# Protective Effects of IMOD and Cimetidine against Radiation-induced Cellular Damage

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## ABSTRACT

Radiation damage is to a large extent caused by overproduction of reactive oxygen species (ROS). Radioprotectors are agents or substances that reduce the effects of radiation in healthy normal tissues while maintaining the sensitivity to radiation damage in tumor cells.

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Recently, a new herbal-based medicine with immunomodulatory capacities, Setarud (IMOD), was introduced as an additional therapy in various inflammatory diseases and HIV infection.

IMOD is a mixture of herbal extracts enriched with selenium. Selenium confers protection by inducing or activating cellular free-radical scavenging systems and by enhancing peroxide breakdown. This article suggests that nontoxic amount of IMOD and cimetidine have radioprotective properties and could reduce cytotoxic effects of radiation.

## Keywords

Radioprotection, Cimetidine, IMOD, Immunomodulator, Free Radical

## Introduction

Realization about the adverse effects of radiation began immediately after the discovery of X-ray in the form of skin cancer. Simultaneously, the awareness about existence of radionucleides intensified the threat of radiation. Rapid advancement in technology also further added varied kinds of radiation stresses [1-3].

Radiation damage is to a large extent caused by overproduction of reactive oxygen species (ROS) which cause disruption of membrane lipids leading to subsequent formation of peroxide radicals. Moreover, certain cells have higher levels of reactive oxygen species (ROS) than normal cells, and ROS are, in turn, responsible for the maintenance of cancer phenotype. There is an equilibrium between a free radical (FR)/reactive oxygen species (ROS) formation and endogenous antioxidant defense mechanisms, but if this balance is disturbed, it can produce oxidative stress. Oxidative stress, which is the imbalance between oxidant and antioxidants in favor of the oxidants, can result in injury to all important

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cellular components like proteins, DNA and membrane lipids causing cell death [3-6].

Although radiation therapy remains one of the most effective modalities for neoplastic disease, the damage caused by ionizing radiation (IR) in the small intestine and bone marrow remains a concern. A major goal of radiation oncology is the radioprotection of normal tissues to improve the therapeutic index. In addition, nuclear accidents lead to risk of radiation exposure, which can cause radiation-induced injury; therefore, effective therapeutic remedies are urgently needed, and identifying effective and useful substances for the prevention or treatment of intestinal and bone marrow injury due to radiation exposure are critical [7-10].

Radioprotectors are agents or substances that reduce the effects of radiation in healthy normal tissues while maintaining the sensitivity to radiation damage in tumor cells. They have the potential to protect non-tumor tissues from the cytotoxic effects of the ionizing radiation, with a relevant impact on the therapeutic index of the radiotherapy treatment [11-13].

Waller Reed Army Research Institute synthesized and tested over 4,000 compounds and found the most effective compound to be WR-2721 (Amifostine) [14]. It is currently being used in cancer patients to reduce the side effects of radio- and chemotherapy. It is limited in use due to its cumulative toxicity in daily administration with radiotherapy, which is manifested as nausea, vomiting, hypotension, allergic reactions, etc. [15-17].

Thus, there is still an urgent need to identify novel, nontoxic, effective and convenient compounds to protect humans [18, 19].

Due to water radiolysis, the most abundant intracellular compounds and various types of free radicals are generated such as hydroxyl radicals ($OH^{\cdot}$), hydrogen radicals ($H^{\cdot}$) and solvated electrons [e - (aq)]. In the presence of oxygen, reactive oxygen species (ROS) such as superoxide anion (O2 ) and hydrogen peroxide (H2O2 ) are also formed leading to induction of more DNA damage and radiation cytotoxicity in cells [20-22]. $OH^{\cdot}$ is generally considered the most damaging of the oxygen-based free radicals and it is believed to account for an estimated 50% of the total damages induced by free radical mechanisms [21, 23].

