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Natural plant products as promising radio protectors

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ABSTRACT
Natural products in form of antioxidants, apoptotic modulators, growth regulators have shown promises in repairing the cellular damages inflicted by harmful ionizing radiation. Radio-protectors offering protection against radiation injury could be used as prophylactic, radiation mitigators, and therapeutic agents. Synthetic drugs approved by FDA such as amifostine- an organic thio-phosphate compound, is reported to have toxic/side effects very near to the prescribed dose and need to be administered under physician's supervision. Natural products including their bioactive secondary metabolites from terrestrial and marine sources, have emerged as source of novel chemotypes and pharmacophores. The prospective of novel microbial sources, particularly those found in extreme environments, is highly promising as potential drug leads. Since only a small segment of the biosphere's biodiversity has been assessed for potential radio-protective activity, many more natural products need systemic investigation to prove their useful.The natural presence of phyto-chemicals in foods provides them with bioactivities essential to protect the living cells against radiation injury. Natural plant products have shown promising results in protection of DNA, lipid membranes, mitochondria, immune-modulation and controlling apoptosis by controlling the production and chain reactions of reactive oxygen species generated upon exposure to ionising radiation. Natural products also exhibit analgesic and antipyretic effects by inhibiting cyclooxygenase-2 (COX-2) mediated inflammatory responses with fewer adverse effects on the gastrointestinal tract and reproductive system. The current review focuses on radio-protective agents based on natural plant products and probable mechanisms of their modulation of major cellular mechanisms by which they afford protection against radiation injury.
Keywords*: Radio-Protective Agents, Natural Products, Phytochemicals, Mitigators, Antioxidants.*

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INTRODUCTION

Irradiation with ionising radiation results in biological damage either by direct DNA strand breaks or the injury may be inflicted indirectly through free radicals caused oxidative stress [1]. Exposure to very high levels of radiation can cause acute health effects due to damage to cellular systems and organs leading to skin burns and acute radiation syndrome. Ionising radiation exposure results in production of free radicals, which react with lipid, protein and other biological macromolecules such as DNA and RNA that cause molecular modifications, incorrect chromosomal segregation, and mitotic death? Upon irradiation the cellular repair mechanisms come into operation to reverse the damage caused. Despite this the repair may not be to the required extent or there may be mis repair, which leads to mutation or cell death [4]. A number of phosphorothioate compounds, for example, amifostine, have been studied in detail for radioprotection. Radio-protectors are known to suppress the formation of free radical molecules and detoxify the same along with enhancement of protective enzymes such as superoxide dismutase and immune-modulators (prostaglandins and interleukins) thereby stimulating DNA repair and suppressing apoptosis and necrosis of cells [2]. However, shortfall exists in terms of Flower efficacies and/or associated toxicities very near to the therapeutic doses. Studies on use of natural products as radio-protectors to mitigate damages to biological system showed promising results. Main benefits that have been observed with the use of phyto-compounds include high therapeutic index and lower side effects when used as radio protector either as prophylactic or in therapy [3]. Flavonoids, polyphenols, saponins, alkaloids, tannins, vitamins and other phyto-chemicals obtained from plants (e.g., *Podophyllum hexandrum, Hippophae rhamnoides, Centella asiastica and Tinosora cordifolia* and sea weeds such as, *Spirulina plantensis, Chlorella vulgaris)*, have shown promising radioprotective properties [5,-10] Taxol, vinblastine, vinca alkaloids, topotecan and vincristine have been used in treatment of cancers [11].This review outlines the oxidative stress mediated cellular damage and other pharmacological effects induced

by ionizing radiation. The role of food ingredients and additives in the management of radiation induced maladies, is discussed. The phyto-chemicals scaffolds including exogenous antioxidants and other natural moieties, can provide promising leads that need to be systematically explored and further optimized. This review elucidates in brief a general understanding of damages caused by ionising radiation and natural products with radio protective potential and their mechanism in modulating the important biological processes through compounds possessing immune-stimulant, anti-oxidant, anti-inflammatory, antimicrobial, haemopoietic stimulation, wound healing and metal chelating properties. To study the role of natural plant products as radio protectors, a general understanding of damages caused by ionising radiation and natural products with radio protective potential and their mechanism in modulating the important biological processes through compounds

CELLULAR DAMAGES CAUSED BY IONISING RADIATION

Ionizing radiations cause direct and indirect effects on human body. Acute destruction of biological molecules such as DNA, protein etc., happens as a direct effect of ionising radiation while production of reactive oxygen species, single and double stranded DNA breaks due to exposure to radiations leads to damages to human body. Ionising radiations cause lysis of water present in body and produces reactive oxygen species that interacts with biological macromolecules such as DNA, protein and lipids. Damage to DNA due to radiation injury may lead to mutations, neurodegenerative diseases and cancer. Translocation of very large portions of DNA and point mutations were the important chromosomal aberrations reported due to exposure to ionizing radiations [12]. Availability of oxygen in cells leads to quick destruction of cells termed as oxygen effect. Once damaged, macromolecules such as DNA undergo processes such as DNA repair, expression of radiation responsive genes and activation of signal transduction pathways related to inflammation of the target region. Therefore, multiple effects of radiation exposure on human body has been reported as a cause for neuro-degenerative disorders, atherosclerosis and cancer.

