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ENHANCED HUMAN EXPOSURE TO RADIATIONS, ROLE OF PHYTOCHEMICALS AS POTENTIAL RADIO-PROTECTANTS: A REVIEW

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ABSTRACT: Science and technology have greatly contributed to man's never-ending quest for quality improvement in different domains of life. But in the process of development, the usage of radiation-based technologies has considerably increased in the fields of medicine, agriculture, aviation, space, warfare, food processing, electronic and communication systems, nuclear-power generation and other industrial activities. These anthropogenic activities, in addition to natural processes, have more and more exposed humans knowingly or unknowingly to different kinds of radiations resulting in morbidity or mortality. In view of the high costs and side effects of the currently available radioprotective drugs, research continues to explore safe and effective radioprotectants preferably natural product-based ones. In the Traditional Indian and Chinese systems of medicine, several plant species have been reported to possess great medicinal values to treat various ailments. This article reviews and updates the promising plants and herbs, their extracts / bioactive principles and their mode of action as radio-protectants. Systematic and scientific studies pave the way to develop efficient drugs/formulations to protect or prevent from radiation injuries.

INTRODUCTION: Apart from medical and therapeutic purposes, in recent decades, usage of different kinds of radiation has enormously increased in several domains of human life including agriculture, food processing-preservation, industry, nuclear power generation, aviation, space, electronics and communications and warfare. Thus, the greatest contributions made in medicine, science and technology benefit mankind to lead a quality life but, at the same time, knowingly or unknowingly humans and other living organisms are being increasingly exposed to different kinds of radiations.

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We knew the damage done to mankind because of nuclear bombing on Hiroshima and Nagasaki and Chernobyl nuclear power plant incident. The global burden of cancer continues to increase and radiotherapy is an unavoidable option in majority of cancer treatments at some stage or other [1]. Radiotherapy inevitably involves exposure of normal tissues apart from targeting cancerous tissues. Radioprotection is an area of great interest due to its wide applications in planned radiotherapy as well as unplanned radiation exposure.

Although some alternatives like lead shielding, lead rubber aprons or other physical measures are suggested for radioprotection, they can't be used in all situations [2]. Hence, pharmacological intervention could be the most sensible approach to safeguard humans against the detrimental consequences of ionizing radiations [3]. Therefore, research in the development of radioprotectors worldwide has focused to screen a variety of chemical and biological compounds. Treatments that reduce the risk or intensity of damage to normal tissue or those that facilitate fast healing of radiation injury are being researched and developed. Various natural and synthetic compounds such as antioxidants, cytoprotective agents, immunomodulators, anti-inflammatory molecules, hematopoietic agents, Vitamins and DNA binding molecules have been evaluated extensively for their radio-protective potentials in both in vitro and in vivo models [4, 5, 6, 7]. However, the strategy becomes jeopardized when it comes to using synthetic molecules due to unwanted side effects. Therefore, this review covers and updates various plant based radioprotectants and their possible mode of action, besides mentioning existing radioprotectants, which may be useful to develop effective drugs/formulations for radio-protection.

Sources of Radiation: Sources of radiations are mainly categorized into naturally occurring (Cosmic rays, Radon) and anthropogenic of which naturally occurring contributes to 80% and manmade occupy 20% as shown in **Fig. 1**.

However, in recent times the percentage of manmade radiations is on raise. Different kinds of rays/radiations emitted during various activities are shown below along with electromagnetic spectrum. Endangered and extinction of several animals/ birds/insect species in the past few decades has also finds its reasons in radiation apart from other causes [8, 9, 10].

