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Radioprotective Efficacy of Marine Algae

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Abstract

Radiation and radiation technology has risen too much from the last few years, hence the chances of radiation contamination increased over the past few years. The need to study radiation protection has become necessary. Commercially available chemical radioprotectors having too many side effects and hence limiting the use. Since the last decade, the study on marine algae has gained impact through the experimental studies marine algae is considered to have many Radioprotective phytochemicals, such as phlorotannins, polysaccharides, carotenoids and other compounds. Chemical radioprotectors having many side effects of the human hence limiting the use. Natural radioprotectors can be used in place of artificial to reduce the side effect and can be used in the long run. Marine algae exhibiting a broad spectrum of antioxidant properties can be used widely as radioprotectors.

Keywords: Radiation • Radioprotectors • Marine algae • Electromagnetic waves

Introduction

Radiation is an emission of transmission of energy which travels in space or through a medium in forms of waves. There are three types of radiation alpha (α), beta (β) and gamma (ϒ), from all these radiation gamma radiations are highly penetrating electromagnetic radiation (visible light, UV light, radio waves, etc.) which comes from radioactive decay. Gamma-ray is a photon of energy generated by nuclear excitation emerging from either radioactive decay or fission reactions [1]. Mostly Gamma rays can pass through physical barriers. The resulting chemistry when one of these photons breaks a bond inside a cell can even kill a cell; or if it is inside a DNA it can cause the cell to mutate which can lead to cancer. At higher exposure levels the damage may become extensive enough to cause radiation burns even immediate deaths [2]. Exposure to high doses of radiation over a short period can cause radiation sickness even death. Some of the symptoms include nausea, vomiting, fainting, diarrhea, confusion, hair fall, skin and mouth sore, and bleeding. Doses of radiation that are given in radiation therapies also cause side effects [3].

Gamma rays and X-rays both are electromagnetic waves emerging from radioactive decay and hence overlap; these radiations can be differentiated on the bases of their origin, Gamma rays originate from nuclear decay whereas X-rays originates from the outside nucleus [4].

Materials and Methods

Effects of radiation

Regardless of where or how an incident involving radiation happens, 3 types of radiation-induced injury can occur.

External irradiation: This exposure to penetrating radiation from a radiation source. People exposed to a source of radiation can suffer radiation illness of their dose is high enough, but they do not become radioactive. External irradiation does not make a person radioactive [5-10].

Radioactive contamination: This occurs when material that contains radioactive atoms is deposited on skin, clothing or any place where it is not desired. If it is important to remember that radiation does not spread or get 'on' or 'in' people, rather it is radioactive contamination that can spread. A person contaminated with radioactive materials will be irradiated until the source of radiation is removed. A person is externally contaminated if radioactive material is on the skin or the clothing. A person is internally contaminated if radioactive material is inhaled, swallowed or absorbed through wounds. The environment is contaminated if radioactive material is spread around [11-16].

Incorporation of radioactive material: Incorporation refers to the uptake of radioactive materials by body cells, tissues and target organs such as bone, liver, kidney or thyroid [17]. In general, radioactive materials are distributed throughout the body based contamination of the materials and can be reduce by various

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complicated by physical injury or illness. In cases like these serious medical problems always have priority compare to concerns about radiation monitoring, contamination control and decontamination [18,19].

Effect of radiation on human health

Ionizing radiation can break down and destabilize the molecules, including DNA. Ionizing radiation breaks the molecule apart and recombines in the undesired ways. A large amount of radiation can have a major biological effect on the body [20]. Within living cells, ionization is often quickly followed by the production of free radicals which may react very rapidly with important biological molecules including genetic material. It is, in the molecules of the cell where genetic material is stored which is very sensitive to radiation. It is many hundred times more sensitive than the remaining cells [21]. In the nucleus the sensitive sites are the chromosomes. These are a double-helical structure made up of DNA and protein. Each chromosome is double because it consists of two sets of identical genetic material. This is to ensure that when a cell divides, the two new cells are identical in their genetic makeup (Figure 1) [22,23].

Figure 1. Break down of ionizing radiation.