EFFECT OF NATURAL PRODUCTS ON BIOLOGICAL PROCESSES IN PREVENTION OF RADIATION INJURY

Bioprospection approaches based on a combination of classical and *in silico* approaches directed towards the discovery of potent radio-protective agents from natural products were utilized in our previous study (data not published). The classical biopros- pection used literature survey of ethno pharmacological literature while *in silico* study screened databases using random and relevant search model and scoring followed by decision matrix approach followed by its validation. We were successful in our aim of discovering potential and promising natural products through a systemic collection and analysis of literary data to obtain a logical output pertaining to identification of radio protective phyto- and phyco-sources. The bioactivity parameters were selected based on literature survey of how radiation affects human body and factors which helps in the faster recovery. Thebiological parameters affected by radiation were antioxidant activity, haemopoietic stimulation, metal chelation activity, anti-inflammatory activity, wound healing activity, immunostimulant activity, antiemetic activity and antimicrobial activity (Scheme 1 : Figure-1). Similar studies were carried out for targeting antibiotic resistance in human pathogenic microorganisms using herbal molecules.

a) Antioxidant activity

Ionizing radiation generates an array of reactive species on reaction with water and lipid molecules available in cellular components and causes damages. Reactiveoxygen speciesproduced include hydrated electron, hydrogen radical, hydroxyl ion, peroxyl ion, superoxides etc (Mauryaet al2006). Self-defence enzymatic mechanism of cells such as glutathione peroxidase and superoxide dismutase reduce hydroxyl andsuperoxide radicals and generates water and hydrogen peroxide, respectively which would be reduced by water upon action of catalase. Direct effects lead to single and double strand DNA breaks which leads to mutation and thereby, apoptosis [13]. Antioxidants and their capability to reduce free radicals by prevention of initiation and propagation of oxidizing chain reactions were reported in treatment of radiation injury. Antioxidants effects of phytochemicals have shown to be having radio protective property. *Zingiber officinale*is reported to protect intestinal mucosal barrier from radiation toxicity partially attributed to its antioxidant and anti-inflammatory properties 6-shogol [99]. Quinic acid found in cinchona bark, coffee beans, sweet potatoes, apples and peaches have antioxidant potential and exhibited radioprotection [14].Thymoquinone from *Nigella sativa* [3], leaves of *Fragariavesca* and *Rubusplicatus* as well as their aglycones and Polyphenolicglycoconjugates from flowers of *Sanguisorba officinalis*, *Erigeron canadensis* [17] [99] are provenantioxidants that contributes radioprotective property. *Mesuaferrea* from Western Ghats having free radical scavenging activity and huge antioxidant potential [18]. Antioxidant activity of *Morus nigra* decreased the radiation induced genotoxicity and cytotoxicity prompted in rodent bone marrow cells and liver [80].Lemon grass and star-anise (*Illicium verum*) extracts helped in reducing radiation induced DNA damage in pBR322 plasmid [19]. Chlorophyllin

helped in survival of mice after whole body irradiation through its antioxidant mechanism and by activation of Nrf-2 and NF-κB pro-survival proteins [81]. Soy isoflavones were reported for their protective roles against gamma radiation induced oxidative damage and are promising radioprotectors [20].

Black tea is a rich source of flavonoids that imparts strong antioxidant activity resulting inradio-protective properties. Mechanism of cytotoxicity protection involved free radical scavenging activity of the antioxidant compounds resulted in reduction of apoptotic signal transduction and regulation of endogenous antioxidant enzymes.Acerola (*Malpighia glabra* L.) is a native fruit of Central America, well known for its rich nutritive value. Its pulp has high antioxidant potential from the mixture of nutrients especially vitamin C in the unripe fruit which will protect the DNA from oxidative stress. Methanolic extract of chicory seeds were found to have radioprotective effect mainly due to its active constituents such as chlorogenic acid and phenolic compounds. Grapes are rich in antioxidants and their activity varies according to variety. Grape extract could be used as an antioxidant against lower doses of ionising radiation (IR) induced oxidative stress to prevent apoptosis. Kiwi leaf extract may protect erythrocyte membrane from radiation induced oxidation as it is a rich source of polyphenols such as phenolic acids and procyanidin dimers. Leaf extract will strengthen the erythrocytes by binding to its hydrophilic part of the membrane and modulates membrane fluidity.*Moringa oleifera* leaves and immature pods are widely used in traditional medicine and as a nutritious food. Their leaf extract exhibits high antioxidant activity due to the presence of variety of polyphenols, phenolic acids, flavonoids, glucosinolates and alkaloids. Administration of the leaf extract prevented radiation induced hepatic lipid peroxidation and also restored hepatic glutathione levels and protected bone marrow chromosomes.*Polyalthia longifolia* leaf extract showed radioprotective effect against X-ray irradiation-induced damages in mice. Animals pre-treated with leaf extract exhibited significant increase in count of haematopoietic elements including red blood cell, white blood cell, platelets and haemoglobin concentration which could be attributed to high antioxidant activity of the leaf extracts which prevented chain reactions of lipid peroxidation. Fruits of *Malus baccata* are rich in phenolics, and they can be used as a radioprotector against gamma radiation induced oxidative damage. Their phenolic compounds effectively acted to improve the activities of antioxidant enzymes like superoxide dismutase and catalase as reported [21-45].

b) Haemopoetic stimulation

Exposure to ionizing radiation affects the stem cells, leading to loss of tissue functionality Moreover, it can impede the communication pathways between the cells and their immediate surroundings. Compounds with hematopoiesis stimulating property, stem cells, blood cells or progenitor cells can mitigate aftereffects of radiation. Haematopoietic system suppression and damage is one of the most risky outcomes of radiation effects. An outcome of radiation exposure can be a distressed blood cells formation, and irregular signal transduction pathways between the cells and their surrounding tissues. Radio protective phytochemicals can excite generation of haematopoietic elements thereby reducing the damaging effects of radiation. Polysaccharides extracted from *Heliantnus tuberosum* L.can act as a radio-protective compound by stimulating hematopoiesis of lymphoid, erythroid and myeloid lineages in spleen and bone marrow of irradiated animals by stimulating erythropoiesis in bone marrow and blood. Water soluble phyto polysaccahrides isolated from *H. tuberosum* (Jerusalem artichoke) weren reported to have radio-protective properties. These are effective in haematopoietic stem cell proliferation and activating regenerative process in organisms by triggering cytokine cascades. This polysaccharides isolated were promising radioprotective agents with immune-modulating and haematopoietic stimulation properties [20]. Aqueous extract of beetroot possesses radio-protective effect contributed from its ability to reduce DNA damage and increase the proliferation and stimulation of hematopoietic progenitor cells. Beet root extract stimulated erythropoiesis by the secretion of IL-3 and also protected bone marrow cells and splenocytes from radiation induced damages [22]. Geraniin, a dehydro ellagitannin isolated from *Nymphaea tetragona* var. *angusta* (water lily) protected mice from radiation injuries by its haematopoietic and antioxidant potential. Geraniin enhanced differentiation potential of splenocytes and haematopoietic proliferation and regulates secretion of IL-3, thereby promoting differentiation of myeloid progenitor cells and accelerated restoration of bone marrow cellularity [5]. Homogenous polysaccharides extracted from roots of *Angelica sinensis* (Oliv.) exhibited radioprotection by decreasing micronuclei in bone marrow and higher cellularity of bone marrow in mice subjected to whole body irradiation [103].