Cimetidine, an antagonist of histamine type II receptors, usually used for peptic ulcer treatment, has been shown to play a role in immune system by anti-suppressor cell activity [24] and also when used with radiation effectively helped recovery of lymphohematopoetic system. At cellular level, it was effective against the clastogenic effects of gamma rays and low doses of neutrons [24, 25].

Cimetidine, a selective histamine-2 receptor antagonist, has attracted interest because of its potential as an immune response-modifying drug. Most data suggest that cimetidine has a stimulatory action on the immune system, possibly by blocking receptors on subsets of T-lymphocytes and inhibiting histamine-induced immune suppression. Several studies have shown that cimetidine can affect a relative number of CD8 + ve lymphocytes and increase the NK cell activity as well as the antibody-dependent cellular cytotoxicity. Cimetidine has also been used successfully to restore immune functions in patients with malignant disorders, hypogammaglobulinemia and AIDS-related complexes [26, 27].

The mechanism by which cimetidine reduces clastogenic effects of radiation is not well understood. We propose that it might act by a radical scavenging mechanism via enzyme catalysis [28, 31].

They can scavenge OH° with rate constant 1.6×1010 mol-1 s -1 and 7.5×109 mol-1 s -1 for cimetidine and ranitidine, respectively [32].

Recently, a new herbal-based medicine with immunomodulatory capacities, Setarud (IMOD), is introduced as an additional therapy in various inflammatory diseases and HIV infection. IMOD Treatment Skews T Helper Cell Polarization Toward Promotes TH2IL-

12p70 expression is necessary for TH1 differentiation, as inhibition of IL-12p70 skews T cells responses toward TH2 cytokines profile [33, 34]. Because IMOD inhibits the production of pro-inflammatory cytokines including IL-12p70, investigated whether IMOD modulated T helper cell polarization. DCs were stimulated with different concentrations of IMOD in the presence or absence of LPS [34, 35]. Subsequently, DCs were washed and mixed with Naïve CD4+ T cells and T cell polarization was investigated. Results show that IMOD-stimulated DCs skewed T cells responses is further supported by the attenuation of T cell activation by IMOD-treated DC. Thus, IMOD strongly counteracts with pro-inflammatory responses which might prevent immune-mediated tissue damage [34, 36].

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This drug is used for the treatment of human immunodeficiency virus (HIV) infection by increasing CD4 lymphocytes [39].

These cells are measured in the blood as CD4 and CD8 counts [39]. The CD4 count is a reflection of immune system efficiency; the lower the CD4 count, the weaker the immune system will be [37].

IMOD has been shown to affect immune responses in animal studies IMOD consisting of a mixture of herbal extracts (Tanacetum vulgare, Rosacanina and Urticadioica) supplemented with selenium. Different herbal ingredients of IMOD possess anti-inflammatory, anti-viral and immune -modulating properties; the lectin and polysaccharide fractions of U. dioica (nettle) exhibit anti-viral and anti-inflammatory properties [34-36].

Selenium is an essential trace element that plays a key role in protecting cells from oxidative stress, and selenium supplementation in the diet may reduce the risk of cardiomyopathy, cancer and immune disorders in humans [34, 40, 41].

## Discussion

Ionizing radiation causes harmful effects through the generation of free radicals. When water, the most abundant intra- and extracellular material, is exposed to ionizing radiation, decomposition occurs through which a variety of ROSs such as the superoxide radical, hydrogen peroxide (H2O2) and the hydroxyl radical (OH–) are generated. These ROSs formed in cells contribute to radiation injury in cells. Although all respiring cells are equipped with protective enzymes such as SOD and CAT or GPX, increased oxidative stress in cells that stem from ionizing radiation may overwhelm the protective systems, leading to cell injury [40-42]. SOD converts superoxide anion radical to H2O2, thus decreasing the amount of and the formation of peroxynitrite anion (ONOO–), a highly destructive product of the interaction between O2 and nitric oxide [42].