The number of chromosomes varies in different organisms. It is unfortunate that in the dividing cells radiation causes the most damage [24]. In cells, which do not divide, the integrity of the nuclear DNA is less critical and their tissues are said to be radio-resistant. In the contrast, in the reproductive organs, blood-forming tissues, the digestive tract and developing embryos the effects of ionizing radiations are served. All of these organs are quite sensitive to radiation [25]. Radiation pollution of the environment is one of the most harmful pollutions as effects of other pollutions occur after long time exposure while radiation pollution can cause irreparable losses even after short term exposure [26]. Radioactive substances are the most toxic substance amongst all the toxic substances known. Radium is 25000 times more toxic than arsenic. The biological importance of radiation became a serious concern with the tragic death of Madame Curie; she died of leukemia due to radiation exposure [27,28].

Mechanism of radiation damage in human body

Whether the radiation is natural or from anthropogenic sources, their extent of danger mainly depends on the following factors

Physical properties of radionuclides such as their half-life, type of emission and energy of emission.

The ability of radionuclides to enter the food chain. Their as should tendency to become concentrated in living tissues.

Exposure to radiation can be devastating to the human body as well as to other living beings. When ionizing radionuclides penetrate the living tissue, they destroy the atoms and molecules. This is particularly true to bio-molecules [29]. The mechanism of destruction starts with the irradiation of water molecule splits into hydrogen ions (H^+), Hydroxide ions (OH^-) and the free radicals H^+ and OH^-. Radiation also produces many other free radicals H_2, H_2O^-, HO_2^+, H_3O^+, e^- and H_2O_2. These free radicals are highly reactive. They react with protein molecules in the cells, setting a chain of events that can destroy living cells or mutate them to function abnormally. The iconic free radicals deactivate the enzymes by dissociating their hydrogen bond [30]. As a result due to inhibition of enzyme activity cell growth may continue but cell division and multiplication may be stopped. As the protein is the bodybuilding material and also plays an important role in the formation of cell membranes so radiation exposure may damage the cell membranes by making them permeable [31,32]. Radiation also results in abnormal interchange of materials through damaged cell membranes causing temporary or permanent injury to the body. Though human tissues can repair some radiation damage but the sensitivity to damage is directly proportional to the cells' reproductive capacity [33].

Radioprotectors and antioxidants

Radioprotectors are compounds that are designed to reduce the damage in normal tissues caused by radiation. These compounds are often antioxidants and must be present before or at the time of radiation for effectiveness. Few of the antioxidants possessing radioprotective activity (Table 1) [34,35].

Table 1. Radioprotective activity.

Sl. No.	Name of the Mitigators	Radioprotectors/ Radioprotective effect and mechanism of action
1.	Cytoprotective agaents approved by FDA: mesna, amifostine.	Reduced toxicity of chemotherapeutic drugs, decreased urothelial toxicity and nephrotoxicity.
2.	Plant extract and single active compounds from plants	Reduction of primary and secondary ROS, reduced DNA effect

3.	Antioxidants	Free radical scavenging, inhibition of chromosomal aberrations and creation of micronuclei in lymphocytes.
4.	Selenum compounds	Preventing mutagenic changes
5.	Nitroxides	Mimic superoxide dismutase and free radical scavenging.
6.	DNA binding ligands	Electron transfer
7.	Chelators	Chelating with transuranium radionuclides
8.	Sulfhydryl compounds	Donation of H-atoms and free radical scavenging.
9.	Immunomodulators	Increased production of cytokines and immune stimulation
10.	Lipopolysaccharides and prostaglandins	Prostaglandin synthesis, DNA repair, elevated levels of cyclic Adinisine Mono Phosphate (AMP)
11.	HMG-CoA reductase inhibitors	Mitigation of radiation enteropathy, pulmonary fibrosis
12.	Steroids and Hormones	Myelopoiesis stimulation and enhancement of circulating neutrophil and platelet numbers.
13.	ACE inhibitors	Inhibition of angiotension 2 production, suppression of proliferation, prevention of development of radiation- induced late effects.
14.	Potassium iodide (KI)	Potective measure to reduce thyroid radioactive materials intake.
15.	Metallo elements and metallo-thione, bismuth subnitrate and manganese chloride	Protection of the hematopoietic system from lethal effects of IR, induction of metallo-thione synthesis in bone marrow cells.