Quercetin and rutin are commonly existent dietary flavonoids in fruits, vegetables and beverages derivedfrom plant (tea and wine etc.) and reported to show radioprotective property in Swiss albino mice by protecting gastrointestinal stem cells, hematopoietic stem cells and intestinal mucosa thereby normalizing haematological parameters [83]. Phytochemical constituents like ace mannans present in *Aloe vera* stimulated interleukins and interferons which enhanced cell growth and haematopoietic

elements such as lymphocytes, monocytes and granulocytes [47]. Root of *Rubia cordifolia* is having potential to reduce haematopoietic damage induced by whole body irradiation along with anti-inflammatory and antioxidant property. Alcoholic extract of root protected mice from radiation induced oxidative damage. Polysaccharides extracted from roots of *Angelica sinensis* have the potential to protect them from haematopoietic damage induced by irradiation. It can increase the cellularity of myeloid tissue and decrease the formation of micronuclei in myeloid tissue in irradiated mice [102-104]. *Podophyllum hexandrum* has inherent antioxidant ability that helps in haematopoietic recovery after irradiation and reduces radiation induced haemolysis and neuronal damage. Active phytoconstituents present in plant contributed to its antioxidant, antitumour and immunostimulant activity [46]. Black seed (*Nigella sativa*) oil is rich in thymoquinone treatment and increased count of haemopoietic elements in rats after whole body gamma irradiation. Immunosuppressive and oxidative effects of ionizing radiation can be successfully prevented by application of nigella sativa oil [23]. *Ocimum sanctum* is well known for its medicinal properties, orientin and vicenin are the major flavonoids reported against radiation induced damage and stem cell death. Ocimum provided significant protection against acute radiation lethality in mice (Nayak and Devi, 2005). Fenugreek (*Trigonella-foenum-graecum* L.) is widely used for culinary purposes in Indian subcontinent and is rich in medicinal properties such as antioxidant, hepatoprotective and anticarcinogenic. Haemoglobin and lymphocytes count significantly increased after treating Wistar rats with fenugreek seed aqueous extract [3].

c) Metal chelating activity

Metals act as contributors for free radicals so that compounds which can chelate metal ions can control this adverse condition to some extent and renders protection.Chelation is a type of bond formation with ions or molecules with metal ions. Reactive oxygen species leads to oxidative stress induced health problems in the body. Metal ions areessential components of enzymatic activity as they act as co factors for the optimum functioning of enzymes. During radiation exposure ROS will be induced in large amount causing damage to the body cells. This chelating agent get bound with the free ion and reduces the ROS. The major cheating agents having effective metal chelation property present naturally are polyphenolic compounds especially flavonoids present in *Ocimum sanctum* (Tulsi), Catechin in *Camellia sinensis*, and quercetin in *Camellia sinensis* [48]. Polyamines are also effective metal cheating agent that reduces oxidative damage. Exposure to ionizing radiation leads to production of ROS, which causes modification in DNA structure. Vitamin C is reported to have antiaoxidant property, but also act as effective metal chelating agents. *In vitro* exposure of calf thymus DNA to radiation with the presence of vitamin C, showed 30-50% less DNA damage [49]. According to a study, radiation exposed mice resulted in haemopoietic and gastrointestinal tissue damage, which can be prevented by injecting the extract of Rhizome of *Podophyllum hexaandrum* (Himalayan mayapple). Injecting this extract two hour prior to the radiation exposure has the ability to protect testicular system from damage [50-60].

d) Immuno-stimulant and anti-inflammatory activity

Spleen and cells of immune system are considered as the most radiosensitive parts of body. Radiation suppresses immunity power and thereby causes associated adverse effects in biological system. Phyto-chemicals have been identified to stimulate immunity power and thereby contribute to radioprotection. The usefulness of polysaccharides in immune-modulation was observed in a study on TB pneumothorax infection in mice and guinea pigs. Srinivasan and Weiss (1992) reported radioprotection using injectable vitamin E (α-tocopherol) in mice exposed to Cobalt radiation of 0.2 Gy/min. Dose reduction factor (DRF) of 1.11 at 95% confidence interval was reported for alpha-tocopherol at a dose of 100 IU/kg b.w.,when given within 15 min post irradiation. Prophylactic survival-enhancing effects of glucan are known to be mediated by several mechanisms which includes increased macrophage-mediated resistance to potentially lethal post irradiation opportunistic infections, increased hematopoietic progenitor cells and accelerated hematopoietic reconstitution. Patchen *et al* [57] demonstrated that β-1,3 polysaccharide enhanced survival of mice on pre-radiation exposure administration. Fungal β-glucans are well known for their notable ability to act as immune-modulators [61]. Basil or sweet basil *(Ocimum basilicum)* is known for ages in Indian system of medicine for its medicinal properties. Dasgupta *et al* [15] investigated the effect of basil leaf extracts on elevating hepatic enzyme and antioxidant enzyme pathway during *in vivo* studies on 8–9 weeks old Swiss albino mice. Tumor regression was also observed with the use of basil leaf extract.

