

Natural Radioprotective Agents against Ionizing Radiation – An Overview

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ABSTRACT: Ionizing radiations are one of the predominant exogenous factors that have deleterious consequences to human life. The biological effects of the radiation cause damages to DNAs, lipids and proteins. Exposure to high amounts of ionizing radiation causes damages to the hematopoietic, gastrointestinal or central nervous systems, depending on radiation dose. Hence, there is an urgent need to prevent such effects due to ionizing radiations. The possible prevention of the effects of ionizing radiations on biological systems by phytochemicals, plants and herbal extracts are known as “Natural Radioprotectants”. This review mainly highlights the strategies relevant to the development of radioprotectors. It also deals on areas of applications, mechanism of action, sources and chemical classifications. Finally, some useful conclusions and future prospects in the area of natural radioprotectors are briefly touched upon.

KEY WORDS: Radio protective agents, free radical scavenging activity, herbal radioprotectors, ionising radiation, antioxidant, micronuclei.

INTRODUCTION

Search for effective and less toxic radioprotectors lead to increasing interest on natural compounds from dietary ingredients to medicinal herbs. The crude extracts of these plants and their preparation constitute several effective radioprotective drugs. They also work as antioxidants and significantly prevent the cellular damage in terms of lipid peroxidation, free radical scavenging activity, protein oxidation, etc. The increased incidences of terrorism have created the fear of nuclear terrorism and the use of bombs with possible radioactive contamination. This has created a global awareness for the search and need for finding radioprotectors. The development of a safe and effective nontoxic radioprotector for human use is yet to be achieved. Therefore various strategies have been developed to protect biological systems by interfering in the development of radiation damage [Fig.1].

Many researches and studies have found that several compounds are very effective as radioprotectors in lab. But, these have failed in the transition to human applications due to toxicity and increasing risk of side effects. [1] The ability of certain substances to provide protection against the damaging

effects of ionizing radiation was first published in 1949. [2] The first report on in vivo radioprotection was reported by Patt et al in 1949 [3], where pre-treatment with a naturally occurring amino acid, cysteine was shown to increase survival of lethally irradiated mice and rats. Later studies showed that aminothiols compounds like cysteine and cysteamine have a structure most favourable for radioprotection and the SH moiety in these compounds are crucial for their radioprotective property. [4] However, these compounds produce serious side effects and are toxic at the doses required for radioprotection.

The Waller Reed Army Research Institute synthesized and tested over 4,000 compounds and found the most effective compound to be WR-2721 (Amifostine). [5] 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 on daily administration with radiotherapy, which is manifested as nausea, vomiting, hypotension, allergic reactions, etc. [6] Thus, there is still an urgent need and want to identify novel, nontoxic, effective and convenient compounds to protect humans. To this problem, natural sources especially edible medicinal plants/herbs might provide ideal solution as these are

regarded as non-toxic even at higher concentrations. In the view of low cost, easy accessibility and less toxic effects, there is a growing interest on ethno medicines even among the common people. [7]

RADIATION- INDUCED DAMAGE

Exposure of biological system to ionizing radiation results in the form of reactive species i.e reactive oxygen species (ROS) and reactive nitrogen species (RNS) and also the generation of free radicals. Free radicals can be defined as atoms or a group of atoms having an unpaired electron. Because of the presence of unpaired electron, free radicals are highly reactive and are capable of altering all biological molecules including lipids, DNA, and proteins. [8] Reactive species include hydrated electron (eaq-), hydrogen radical (H), hydroxyl radical (.OH), H_2O_2 , peroxy radical (ROO.), $O_2^{.-}$, singlet oxygen (1O_2) etc resulting from radiolysis of aqueous solutions. Hence the most oxidizing species formed in biological systems during exposure to radiation are O_2 and .OH. These two ROS along with other reactive species are capable of including severe and undesirable alterations

in many biological molecules. The health effects resulting from exposure to ionizing radiation are two categories: stochastic (Probabilistic) and deterministic. The former may take several years to develop (eg: cancer appearing several years later after exposure), while deterministic effects (eg: cataract induction, hematologic deficiencies, erythema, damage to skin and fertility impairment) at high radiation doses are manifested with certainty above a threshold. On the other hand, radiation injury refers to the acute or delayed consequences of exposure of a small part of the body to high doses of ionizing radiation resulting in severe burns, induction of cataract, pneumonia and hypothyreosis. [9] Damage to the DNA results due to ionizing radiation is the most important factor in cell death. It is followed by altered cell division, depletion of stem cells, organ system dysfunction and, if the radiation is sufficiently high, the organism will die. Exposure to high amount of ionizing radiation will also results in damage to the hematopoietic, gastrointestinal, central nervous systems, reproductive systems, depending on radiation dose.