Amifostine (WR2721): Selectively protects a broad range of normal tissues including the oral mucosa, salivary glands, lungs, bone marrow, heart, intestines and kidneys. It is a pro-drug, which cannot readily permeate cell membranes but on administration undergoes metabolism and get converted into WR1065, which can readily permeate the cell membrane [36]. A phase three study of patients who received radiotherapy for head and neck cancer demonstrated that those who received 200 mg/m of amifostine IVP 15-30 min before radiation daily, had a statistically decrease in acute and late; grade two xerostamia [37]. Amifostine may be administered intravenously or subcutaneously and should be dosed daily before radiation therapy. Side effects include nausea, vomiting, hypotension. A major mechanism underlying the radioprotective effect of WR2721 is the scavenging highly reactive free radicals induced by ionizing radiation [38]. Amifostine also protects against the cytotoxic effects of chemotherapeutic agents. It offers significant protection against nephrotoxicity, ototoxicity, neuropathy, associated with cisplatin and hematological toxicity associated with cyclophosphamide [39].

Nitroxide: Nitroxide is among the most promising agents for future use as radiation protectors. Laboratory studies have shown that stable Nitroxide-free radicals and their one-electron reduction products, hydroxylamine, are recycling antioxidants that protect cells when exposed to oxidative

stress, including superoxide and hydrogen peroxide. Likewise, preclinical studies have shown that the oxidized form of a Nitroxide is a Radioprotector in both *in vitro* and *in vivo* models. Identification of nitroxide radioprotectors. Although hydroxylamine exhibits antioxidant activity it is incapable of protecting against radiation damage. The lead compound from this class for radioprotection in tempol [40]. Tempol protects against radiation-induced damage to salivary glands and does not alter tumor growth after irradiation suggesting that delivery of the agent before irradiation would not alter tumor control. In the oxidized form, tempol is paramagnetic and provides a T1 contract on MRI. Because of this unique property, the active, radioprotective form of tempol can, therefore, be followed and temporally using MRI. Tumors were grown on the neck of a mouse that would allow a single MRI slice to include the tumor salivary gland area and normal leg muscle [41]. These preclinical findings provide feasibility to evaluate tempol as a radioprotector in clinical trials for cancer patients treated with radiation. Coupling MRI with such a trial would give a novel dimension that could provide extremely important information concerning the timing of tempol administration and radiation treatment [42].

Other antioxidants: With the understanding that free radicals perpetuate a significant amount of the damage caused by ionizing radiation, multiple vitamin antioxidants have been tested as a method to reduce the toxicity of radiotherapy. Preclinical and clinical effects of combining radiotherapy with antioxidants [43]. In general, the efficacy of these naturally occurring agents as radioprotectors is less than compared to that of the synthetic agents previously described. One of the concerns with the use of supplemental nutritive antioxidants or other antioxidants during radiotherapy is the possibility of tumor protection through non-selective free radical scavenging. Several trials have been performed with antioxidants delivered during radiotherapy, to reduce normal tissues toxicity, in many instances with promising results. Antioxidants have been delivered concurrently during radiotherapy to reduce xerostomia, mucositis, pulmonary fibrosis, cystitis and alopecia. Unfortunately, the use of antioxidant vitamins such as alpha-tocopherol and beta-carotene, during radiotherapy was with evidence of poorer tumor control in randomized trials [44]. The lower toxicity associated with the use of these agents is appealing, but not at the cost of poorer tumor control. These findings hold the importance of preclinical testing of radioprotectors to verify a lack of tumor protection. Topical application has been used to minimize the possibility of systemic absorption and interference with tumor response to radiation; however, caution is advised because even topical applications for the prevention of mucositis in head and neck cancers have been associated with evidence of poorer tumor control [45]. When discussing antioxidant as radio protectors it is worth mentioning the use of Superoxide Dismutase (SOD) as a method to prevent radiotherapy-induced toxicity. Ionizing radiation results in the formation of superoxide radicals that are highly reactive and potentially damaging to cells. SOD (Superoxide Dismutase) is an enzyme that is naturally present in human cells. It catalyzes the conversion of superoxide to oxygen and hydrogen peroxide and functions as an antioxidant during normal conditions after radiation. SOD as a radio protector has used gene therapy to increase the levels of SOD in tissues to be irradiated to prevent or decrease the radiation-induced mucositis, esophagitis, pneumonitis and fibrosis in animals [46-50].