Mangiferin (MGN), a gluosylxanthone, present in *Mangifera indica* at the rate of 2.0 mg/kg was found to reduce symptoms of radiation sickness,delayed onset of mortality and also in mice in comparison to control mice [33]. Radiation suppresses production of anti-inflammatory cytokines and induces certain signal transduction pathways which leads to cell death. Bioactive compounds with anti-inflammatory property stimulates production of cytokines and inhibit radiation induced signal transduction pathways. Sebastia et al [78] studied natural occurring polyphenols such as curcumin and *trans*-resveratrol for their

antioxidant, anti-inflammatory, immune-stimulant and an9ti-carcinogenic properties. Pre-treatment significantly protected normal lymphocytes against γ-radiation induced cellular damage. *Trans*-resveratrol present in berries like grapes possess antioxidant, anti-inflammatory, immune-stimulant or anti-carcinogenic properties. Human lymphocytes were studied for radiation-induced chromosomal damage *in vitro*. Increased sister chromatid exchange (SCE) index and enhanced cell proliferation rates were observed on polyphenol supplementation of cell cultures [79]. *Aegle marmelos* possess anti-diarrheal, microbicidal, radioprotective, cancer-inhibiting, antipyretic, healing, diuretic, antifertility and anti-inflammatory properties, and is useful for the prevention and treatment of many diseases (Rahman and Parvin, 2014).Baicalein is a flavonoid, obtained from the root tissue of *Scutellaria baicalensis* and *S. lateriflora*. Ionizing radiation-induced cell death in splenic lymphocytes were inhibited using baicalein, a glucuronide of baicalein.Therefore, radiation-induced mortality in mice was prevented by augmented hematopoietic stem cell abundance and inhibiton of Nrf-2 (Patwardhan et al 2014). Suryavanshi et al (2015) reported improved hematopoietic stem/begetter cells in mice involving chlorophyllin which animated granulocyte creation in bone marrow, by increasing serum GCSF levels. Chlorophyllin radiation-caused hematopoietic condition and mortality were annulled in mice and furthermore forestalled radiation-actuated atypia in lungs. Radiation injury induces pneumonitis and fibrosis during radiotherapy for lung cancer. Soy isoflavones showed immense potential in shielding typical lung from radiation injury while sensitising tumor nodules to effects of radiation. This effect could be attributed to their action in mitigation of inflammatory infiltrates and radiation-induced lung injury [34, 1] [1].

Radio-protective effects of Salvianic acid A (SAA), an active ingredient found in *Salvia miltiorrhiza* were tested for mitigating γ-radiation-induced apoptosis in cultured human embryo liver cell line. Decreased production of ROS, inhibition of mitochondrial cytochrome C, inhibition of caspase-3 activation and down regulation of expression of Bax and P53 proteins and over expression of *Bcl-2* could be attributed for this. Targhi et al [94] studied on the radio defensive nature of mulberry separate in rodent liver and decreased degrees of malondialdehyde and superoxide dismutase (SOD), as well as improved thiol content and catalase action in contrast with the non-treated group. Phyto-chemicals from Rosaceae and Asteraceae families ensured high radioprotection and resembled mode of action of quercetin. Glycoconjugates isolated from the plant families reduced radiation-induced cellular genotoxicity than aglycones of the same plant species. Polyphenolic glycoconjugates such as aglycones are less toxic than quercetin and may find applications as radioprotective agents [99].

e) Wound healing activity

Upon exposure to radiation cellular mechanisms controlling growth and maintenance of cell loose normal functionality. An ideal radio-protector should improve wound healing activity of the cells to aid in fast recovery. Wound healing process includes three major phases namely edema, cell division and reconstruction of skin layer. Herbs which are found to be have noted wound healing capacity are *Aloe arborescens*, *Terminalia chebula*, *Euphorbia neriifolia*, *Biophytum sensitivum,* Schisandra chinensis, *Dilleniaindica*, Mesuaferrea, *Rhodiola imbricate*, *Curcuma longa*, and *Hippophaerha mnoides*. *A. arborescens* is known for its phytotherapeutic, anticancer andradioprotective properties and used as a common pharmaceutical ingredient for healing wound and burn healing properties (Lucciaet al2013).

Terminalia chebula has been demonstrated to possess multiple pharmacological and medicinal activities. Ethanolic extracts of *T. chebula* heals faster with enhanced rate of contraction and decreased period of epithelization on dermal wounds of rats [10]. Euphol compound isolated from the leaves of *Euphorbia neriifolia* have potential to act against radiation induced chromosomal aberrations. Aqueous extract of latex facilitated healing process by increasing DNA content, epithelisation and angiogenesis. Experiment were conducted in Guinea pigs and effect was evaluated by excision wound and dead space wound methods. Extract improved the hydroxylproline content, protein content, CAT level and decreased SOD level in granulation tissue [43]. Calendula flower infused black seed oil and wheat germ oil can be used as a protective agent against oxidative stress and this formulation exhibited biological effects such as stimulating wound repair and provides radioprotection in cell line [16].

