ABSTRACT

Eighty percent of cancer patients need radiotherapy at some time or other, either for curative or palliative purpose. To obtain optimum results, a judicious balance between the total dose of radiotherapy delivered and the threshold limit of the surrounding normal critical tissues is required. The radioprotective agents have been used to reduce morbidity or mortality produced by ionizing radiations. A great deal of research has been carried out on the radioprotective action of chemical substances. The radioprotectives from natural origin and synthetic compounds are found to be very effective as well as they are preventing or minimizing the toxic effect of ionizing radiations. The present review summarizes about radioprotectives, their ideal properties, classifications, mechanism of action with few examples.

Keywords: Radiotherapy, Ionizing radiations.

INTRODUCTION

What are radioprotectives?

People may be exposed to ionizing radiations during radiotherapy or following exposure to radionuclides in nuclear medicine. Radiotherapy is the most common modality for treating human cancers. The aim of radiotherapy is to destroy cancer cells with as little damage as possible to normal cells (1). Eighty percent of cancer patients need radiotherapy at some time or other, either for curative or palliative purpose. To obtain optimum results, a judicious balance between the total dose of radiotherapy delivered and the threshold limit of the surrounding normal critical tissues is required. In order to obtain better tumor control with a higher dose, the normal tissues should be protected against radiation injury. Thus, the role of radioprotective compounds is very important in clinical radiotherapy (2).

Ionizing radiation has proven to be a double-edged sword since its discovery by Dr Roentgen in 1895. Radiation is a potent mutagen and carcinogen; however, it is also used in the diagnosis and treatment of human diseases (3).

What is the need of radioprotectives?

Ionizing radiation causes damage to living tissues through a series of molecular events, such as photoelectric, Compton and Auger effects, depending on the radiation energy. Because human tissues contain 80% water, the major radiation damage is due to the aqueous free radicals, generated by the action of radiation on water (2).

Ionizing radiations interact with biological molecules inducing radiolytic products like e(aq), *OH, *H, _OH, +H, O2, and peroxides. These free radicals damage important biomolecules and subsequently inflict deleterious effects in the organism. Whole-body exposure to ionizing radiation results in central nervous system, gastrointestinal tract, and bone marrow syndromes, whereas chronic irradiation causes cancer, birth anomalies, erythema, and dysfunctions to almost all organ of the body depending on the total dose and site of irradiation (4). It has long been recognized that the damaging effects of ionizing radiation are brought about by both direct and indirect mechanisms. The direct action produces disruption of sensitive molecules in the cells, whereas the indirect effects (approximately 70%) result from its interaction with water molecules, which results in the production of highly reactive free radicals such and their subsequent action on subcellular structures (5).

These free radicals react with cellular macromolecules, such as DNA, RNA, proteins, membrane, etc. and cause cell dysfunction and mortality. These reactions take place in tumor as well as normal cells when exposed to radiation.

The radiation damage to a cell is potentiated or mitigated depending on several factors, such as the presence of oxygen, sulfhydryl compounds and other molecules in the cellular milieu. In presence of oxygen, hydrated electrons and H atoms react with molecular oxygen to produce radicals, such as HO2, O2−, apart from other aqueous free radicals (2).

The radioprotective agents have been used to reduce morbidity or mortality produced by ionizing radiations. Radio-protective action is a quality of some drugs, foods, or lifestyles that may protect healthy tissue from the toxic effects of anticancer drugs, or carcinogens in the environment (6). The search for radioprotective agents began soon after atomic explosions in Hiroshima and Nagasaki. Thousands of radioprotective agents varying from snake venom to ethanol were identified. Most of them were toxic to humans. Radioprotective agents are synthetic compounds or natural products that are immediately administered before irradiation to reduce injuries caused by ionizing radiations (1).

The use of chemical agents to provide protection against radiation injury has been a major field of study and historically the discovery of radioprotective effects of cysteiene in rats and mice by Patt et al (1949) paved the way for research on radiation protection in...
humans. Since then there has been an explosion in studies on radioprotective action of chemical substances. These substances have shown to reduce mortality when administered to animals prior to exposure to a lethal dose of radiation (3).