Radiation chemical studies have shown that free radicals are primarily responsible for the indirect effects of radiation. These drugs, when applied in vivo, also showed radioprotective effects on mouse bone marrow erythrocytes [24, 45].

Cimetidine was found more effective when used in vivo (Mozdarani and Gharbali 1993) [28]. This effect might be due to the augmentation of the presence of Sulphur atom in the compound which is important for their scav-

enging activity [46].

A study by S. Kabodanian Ardestani con¬firmed that cimetidine and ranitidine could control these changes; therefore, they can be used as radioprotective drugs [32]. H2-receptor antagonists are scavengers of hydroxyl radicals with a very high rate constant [47, 48].

H2-receptor antagonists effectively reduce the clastogenic effects of radiation with a dose reduction factor (DRF) of 1.5-2 in human lymphocytes in vitro. The way in which these drugs reduce the clastogenic effects of radiation might be via radical scavenging mechanism [46, 49].

IMOD is a mixture of herbal extracts enriched with selenium [38, 50]. Selenium confers protection by inducing or activating cellular free-radical scavenging systems and by enhancing peroxide breakdown [51, 52].

Selenium is an essential constituent of glutathione peroxidase. This enzyme destroys hydrogen peroxide and organic hydroperoxides by using reducing equivalents from glutathione [53]. Nontoxic levels of Na2SeO3 (selenium) significantly inhibit cellular transformation by x-rays, benzo[a]pyrene and tryptophan pyrolysate; studies show that when selenium is added to C3H/1OT-1/2 cells as Na2SeO3 at concentrations of 2.5 tiM, it inhibits transformation induced by x-rays and by two chemical carcinogens, benzo[a]pyrene, an environmental pollutant and tryptophan pyrolysate (Trp-P-2), a pyrolysis product from broiled protein foods [54, 55].

All three oncogenic agents are producers of free oxygen species for selenium inhibits radiation-induced agents [56].

Mutlu-Türkoglu et al. demonstrated a protective effect of selenium and vitamin E on rat intestine that correlated with an increase of intestinal GPX activity [57]. These results seem to indicate a radioprotective effect of selenium on normal tissues. Hehr et al. showed a radioprotective effect of selenium in normal tissues (fibroblasts) but not in tumor cells [58]. Schleicher et al. found a stronger radioprotective effect in human endothelial cell lines than in cervix squamous carcinoma cells [58-60].

Biologically active compounds of Laminaria digitata Khorbi, particularly oligoglucan Laminarin (a linear beta-1,3 glucan) were identified as immune-modulator enhancing monocyte-macrophage activity [61].

Homeostasis among leukocytes was obtained in short periods (3 weeks). According to the results revealed in this study, nutraceuticals with such radioprotective properties are strongly recommended in radiation

protection, particularly because some interventional procedures with long screening periods and multiple image acquisition may give rise to deterministic effects in both staff and patients [62-64].

Ching et al. (1993) demonstrated that histamine H2-receptor antagonists such as cimetidine, ranitidine and famotidine are, in addition to being good inhibitors of histamine-stimulated gastric acid secretion, highly powerful hydroxyl-radical scavengers [30, 65, 66].

H2-receptor antagonists such as cimetidine could inhibit hemopoietic reconstruction in regenerating bone marrow after sublethal gamma ray irradiation. Therefore, it is probable that cimetidine is unable to help bone marrow cell reconstruction after gamma irradiation [24, 30, 65].

Because of radioprotective effects of cimetidin and IMODE, the use of both drugs can cause more effective protection of cells from adverse effects of ionization radiation.

## Conclusion

Radioprotectors protect against the deleterious effects of ionizing mainly by scavenging by-products from the biological environment. Oxidative molecules or ion¬izing radiation may be an effective approach in diminishing undesirable effects of radia¬tion byproducts. This article suggests that nontoxic amount of IMOD and cimetidine demonstrate radioprotective properties which could reduce cytotox-

ic effects of radiation.

## Conflict of Interest

None

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