Biophytum sensitivum is a medicinal plant used in traditional folk medicine its powdered leaves and seeds were applied on wounds. Crude extracts showed various activities such as antioxidants, anti-inflammatory and antitumor activity [80-86]. *Schisandrachinensis* is a medicinal plant used in modern Chinese medicine is reported to have stress protective effect and increased physical working capacity. *Schisandrachinensis* effective against harmful factors such as heat stroke, skin damage due to burning, cooling, frost bite,heavy metal toxicity etc.,also exhibited wound healing activity. *Schisandra* have shown enhancement in healing by 97.7% and out of which 92.5% of these patients did not report persistent ulceration [65, 90, 96]. *Dillenia indica* fruit extracts improved healing of psoriasis like wounds in rats and lowered inflammation by protecting against oxidative damage of biomolecules. Betulinic acid may be the active constituent present in the extract and maximum concentration of betiulinic acid was obtained in

ethyl acetate extract [40]. Mesuaferrea is used in traditional medicine for the treatment of fever, dyspepsia, microbial infections, renal diseases and liver disorders. Plant extracts can mitigate radiation induced toxicity and is reported to have wound healing,anti-inflammatory, antioxidant, anticancer, analgesic, antiarthritic and immune-modulatory activity. Mixture of its kernel powder and seed oil is used in healing of wounds and also used in treatment of skin itching and eruptions. Mesuaferrea seed oil contains a number of phyto-chemicals with medicinal properties [57]. Bergenin,a polyphenolic compound extracted from various medicinal plants exhibits burn wound healing property along with antiulcer, antifungal and immune-modulatory activities [67].*Rhodiola imbricata* is a Trans-Himalayan adaptogen exhibiting various properties such as anticancer, antimutagenic, anti-inflammatory and anti-aging. Ethanolic extracts prepared from the root is reported to have significant wound healing activity [13]. *Hippophaerhamnoides* commonly known as seabuck thorn leaves were reported to have a positive influence in treating free radical mediated diseases, inflammatory, wound healing, radioprotection and in stress management. Phenolic constituents of the plant extract especially quercetin derivatives contribute for its antibacterial activity. They are widely used in traditional medicine due toits power to stimulate wound healing and used in the treatment of skin disorders and other infectious diseases [95].β-glucans are natural polysaccharides present in theprotective cell wall in bacteria, fungi including yeast, algae, and cereals, have beneficial effects including immune-modulation, anti-inflammatory, haematopoietic stimulation, antibacterial, radioprotection and wound healing (Hanet al2017).Curcumin isolated from rhizomes of *Curcuma longa* (turmeric)is used for treatment of common cold, skin diseases, wound healing and inflammation [86]. C-phycocyanin is a pigment-protein complex belonging to phycobilic protein family and areusually found in cyanobacteria. It is reported as a wound healing agent and mechanism of action includes relocation via the cyclin-dependent kinase pathway and regulation of plasminogen activator at transcriptional level thereby stimulating the fibroblast proliferation [70].

f) Antiemetic activity

During the incidents like terrorist attack using improvised radiation emitting weapons, radiological warfare, accidents in industries and radiation therapy with high dose of radiations, the medical treatment for handling the hazard may not be available readily. Basic fundamental knowledge for treating the CBRNE (chemical, biological, radiological, nuclear, and explosive) exposed population is less among the medical professionals. Only a few health care professionals (HCP) are available for diagnosing and treating the radiation exposed victims. Irrespective of the source of radiation, the injury requires a proper acute, critical and long term treatment. For this health care professionals should be given proper training by experts and provided with specialized equipment to handle the emergencies arising out of radiation hazard. Awareness should be created among population regarding the radiation exposure and its health implications, so that population could stay alert and prepared for radiological threats [56]. Radio protective foods are the latest findings which are of great application during the intentional and unintentional radiation exposure to protect the body from toxicity. Foods with nutraceuticals elements have protective effect owing to their antiemetic activity, anti-inflammatory activity and antioxidant activity. Exposure to radiation will lead to various health hazards including nausea and vomiting. This can be prevented by using plants having antiemetic activity such as *Centella asiatica* commonly known as Gotu Kola, *Mentha piperita* commonly known as hybrid mint, a cross between water mint and spear mint, *Zingiber officinale* commonly known as ginger. Ginger (*Zingiber officinale)* is effective against nausea and vomiting induced by chemotherapy and it protects the body from gastrointestinal bleeding, and the antiemetic property is due to the presence of shogaols (6-,8-,10- shagaols)and gingerols (6-,8-,10-gingerols), which are bioactives and are responsible for protective action [6].

g) Antimicrobial activity

Antimicrobial activity is important to radioprotection because infection caused by translocation of intestinal Gram negative bacteria is one of the main cause of death by radiation induced myelo suppression. Antimicrobial compounds can prevent infections and provides protection.Antioxidants and phyto-chemicals are the functional components present mainly in plant foods including edible algae, mushrooms, which are commonly considered as antimicrobial. These functional compounds provide protection against hazards induced by ionizing radiation. Naturally present anti-oxidants like various selenium components and vitamin E (Tocopherol) will show a prominent effect against toxicity of lower degree radiation, when administered in particular dose level. Phyto-chemicals like caffeine (present in coffee), genistein (present in soya bean), and melatonin, express radio-protective activities by imparting antimicrobial effects in the body [101]. When the population is exposed to radiation, it results in lowered immunity which leads to infection mainly from gram negative gastrointestinal bacteria. Hence to prevent this infection, natural antibiotics like aminoglycosides is used. Day to day using commonly having anti-microbial properties are *Ocimum sanctum* (Tulasi), *Podophyllum hexaandrum* (Himalayan mayapple), *Mentha arvensis (*Mint leaves), *Stephania tetrantra* (Fang ji), *Hypericum perforatum* (St. John's wort). The

major components which are responsible for radio protective activity present in them are tannins, benzopyrans, flavonoids, and xanthones (Arora et al 2004). During burns from explosive conditions, the population will be prone to severe kind of infections from bacteria and viruses, due to the compromised immune system (Reticulo-endothelial system) of the body. Bacteria namely *Corynebacterium parvum* is known to stimulate the reduced function of reticulo-endothelial system after injecting it and increased production of macrophages, which makes the body resistant from any microorganism.