**ROLE OF NATURE IN THE DEVELOPMENT OF RADIOPROTECTIVES:**

The development of safe, non-toxic, yet effective radioprotective drugs remains an unaccomplished task. Natural products offer a reliable alternative to the synthetic compounds since they possess a repertoire of chemical compounds possessing exceptional biological activities. The plants growing in the high altitude (>3000 m) of the Himalayan region, have developed capabilities to sustain themselves admit the highly unfavourable conditions by synthesizing secondary metabolites with amplified reducing potential. Herbal radioprotectors has focused on investigation of the diverse biological activities of several high altitude plant species like Hippophae rhamnoides, Tinospora cordifolia, Podophyllum hexandrum, Rhodiola imbricata, etc. for developing potent anti-oxidative and radioprotective agents. These plants have rendered radioprotection in *in-vivo* and *ex-vivo* models against 10 Gy (absorbed radiation dose due to ionizing radiation) lethal gamma radiations (7).

Since exposure to irradiation in radiotherapy, or accidental exposure to radiation, can produce significant unwanted side effects, it is important to ameliorate such effects by use of radioprotective drugs (1).

The differences between normal therapeutics and radioprotective drugs need to be addressed and should be critically evaluated. Synthetic compounds have nearly failed their test of time. This has forced researchers to take recourse to nature, and look for radioprotective agents from plant sources since they have been the key source of new drug development. Keeping this in mind, a large number of plants and their bioactive phytochemicals have been evaluated for radioprotective efficacies in recent years. It has been recognized that protecting only one single target system cannot render effective radioprotection. Radioprotection is a multi-faceted phenomenon and drugs that can protect multiple target organs are definitely more effective. Herbal drugs contain several bioactive molecules and these can target and protect several organ systems simultaneously (7).

Synthetic compounds have nearly failed their test of time. A majority of potential radioprotective synthetic compounds have demonstrated limited clinical application owing to their inherent toxicity, and thus, the attractive alternative is of naturally occurring herbal products (7). Keeping this in mind, a large number of plants and their bioactive phytochemicals have been evaluated for radioprotective efficacy world-wide in past few years. Herbal drugs contain several bioactive molecules and these can target and protect several organ systems simultaneously. The increasing research on plant extracts suggests that phytoconstituents are the important, effective and safe radioprotectives than the synthetic compounds. This thirst amongst the scientist may lead to the development of an ideal radioprotective agent derived from plant.

Till date, there is not a single safe radioprotector available for human use, mainly because the wish list of an ideal radioprotector is long.

**IDEAL PROPERTIES OF RADIOPROTECTIVES:**
The ideal radioprotective agent should fulfill several criteria

1. It must provide significant protection against the hazardous effects of radiation.
2. It must have a general protective effect on the majority of organs.
3. It must have an acceptable route of administration (preferably oral, or alternatively intramuscular).
4. It must have an acceptable toxicity profile and protective time-window effect.
5. It must have an acceptable stability profile (both of bulk active product and formulated compound).
6. Have compatibility with the wide range of other drugs that will be available to patients or personnel (1).

**ADVANTAGES:**
Radioprotection is a multi-faceted phenomenon and drugs that can protect multiple target organs are definitely more effective. Herbal drugs contain several bioactive molecules and these can target and protect several organ system simultaneously (7). Radioprotective substances have shown to reduce mortality when administered to animals prior to exposure to a lethal dose of radiation.

**CLASSIFICATION OF RADIOPROTECTING AGENTS:**
Radioprotecting agents can be classified into three groups: 1) radioprotectors, 2) adaptogens and 3) absorbents. The first group, radioprotectors are generally sulfhydryl compounds and other anti-oxidants these include several myelo- , entero- and cerebro- protectors. Adaptogens act as stimulators of radioresistance. These are natural protectors, which offer chemical protection under low levels of ionizing radiation. These are generally extracted from the cells of plants and animals and have least toxicity. They can influence the regulatory system of exposed organisms, mobilize the endogenous background of radioresistance, immunity, and intensify the overall nonspecific resistance of an organism. Absorbents protect organisms from internal radiation and chemicals. These include drugs which prevent the incorporation of radioiodine by the thyroid gland and the absorption of radionuclides $^{137}$Cs, $^{90}$Sr, $^{239}$Pu, etc.