Melatonin: Melatonin is thought to act as an antioxidant itself but also acts to increase the expression of antioxidant enzymes such as SOD and glutathione peroxidase. Radioprotection with melatonin analogs has been shown to have direct antitumor effects and has been described as a radiation sensitizer for tumors in animal models [51]. The use of melatonin as a radiation sensitizer for tumor cells and as a radioprotector for normal cells was tested clinically in a phase 2 radiation therapy oncology group trial. In that study, patients were randomized to either morning or night time high dose melatonin during radiotherapy. Melatonin was continued after radiotherapy until progression or until six months [52,53].

Novel radioprotectors: Tetracycline and Fluoroquinolones, which share common planar ring moiety, were found to be radioprotective. Tetracycline protected murine hematopoietic stem cell and progenitor cell populations from radiation damage and allowed 87.5% of mice to survive when given before and 35% when given 24 hours after lethal TBI. Tetracycline and ciprofloxacin also protected human lymphoblastic cells, reducing radiation-induced DNA ds breaks by 33% and 21% respectively. The effects of these agents on radiation lethality are not because of the classic mechanism of free radical scavenging but potentially through activation of the Tip 60 histone acetyltransferase and altered chromatin structure [54,55].

Marine algae as radio protectors: Marine algae considered as promising source of many novel compounds which is considered to have many therapeutic effects or pharmacological effects. Polyphenols isolated from marine algae consists of many beneficial properties such as antioxidant activity, anti-diabetic, anti-inflammatory, and anti-proliferation activity. Antioxidant properties of these compounds have been studied widely experimentally [56]. The different extracts with some other solvent shows a huge anti-proliferative action on different cancer as well as on different leukemia cell lines. In the last decades, an increased attention has been paid to the commercial and industrial potential of microalgae. Many species are currently being experimentally studied for their ability to synthesize important secondary metabolites (pigments, lipids, carotenoids, etc.) for biofuel production, pharmaceutical industry or aquaculture applications. Other fields of investigation include nanotechnologies, Environmental survey, forensic sciences and paleontology (Table 2).

Table 2. Radioprotective effect of marine algae at Tamil Nadu coast.

Name	Location	Literature
Gracilaria foliifera	Tiruchendur	Bioactivities from marine algae of the genus *Gracilaria*.
	Pudumadam	Molecular Phylogeny of *Gracilaria* species inferred from molecular markers belonging to three different genomes.
	Cape coromin	*In vitro* antioxidant activities of selected seaweeds from Southeast coast of India.
	Idinthakarai	FTIR characterization and antioxidant activity of water soluble crude polysaccharides of Sri Lankan marine algae.
	Covelong, Mandapam, Kilakarai	*In vitro* Antioxidant activity of Marine Red Algae *Gracilaria foliifera*
Padina pavonica	Indian and Pacific Ocean	Silver Nanoparticles Biosynthesis Using Marine Alga *Padina Pavonica (Linn.)* and its microbicidal Activity.
		Antioxidant and Antifungal activities of *Padina Pavonica* and *Sargassum Vulgare* from the Lebanese Mediterranean Coast.
		Active ingredients fatty acids as antibacterial agent from the brown algae *Padina pavonica* and Hormophysa triquetra.
		Antimicrobial activities of bacteria associated with the brown alga *Padina pavonica.*
Ectocarpus siliculosus	Found throughout the world, out of which 16 species are found in India they are commonly found in the western coast	Development and physiology of the brown alga *Ectocarpus siliculosus*: Two centuries of research.
		The cell wall polysaccharide metabolism of the brown alga *Ectocarpus siliculosus*.
		Normalisation genes for expression analyses in the brown alga model *Ectocarpus siliculosus*.
		Copper-induced intra-specific oxidative damage and antioxidant responses in strains of the brown alga *Ectocarpus siliculosus* with different pollution histories.