CONCLUSION

Damage to macromolecules such as DNA, protein and lipids and thereby arrest of cellular functions leading to apoptosis and necrosis could be reduced by usage of natural antioxidant molecules as suggested by recent clinical investigations. Thus, natural products are promising sources which could be used in combination to synthetic drugs which may reduce the onset of carcinogenesis, a well reported effect on exposure to ionising radiations. These compounds could be tested as prophylactics and therapeutics on human subjects exposed to indirect radiation exposures while operating equipment related to radiation imaging, cancer patients undergoing radiotherapy, frequent fliers and astronauts on space missions. Natural products are based on phyto-chemicals which are secondary metabolites, has to be subjected to rigorous clinical testing before use as therapeutic molecules or nutraceuticals but intake of such natural compounds in form of functional food may be useful to protect the human body against ill effects of radiation exposure. Furthermore, understanding of the effect or mechanism of action, of reported natural products on crucial biological processes pertaining to radiation exposure has to be studied in detail at cellular level to support the claims reported.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest. The research received no specific grant from any funding agency in the public, community, or non-for profit sectors.

Table 1. Traditional herbal plants and sea weeds showing therapeutic properties relevant to radioprotection

Sl no	scientific name	Common name	Radio protective properties	Antioxidant properties	Optimum Radio protective dose	DRF	Reference
1	*Acanthopanaxsenticosus*	Siberian ginseng, shigoka	Protects against radiation induced Suppression of hemopoiesis. Pre-irradiation administration of shigoka extract increased leukocyte counts and diminished cerebral haemorrhage .	Fruit extract was able to effectively reduce free radicals, Free radical scavenging activity has been confirmed by means of TLC-DPPH∗ dot-blot test.	24 mg/kg.b.w	N.A	[80, 81, 104]
2	*Acoruscalamus*	Sweet flag	Protect prenatal irradiation induced development The comet parameters were found to decrease with postirradiation time, indicative of a decrease in radiation-induced DNA lesions due to DNA repair. The administration of the extract enhanced DNA repair, as can be inferred from the rate of post irradiation decrease of the comet parameters.	The water: ethanol, 1:1 fraction of the extract scavenged free radicals, protected DNA from radiation evoked strand breaks and increased the DNA repair process	250 mg/kg b.w	N.A	[75, 77]
3	*Adhatoda vasica Nees*	Malabar nut	Leaf extract pre-treated irradiated animals exhibited radioprotection by an increase in GSH content and decrease in Lipid Per Oxidation (LPO) level. A significant increase in the serum alkaline phosphatase activity and decrease in acid phosphatase activity was also observed.	The ethanolic extract of *A. vasica* showed high antioxidant activity with cytoprotective potential in cell culture. The methanolic and aqueous extract of *A. vasica*has potential phytochemical composition of flavonoids, phenols with antioxidant and cytotoxic effect	800mg/kg. b.w	1.6	[45, 39]
4	*Aegle marmelos Corr. Ex Roxb*	Bel ,Wood apple	Administering mice with extract before irradiation reduced the symptoms of radiation sickness and delayed death.	extract pre-treatment arrested glutathione decline and lipid peroxidation significantly	15 mg/kg.b.w	1.15	[32]

5	*Ageratum conyzoides L.*	Goat weed	The treatment effectively protected mice against the gastrointestinal as well as bone marrow related death, as revealed by the increased number of survivors at all irradiation doses	Leaf extract exhibited strong antioxidant DPPH radical scavenging activity with IC50 value of 9.3 and 24.8 µg/ml for ascorbic acid and alcoholic leaves extract respectively. The absorbance for reducing power was found to be 0.0390, 0.0989 for ascorbic acid and alcoholic leaves extract respectively.	75 mg/kg.b.w	1.3	[33]
6	*Allium cepa L.*	Onion	Provided protection against X-ray induced chromosomal aberrations	The outer dry layers of red and violet varieties showed better inhibition of lipid peroxidation. The non-site-specific inhibition of hydroxyl radical induced deoxyribose degradation was also higher in the outer dry layers of red and violet varieties than in their middle and inner layers.	20 mg/kg.b.w	N .A	[63]
7	*Aloe vera*	Aloe vera	Administering the mice with Aloe before ɣ- Irradiation delayed the onset and reduced the severity of radiation sickness. Aloe vera extract treatment pre and post irradiation resulted in protection against radiations by restoring the levels of Fe and Cu in the liver and intestine, intestinal Zn. Protected against oxidative stress	higher concentrations of total polyphenols, total flavonoids, and total non-flavonoids, as well as higher antioxidant capacities using ORAC and FRAP analyses are seen in the extracts	750 mg/kg.b.w	1.47	[71, 49, 48]
8	*Amaranthuspaniculatus Linn*	Ragira	A. paniculatus leaf extract (600 mg/kg b.w./ day for 2 wks) protected mice against 5 Gy by reducing lipid peroxidation, glycogen and cholesterol levels in brain	Leaves and flowers of *Amaranthus* as well as their extracts were shown to possess highest antioxidant activities compared to other parts; rutin being the major radical-scavenger	600 mg/kg.b.w	1.36	[37, 38]
9	*Aphanamixis polystachya*	Amoora Rohituka, Pithraj tree	Extract protects mouse bone marrow cells against radiation-induced chromosomal aberrations and this reduction in radiation-induced chromosome damage may be due to free radical scavenging and reduction in lipid peroxidation	The Extract showed a concentration dependent scavenging of hydroxyl, superoxide, DPPH) radicals and the ABTS cation radicals *in vitro*.	7.5 mg/kg.b.w	N.A	[31]
10	*Archangelica officinalis Hoffm*	Mountain angelica	Administration of a combination of Archangelica officinalis and Ledumpalustre extracts to mice 5–15 min before irradiation [7.5 Gy (LD 90/30)] rendered 70% survival	Angelica efficient in clearing superoxide radical generated through hypoxanthine –xanthine oxidase system and inhibiting lipid peroxidation	N.A	1.48	[50, 51]
11	*Beta vulgaris*	Beet root	administration of beetroot extracts along with c-ray irradiation can induce significant decrease in the DNA damage and significant increase in proliferation and the stimulation of hematopoietic progenitor cells suggesting protective effects of beetroot against ionized irradiation	beetroot pomace showed the antiradical activity towards DPPH and hydroxyl radicals , beetroot juice protected male Wistar rats from oxidative stress induced by carbon tetrachloride and reduced plasma protein carbonyls and DNA damage in blood leukocytes.	N.A	1.1	[38, 99]
12	*Biophytum sensitivum*	Lajjalu	protective effect of *B. sensitivum*on Radiation-Induced haemopoietic damage is mediated through immunomodulation as well as sequential induction of IL-1beta, GM-CSF and IFN-gamma	*B. sensitivum* diminishes the elevated concentrations of Alkaline phosphatase, serum glutamic pyruvic transaminase and LPO levels in irradiated animals.	50 mg/kg.b.w	N.A	[23]