The ensuing discussion focuses on different radioprotectors, depending on their molecular structure, therapeutic activity or metabolic function (8).

**GENERAL MECHANISM OF RADIOPROTECTIVE ACTION:**
The radioprotective agents mainly act by two mechanisms

1. Free radical scavenging
2. Immunomodulation

**Free radical scavenging**
Ionizing radiations interacting with water in cells can produce reactive free radicals such as hydroxyl radiations, hydrogen radicals and hydrogen peroxide, which have the toxic effect on critical macromolecules. The elimination of free radical species from the cell environment can inhibit the side effects induced by irradiation. The presence of sulfhydryl group or other molecules capable of scavenging the
radiolysis radicals arising from irradiation of water molecules can confer protection to radiation. Due to very short life of radicals, such protective agents need to be present in the cell environment before the production of free radicals in order to neutralize their destructive properties.

Increasing the partial pressure of oxygen in the cell environment sensitzes tissues to radiation. Radioprotective agents induce hypoxia and consumption of oxygen in the cells to decrease the levels of reactive oxygen species (ROS) and hydrogen peroxide. The aminothiols can decrease oxygen levels in the cells. The thiol radioprotectors consume oxygen by forming byproducts, such as disulfide and hydrogen peroxide.

2. Immunomodulation

Radioprotective agents can act via stimulation, proliferation and modification of the function of haematopoietic and immunopoietic stem cells. This class of agents is commonly referred to as immunomodulators. These agents make the stimulated cells release a variety of cytokinins that act on pluripotent bone marrow stem cell to stimulate their production and differentiation. These agents mitigate radiation-induced haematopoietic injury and reduce mortality. Cytokines activate cellular signaling transduction pathways by binding to high-affinity membrane receptors. Activation of cytokine cascade results in the release of intracellular protein messenger. Cytokine activation affects many cell functions, including growth, proliferation, differentiation, death caused by apoptosis and growth inhibition (1).

APPLICATIONS:

1. Radioprotective agents have been used to reduce morbidity or mortality produced by ionizing irradiation.
2. Radioprotective agents are synthetic compounds or natural products that are immediately administrated before irradiation to reduce injuries caused by ionizing radiation.
3. The development of radioprotective agents is important for protecting patients from the side effects of radiotherapy, as well as the public from unwanted irradiation.

EXAMPLES OF SOME RADIOPROTECTIVES:

Ginseng, a medicinal plant with worldwide distribution, and in addition to its anti-tumor properties, ginseng appears to be a promising radioprotector for therapeutic or preventive protocols capable of attenuating the deleterious effects of radiation on human normal tissue, especially for cancer patients undergoing radiotherapy. Results indicate that the water-soluble extract of whole ginseng appears to give a better protection against radiation-induced DNA damage than does the isolated ginsenoside fractions. Since free radicals play an important role in radiation-induced damage, the underlying radioprotective mechanism of ginseng could be linked, either directly or indirectly, to its antioxidant capability by the scavenging free radicals responsible for DNA damage. In addition, ginseng’s radioprotective potential may also be related to its immunomodulating capabilities (9).

The effect of various doses of 50% ethanolic extract of Chyavanaprasha (an Ayurvedic rejuvenating herbal preparation) was studied on the survival of mice exposed to 10 Gy of radiation. Treatment with chyavanaprasha, consecutively for five days before irradiation, delayed symptoms of radiation sickness and onset of mortality when compared with the non-drug treated irradiated controls. All doses of chyavanaprasha provided a significant protection against gastrointestinal (GI) death (death of animals within 10 days after exposure to radiation); however, highest protection against GI death was observed for 15 mg/kg chyavanaprasha (10).

Herbal preparation of Podophyllum hexandrum has already been reported to provide protection against whole body lethal gamma irradiation (10 Gy). It offers radioprotection at biochemical and cytogenetic level by protecting antioxidant enzymes, and increasing thiol content. It has also been reported to render radioprotection to germ cells during spermatogenesis (11).

The effect of various doses (0, 5, 10, 20, 40 and 80 mg/kg body weight) of 50% ethanolic extract of Abana®, a herbal preparation, widely used in India for the treatment of heart ailments, was studied on the radiation-induced mortality in mice exposed to 10 Gy of gamma-radiation. Treatment of mice with different doses of Abana® delayed the onset of mortality and reduced the symptoms of radiation sickness as compared to the irradiated controls (12).