Dictyota cililata	West coast of Tamilnadu	Protective effect of fucoidans from tropical seaweeds against oxidative stress in HepG2 cells.
		Phenolic substances of brown algae and their antioxidant activity.
		Potential antioxidant and anti-proliferative activities of biologically active marine algae extracts.
Spatoglossum asperum	Gujrat	*In vitro* antioxidant and antibacterial activity of sulfated polysaccharides isolated from *Spatoglossum asperum*.
	Malvan	Minerals, PUFAs and antioxidant properties of some tropical sea weeds from Saurashtra coast of India.
	Ratnagiri (Maharashtra)	Antibacterial activity of various solvent extracts of marine brown alga *Spatoglossum asperum*.
	Goa, Karwar, Bhatlakl (Karnataka)	Antifungal activity of various solvent extracts of marine brown alga *Spatoglossum asperum*.
Steochospermum marginatum	Gujrat	Anti-proliferative and angio-suppressive effect of Stoechospermum marginatum *(C. Agardh)* Kutzing extract using various experimental models.
	Ratnagiri	Determination of various bioactive potential of *Stoechospermum Marginatum (C. Agardh)* Kutzing *in vitro*.
	Malvan (Maharashtra), Goa, Karwar, Bhatlakl (Karnataka).	Components and Antimicrobial Activity of Polysaccharides Extracted from Thai Brown Seaweeds.
Colpomenia sinuosa	Europe	Antimicrobial and antioxidant activity of brown algae from the Aegean Sea.
	Atlantic islands, Central, and South America,	Antioxidant Activities of Chlorophyta and Phaeophyta from Jeju Island.
	Indian Ocean islands, South-west Asia,	Comparison of antioxidant activity and total phenolic contents of some persian gulf marine algae.
	Asia Russia, Pacific islands, Antarctic islands.	Nephroprotective effects of *Colpomenia sinuosa* against carbon tetrachloride induced kidney injury in Wistar rats.

Chnoospora minima	Widely distributed in tropical seas. In South-East Asia both species occur in Vietnam, Indonesia, the Philippines, and Papua New Guinea.	The potential of fucoidans from Chnoospora minima and Sargassum polycystum in cosmetics: Antioxidant, anti-inflammatory, skin-whitening, and antiwrinkle activities.
		FTIR characterization and antioxidant activity of water soluble crude polysaccharides of Sri Lankan marine algae.
		A fucoidan fraction purified from Chnoospora minima; a potential inhibitor of LPS-induced inflammatory responses.
		Evaluation of biochemical composition and *in vitro* antioxidant properties of selected seaweeds from Kanyakumari coast, Tamil Nadu, India.
Hormophysa triquerta	Throughout the Indo-Pacific. In Australia. Gulf of Mannar.	Active ingredients fatty acids as antibacterial agent from the brown algae *Padina pavonica* and *Hormophysa triquetra.*
		Terpenes and Sterols composition of marine brown algae *Padina pavonica* (Dictyotales) and *Hormophysa triquetra* (Fucales).
		Hormophysa triquerta polyphenol, an elixir that deters CXCR4- and COX2-dependent dissemination destiny of treatment-resistant pancreatic cancer cells.

Conclusion

Marine algae can be the greatest source of many pharmacological products. Marine algae exhibit a broad spectrum of antioxidant such as cystiene, melatonin, mesna, Glutathione, Gallic acid, etc. these antioxidants can be used for production of natural radioprotectors which will severe better as compared to chemical radioprotectors. Chemical radioprotectors comes with lots of side effect and hence limits the usage. Natural radioprotectors will reduce the effects or radiation and can be used on the long run.

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