13	*Centella asiatica*	Centella, gotu kola	Oral administration of the extract increased the survival time, reduced body weight loss in irradiated animals . The extract significantly reduced the radiation induced damage to DNA	Compounds in the extracts were capable of scavenging the DPPH free radical and reducing ferric ions. *C. asiatica* leaves exhibited higher antioxidant activities using boiled aqueous extraction compared to aqueous extract in DPPH and FRAP assays	100 mg/kg.b.w	N.A	[80]
14	*Chlorella vulgaris*	chlorella	Oral administration of an algal mutant C. vulgaris E-25, 1 hr before or immediately after exposure to sublethal gamma-rays increased the number of endogenous spleen colony forming units (E-CFU). The magnitude of radioprotection was dependent on both, the dose of C. vulgaris fed and the time of administration	The total phenolic compounds were 24.95 mg in 1 g of dry alga matter from methanolic extract and five phenolic acids were identified. The phenolic compounds salicylic, trans cinnamic, synaptic, chlorogenic, chimic and caffeic acids found in the methanolic Chlorella extract may be responsible for its higher antioxidant activity.	500 mg/kg.b.w	Pre treated 1.11 Post treated 1.15	[46, 85]
15	*Coronopus didymus*	Lesser swinecress	Free radical scavenging activity protected mice against radiations	The ethanol extract showed high radical scavenging activity towards DPPH and ABTS radicals with IC_{50} values of (7.80×10^2) and (4.32×10^2) µg/mL, respectively. The most active ethanol extract had a FRAP value of 1921.7 µM Fe (II) equivalent.	400 mg/kg .b.w	1.07	[54, 64]
16	*Curcuma longa Linn.*	Turmeric	Pretreatment with curcumin analog protects the hepatocytes against ɣ radiation induced cellular damage. Curcumin: copper(II) complex protected against irradiation by reducing the decline in levels of GSH, GST, SOD, Catalase and total thiols, and reduced lipid peroxidation .Curcumin prevents follicular Artesia in radiation induced apoptosis in ovarian follicles Curcumin pretreatment accelerated healing of irradiated wound	Curcumin (Diferuloyl methane) restored the specific activity of glyoxalase system in irradiated mice due to its free radical scavenging property.	30 µg/mL	N.A	[84]
17	*Glycyrrhiza glabra L.*	Licorice	70% methanolic extract protected rat microsomal membranes from ɣ radiation induced lipid peroxidation	Glycyrrhizaglabra finds usedue to its antibacterial,antiinflammatory, antiviral, antimutagenic, antioxidant free radical scavenging and immunomodulating activities .	30 mg/kg.b.w	N.A	[37, 83]
18	*Mentha arvensis Linn.*	Wild mint	Mint extract treatment protected the mice against gastrointestinal death and bone marrow related death	The total phenolic content and total flavonoid content was found to be 9.12 and 32.14 mg/g respectively. The percentage inhibition values of DPPH scavenging for methanol extract were found to be 35.83%. The percentage inhibition values of Nitrous oxide scavenging for extract were found to be 39.11%, the percentage inhibition values of H2O2 scavenging for extract were found to be 21.72%.	10 mg/kg .b.w	1.2	[30]

19	*Moringa oleifera Lam.*	Moringa	One hour prior i.p administration of 50% leaf methanolic extract showed significant radiation protection to bone marrow chromosomes in mice.	; Leaf extract treatment restored GSH in liver and prevented radiation induced augmentation in hepatic lipid peroxidation	150-300 mg/kg b.w	N.A	[68, 69]
20	*Myristica fragrance*	Nutmeg	Administration of MF significantly enhanced GSH and decreased testicular lipid peroxidationlevel whereas acid phosphataseand alkaline phosphataseactivity did not show any significant alteration.. MF pretreatment effectively protected against radiation induced biochemical alteration as reflected by a decrease in LPO level and ACP activity, and an increase in GSH and ALP activity.	Pretreatment decreased lipid peroxidation Nutmeg, the dried seed kernel of Myristicafragrans, MF possesses antifungal, hepatoprotective and antioxidant properties	N.A	1.3	[81]
21	*Ocimum sanctum*	Holy basil	Flavonoids orientin and vicenin isolated from plant protected mice when either compound administered i.p. 30 minutes before irradiation, protected against the gastrointestinal syndrome and bone marrow syndrome.	Radical scavenging property was also observed In the plant extract .Patients suffering from the squamous cell carcinoma of oral cavity and oropharynx undergoing radiotherapy were used in study by providing flavonoid capsules from holy basil plant, significant increase in SOD was observed	0.05-1.32 mg/kg .b.w	1.37 (vicenin) 1.30 (orientin).	[19]
22	*Phyllanthus embelica*	Amla	Ethanolic extract of amla(eAE) efficiently reduced pro-inflammatory cytokine (TNF-α and IL-1β) levels and appreciably upregulate anti-inflammatory cytokine (IL-10) concentration. gastric ulcer healing induced by eAE was driven in a dose-specific manner through the harmonization of the antioxidative property and modulation of anti-inflammatory cytokine level.	fruits are reputed to contain high amounts of ascorbic acid (vitamin C), up to 445 mg per 100 g.It also contains punicafolin and phyllanemblinin A, phyllanemblinother polyphenols, such as flavonoids, kaempferol, ellagic acid, and gallic acid	900 mg/kg.b.w	1.12	[1, 94]
23	*Piper longum*	Long Pepper	Ethanolic extracts of fruit reduced the elevated levels of Glutathione Pyruvate Transaminase, Alkaline phosphatase and lipid peroxidation in liver and serum of irradiated swiss mice	both aqueous and methanolic extract of long pepper seeds have significant antioxidant and anti-haemolyticactivity. both the extracts are significantly potent in antioxidant activity, methanolic extracts demonstrated increased radical scavenging activity	N.A	N.A	[91]
24	*Podophyllum hexandrum*	Indian may apple	i.p administration of extract showed protection against the radiation induced damage in different types of cells 1present in testicular region. Partially purified fraction protected mice against lethal doses of ɣ irradiation Scavenged radiation inflicted free radicals and protected mice	*P. hexandrum* extract significantly reduced the formation of radiation-induced superoxide anions. Increased levels of mitochondrial glutathione were observed upon irradiation, whereas in the case of pre-irradiation treatment,levels were found to be significantly higher at alltime periods studied, indicative of stimulation of endogenous antioxidants.	200 mg/kg b.w	N.A	[41, 74, 75]