The effect of 5, 10, 20, 40 and 80 mg/kg body weight of hydroalcoholic extract of Geriforte® (an Ayurvedic herbal medicine) administered by intra-peritoneal route was studied on the radiations-induced mortality in mice exposed to 10 Gy of gamma-radiation. Treatment of mice with different doses of Geriforte® consecutively for 5 days before irradiation delayed the onset of mortality and reduced the symptoms of radiation sickness when compared with the non-drug treated irradiated controls. A maximum protection was observed for 10 mg/kg geriforte, where a highest number of survivors were reported by 30 days post-irradiation and further experiments were carried out using this dose of geriforte (13).

Curcumin has been found to exert a dual action after irradiation depending on its dose. It has been reported to protect various body systems against the deleterious effects induced by ionizing radiation and to enhance the effect of radiation. Therefore, curcumin can be very useful during radiotherapy of cancer. Administration of curcumin in patients will be able to kill the tumor cells effectively by enhancing the effect of radiation and, at the same time, protect normal cells against the harmful effects of radiation. The available information on curcumin suggests that the radioprotective effect might be mainly due to its ability to reduce oxidative stress and inhibit transcription of genes related to oxidative stress and inflammatory responses, whereas the radiosensitive activity might be due the upregulation of genes responsible for cell death (4).

Melatonin (N-acetyl-5-methoxytryptamine), the chief secretory product of the pineal gland in the brain, is well known for its functional versatility. In hundreds of investigations, melatonin has been documented as a direct free radical scavenger and an indirect antioxidant, as well as an important immunomodulatory agent. The radical scavenging ability of melatonin is believed to work via electron donation to detoxify a variety of reactive oxygen and nitrogen species, including the highly toxic hydroxyl radical. The hydroxyl radical scavenging ability of melatonin was used as a rationale to determine its radioprotective efficiency. Indeed, the results from many in-vitro and in-vivo investigations have confirmed that melatonin protects mammalian cells from the toxic effects of ionizing radiation. Furthermore, several clinical reports indicate that melatonin adminis-
Radiotherapy, either alone or in combination with traditional radiotherapy, results in a favorable efficacy: toxicity ratio during the treatment of human cancers (5).

Several studies revealed the radioprotective action of *Apis mellifera* honeybee venom as well as that of its components mellitin and histamine. Radioprotective activity of bee venom involves mainly the stimulation of the hematopoietic system. In addition, release of histamine and reduction in oxygen tension also contribute to the radioprotective action of bee venom (14).

*Eugenol* exerts significant protection against oxidative stress and has a radioprotective potential (15).

**Acidic polysaccharide of Panax ginseng** (APG) is a radioprotective agent for Bone marrow cells (9).

**Hawthorn** fruit extract has the antioxidant activity and reduces the genotoxicity induced by gamma irradiation in bone marrow cells (16).

**Anthramycin** increases the host resistance to irradiation when it is injected prior to exposure (17).

**Citocline liposomes** have shown radioprotective effect at higher doses (18).

**Silymarin** produces protective effect in radiotherapy because of its antioxidant and free radicals scavenging properties (19).

**Vitamin E** acts as a good radioprotector against lethal doses of cobalt-60 radiation (20).

**Aminothiol (20-PRA)** is newer radioprotective agent (21).

**Rhodiola imbricata** is a Indian medicinal plant, was investigated for protection against whole-body lethal gamma irradiation (22).

**Aloe polysaccharide (AP)** shows satisfactory radioprotective effect on non-malignant cells. This effect is attributed to its alleviating the cell cycle turbulence (23).

**CONCLUSION:**

Radiotherapy is the most common modality for treating human cancers. Eighty percent of cancer patients need radiotherapy at some time or other, either for curative or palliative purpose. To obtain optimum results, a judicious balance between the total dose of radiotherapy delivered and the threshold limit of surrounding normal critical tissues is required. There are numeral differences between normal therapeutics and radioprotective drugs which need to be addressed and should be critically evaluated. Synthetic compounds have nearly failed their test of time.

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