Figure -1

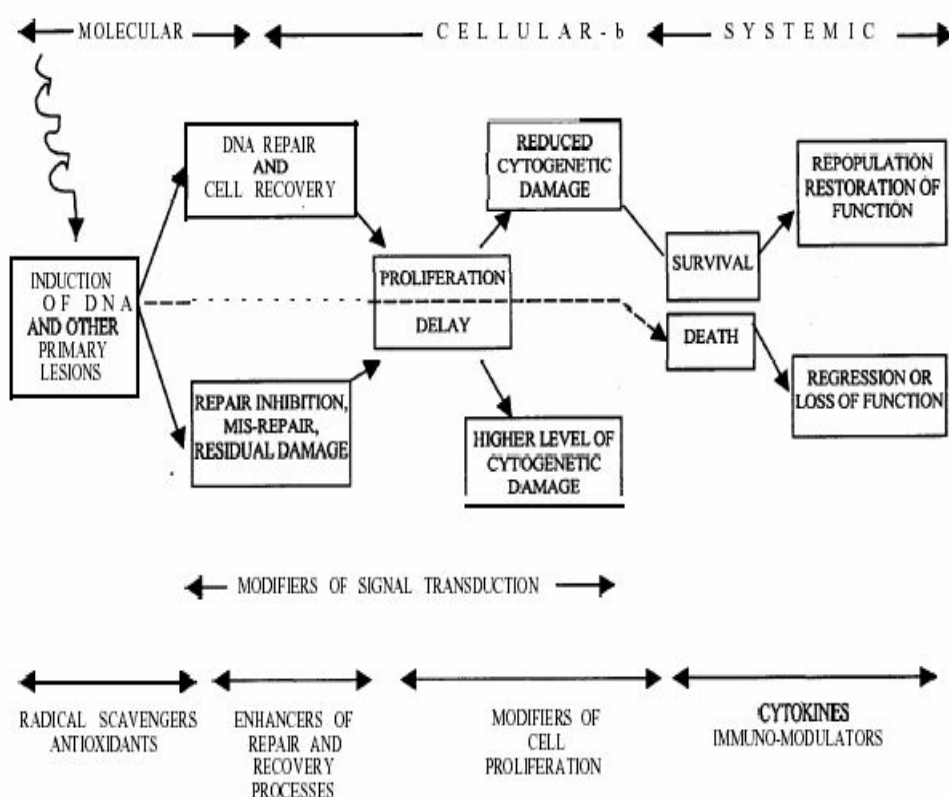


Figure 1. Biological response to radiation damage and strategies for protection

NEED FOR RADIOPROTECTORS

Several chemical compounds and their analogues have been screened for their radio protective ability. However, the practical applicability of the majority of these synthetic compounds remained limited, owing to their toxicity at their optimum protective dose. To reduce the toxic effects of synthetic compounds, there is a need to explore the compounds; which could be less toxic and highly effective at non-toxic dose. An intensive area of research promotes such type of compounds lies in the use of natural compounds. The use of natural compounds for improving one's health has augmented in modern time. Therefore, it is quite efficient that the choice of alternative radioprotectors falls on plants/plant products. But, their use as radioprotectors needs scientific evaluation and validation. Once this is done, natural radioprotectors could be more successful than synthetic chemicals.^[10]

An ideal radioprotectors should have the following abilities functionally:

1. Free radical scavenging
2. Radio oxidative damage
3. Facilitate DNA and cellular repair
4. Immuno modulation and
5. Facilitate repopulation of damaged and affected organs.

MECHANISM OF ACTION OF NATURAL RADIOPROTECTORS

The natural radioprotectors exert their protective actions by several mechanisms such as

1. Scavenging of free radicals (antioxidant mechanisms).^[11]
2. Up regulate mRNAs of antioxidant enzymes such as catalase, glutathione transferase, glutathione peroxidase, superoxide dismutase.^[12]
3. Promoting the recovery of hematopoietic and immune functions.^[13]
4. Compaction of DNA.^[14]
5. Triggering the DNA repair enzymes.^[15]
6. Detoxifying the radiation induced reactive species.^[16]
7. Delay of cellular division and inducing hypoxia in the tissues.^[17]
8. Reduction in lipid peroxidation and elevation in non-protein sulphhydryl groups.^[18]
9. Inhibit activation of protein kinase, nitrogen activated protein kinase, cytochrome P-450, nitric oxide. Table 1 indicates the list of natural radioprotective agents against toxicity induced by ionizing radiations.