25	*Punica granatum*	Pomegranate	Peel extract administering Protected mice against damage caused due to X- ray irradiation by reversing the leucocyte apoptosis and cell death reduction	the methanol extract of seeds showed 22.6 and 23.2% antioxidant activity at 100 ppm using the beta-carotene-linoleate and DPPH model systems, respectively.It also showed 56, 58, and 93.7% inhibition using the thiobarbituric acid method, hydroxyl radical scavenging activity, and LDL oxidation, respectively, at 100 ppm.	50 mg/kg.b.w	N.A	[88]
26	*Saraca indica*	Ashoka tree	Hydro alcoholic extract showed radiation antagonistic property and reduced cytotoxicity and genotoxicity induced by irradiation of v79 cells with x rays .	Pretreatment with Hydro alcoholic extract of the plant increased levels of Glutathione S- Transferase, Catalase and lowered lipid peroxidation. The protection mechanism may be attributed to free radical scavenging and elevating in antioxidants.	400 mg/kg.b.w	1.39	[89]
	Spirulina platensis	Spirullina	extract caused a significant reduction of the micronucleus frequencies induced by gamma-radiation.. Results suggest that Spirulina modulate the radiation induced hematological and biochemical alterations in Swiss albino mice.	. Treatment with Spirulina also caused a significant decrease in malondialdehyde (MDA) formation in the liver, suggesting its role in protection against radiation induced membrane and cellular damage	--	--	[92, 98]
27	*Tephrosia purpurea (L.) Pers.*	Wild indigo	Tephrosia extract (200 mg/kg b.wt) protected Swiss albino mice against radiation (5 Gy)-induced haemopoieticinjury.Showed selective effect on erythroid compartment by protecting against haemopoietic injury	Extract Showed free radical scavenging property	200 mg/kg.b.w	1.16	[94]
28	*Zingiber officinale*	Ginger	Hydro alcoholic extract exhibited radical scavenging capability and protected mice against radiation induced injury Reduces the severity of radiation sickness and mortality. Protects mice from GI and bone marrow syndromes.	Preclinical studies carried out in the last decade has shown that ginger and its phytochemicals dehydrozingerone, zingerone possess radioprotective effects in laboratory animalsand in cultured cells *in vitro*. Mechanistic studies haveindicated that the free radical scavenging, antioxidant affects anti-inflammatory and anti-clastogenic effects maycontribute towards the observed protection	250 mg/kg	1.4	[27]

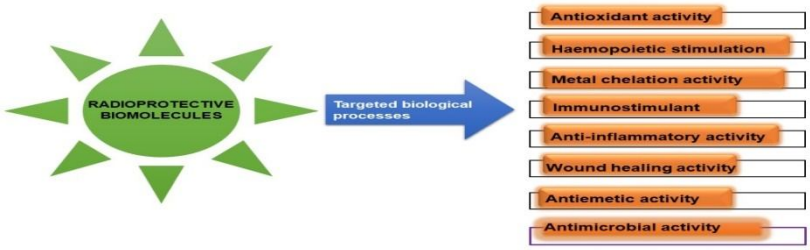

Figure 1: Scheme-1

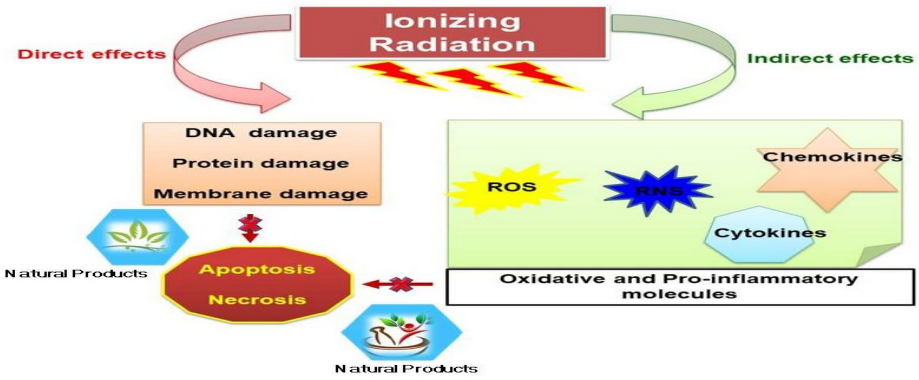

Figure 2: Oxidative and Pro Inflammatory Effect

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