are easily available and inexpensive, and have shown good radioprotection in preclinical studies.

Further, accessibility to different organs following oral administration, relatively easier excretion of undesirable toxic components after absorption of active and effective components, are some of the other promising aspects. Elucidation of the mechanisms of action, partial purification (fractionation) to reduce toxicity without compromising efficacy, information on pharmaco-kinetics, and bioavailability for many of the currently investigated complex natural products, should make these an attractive class of radioprotectors in the future. Identification of two flavonoids, orientin and vicenin as active components of *Ocimum sanctum* has been done[83,84,95]. Elucidation of their mechanisms of action is an important advancement in this direction. Further, combining some of the chemical radioprotectors with herbal extracts, as has been shown in the case of WR-2721 and *Ocimum sanctum*[72], is also an attractive approach.

Diseased sites in all the organs namely brain[96,97], easophagus[98], lungs[99], breast[100,101], kidney[102], cervix[103] are accessible to different types of chemotherapeutic agents. It is possible that the onset of carcinogenesis or tumor genesis due to ionising radiation exposure can be regressed by suitable choice of chemical radioprotectors with proper combination of radiotherapy. It has been recently observed that radioprotectors present in herbal extracts show minimum toxicity and are tolerated to the maximum extent. If the active principles of their radioprotective efficacy could be worked out, these may prove to be of utmost use. Alternatively, if the synthetically prepared radioprotectors are so designed that these will give minimum toxicity and maximum radioprotective efficacy, these may also be developed further.

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