To put these herbal drugs as radioprotectors, one needs to know the following:

1. The exact composition
2. Mechanism of action of each component
3. Possibility of synergistic action between different components
4. Exploration regarding mechanism of action as radioprotectors
5. Elimination of the toxic components from the extract
6. Pharmacokinetics of the different components in the body organs
7. 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.

CONCLUSION

Exposure of humans to ionizing radiation is increasing due to the development in science and technology. The development of radioprotective agents is important for protecting patients from the side effects of radiotherapy, as well as the public from unwanted irradiation. Recently, focus of radiation protection has shifted to test the radioprotective potential of plants and herbs in the hope that one day it will be possible to find a suitable pharmacological agents/s that could protect humans against the deleterious effects of ionizing radiation in clinical and other conditions as well as during nuclear terror attack. Majority of plants and herbs described in this review have medicinal properties and being used in traditional Ayurvedic or Chinese systems of medicine to treat various ailments in humans. It provides a broad idea on the physiochemical role of ionizing radiation on cellular systems and highlighting the importance of developing new natural radioprotectants. The search for radioprotective agents, should therefore aim for compounds with higher prophylactic and therapeutic actions have been included.

FUTURE PROSPECTS

Medicinal plants like Aconitum heterophyllum, Bergenia stracheyi, Bunium persicum, Dactylorhiza hatgireya, Ephedra Gerardiana, Pichorrhiza kurroa, etc., are some of the plants that need elaborate investigations. Further, new combinations of radioprotectants may also evaluate for attaining higher specificity. Fractionation guided evaluation may results in the development of ideal radioprotectors in the near future.

Table-1

AGENT	TEST SYSTEM	ROUTE / DOSE (mg/kg)	OBSERVATION	REFERENCES
Ageratum conyzoides	Mice	i.p / 75	Radiation sickness, GI & BM deaths, DPPH radical	[19]
Aegle marmelos	HPBLs, Mice	i.p / 15	Micronuclei, free radicals	[20],[21]
Aphanamixis polystachya	Mice	i.p / 7.5	Aberrant cells, chromatid breaks, chromosome breaks, dicentrics, acentric fragments and total aberrations	[22]
Amaranthus paniculatus	Mice	p.o / 800	Spleen weight, lipid peroxidation, GSH	[23]
Ambrosia maritima	Rats	p.o / 15g	Neurotransmitter disturbances	[24]
Centella asiatica	Rats, Mice	p.o/100	Taste aversion, weight loss	[25],[26]
Citrus aurantium	Mice	i.p / 250	Clastogenic effects, MnPCEs, MnNCEs	[27]
Emblica officinalis	Mice	p.o / 100	Survival, weight loss	[28]
Gingko biloba	Human	i.v / 100mg/person	Brain oedema, clastogenic factors	[29],[30],[31]
Hippophae rhamnoides	Rats, Mice	i.p / 30	Survival, ACTH	[32]
Crategeus microphylla	Mice, HPBLs	i.p / 200	Micronuclei, MnPCEs.	[33]
Mentha piperita	Mice	p.o / 40 μ oil	Hematological constituents, serum phosphatase, chromosomal damage	[34]
Mentha arvensis	Mice	i.p / 10	Radiation sickness, GI&BM deaths	[35]
Myristica fragrans	Mice	p.o / 10	GSH, LPO, GI damage.	[36]
Osmium sanctum	Mice		Lipid peroxidation, glutathione, chromosomal damage	[37],[38]
Panax ginseng	Mice	i.p / 200	Apoptosis, testicular enzymes	[39],[40]
Podophyllum hexandrum	Mice		GI damage, GST, GOD	[41],[42],[43]
Phyllanthus amarus	Mice	i.p / 900	Glutathione reductase, catalase, WBC, SOD, GST	[44]
Piper longum	Mice		Lipid peroxidation, glutathione pyruvate transaminase, alkaline phosphatase, α -esterase, WBC	[45]
Szygium cumini	Mice, HPBLs	i.p / 80	Micronuclei	[46]
Spinacia oleracea	Mice	p.o / 1100	Oxidative stress	[47]
Tinospora cordifolia	Mice	i.p / 200	CFU, blood cells	[48],[49]
Zingiber officinalis	Rats	i.p / 10 or 250mg/ oral	Radiation sickness, GI&BM deaths, free radicals, lipid peroxidation	[50],[51]

GSH: glutathione; GST: glutathione-s-transferase; SOD: superoxide dismutase; GI: gastro intestinal; BM: bone marrow; HPBLs: human peripheral blood lymphocytes; DPPH: diphenyl picryl hydrazyl radical; LPO: lipid peroxidation; MnPCEs: micronucleated polychromatic erythrocytes; MnNCEs: micronucleated normochromatic erythrocytes.

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