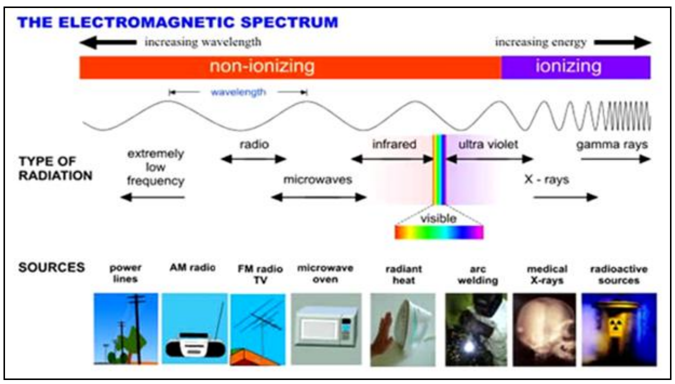

FIG. 1A: TYPES OF RADIATION

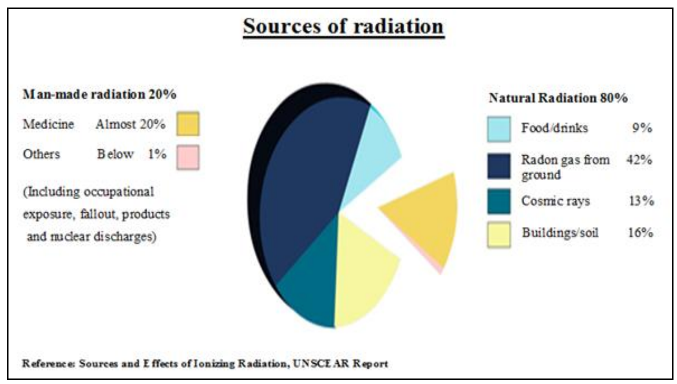

FIG. 1B: SOURCES OF RADIATION

Effects of Radiation: Radioactive materials that produce ionizing radiation spontaneously have sufficient energy to strip away electrons from atoms or to break some chemical bonds. The most common forms of ionizing radiation are alpha and beta particles, or gamma and X-rays. As shown in **Fig. 2**, the living tissues in the human/animal body can be damaged by ionizing radiation in a unique manner. During cancer therapy, radiation or radioactive substances are widely used to destroy cells having rapid cell division.

So, in addition to rapidly dividing cancer cells, some of the bone marrow cells that show swift cell division may also get destroyed. Ionizing radiation generates various reactive oxygen species in a biological system, known as reactive oxygen species (ROS). These ROS such as OH, H, eqa-, HO_2, H_3O^+, *etc*., deplete cellular antioxidant stores and react with cellular macromolecules, such as DNA, RNA, proteins, membrane lipids, *etc*. and cause cell dysfunction and mortality. Radiation-induced lipid peroxidation alters cell membrane fluidity leading to degradation and impaired biological defense [11]. Exposure to high amounts of ionizing radiation results in damage to hematopoietic, bone marrow, gastrointestinal system, central nervous systems and others depending on radiation dose [12, 13, 14].

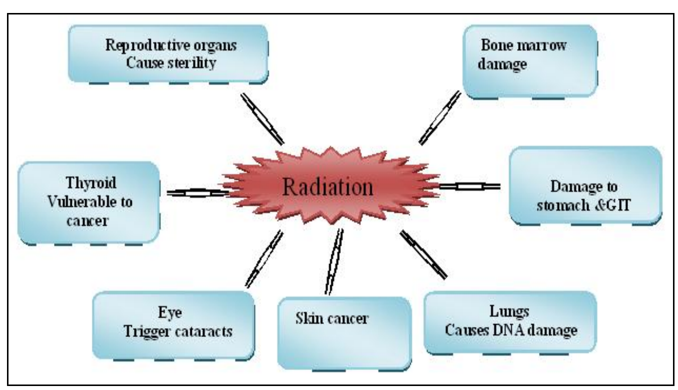

FIG. 2: EFFECT OF RADIATION ON VITAL PARTS OF HUMAN BODY

In general, the amount and duration of radiation exposure affects the severity or type of effect on health which may be stochastic or non-stochastic. Radiation can cause changes in DNA, the "blueprints" that ensure cell repair and produces a perfect copy of the original cell. Due to the production of pro-inflammatory cytokines and reactive oxygen metabolites, increased apoptosis in the intestinal epithelium leading to loss of intestinal structure and function occurs [15, 16]. Radiation enteritis is a serious health problem induced by the cytotoxic effect of radiotherapy on the intestinal mucosa [17]. Higher radiation doses used in treatment sex tend beyond the treated area and cause tissue inflammatory response in normal tissue under the irradiation beam. Being transitory in nature, acute toxicities resolve weeks after completion of treatment. Occurrence of late manifesting toxicities in patients treated with radiotherapy is a growing concern. Hence, to reduce these toxicities and improve the therapeutic ratio (that is ratio of cancer cell killing to normal tissue toxicity caused by a given dose), radioprotective drugs are receiving significant interest [18].

Consequences on Immune System: The immune system consists of cells and tissues spread widely throughout the body that protect against infections and cancer. The cells of the immune system arise in the bone marrow from pluripotent stem cells by a process called hematopoiesis. Radiation-induced effects on the immune system have attracted interest from the research community for several decades, and lymphocyte radiosensitivity was one of the earliest subjects of experimental radio-biology [19]. Immune-suppression is a consequence of whole-body irradiation at medium to high doses. In contrast, it has been reported that very low doses of ionizing radiation may give rise to immuno-stimulatory effects, particularly at short times after irradiation [20]. Because of these divergent effects, ionizing radiation is probably better considered as an immunomodulatory rather than as an immuno-suppressive agent **Fig. 3**.

Hematopoietic stem cells and blood cell progenitors seem to be the main target of chronic Low Dose (LD) irradiation. Direct radiation damage to the immune system results in a decrease of stem cell fraction. Thus leads to disturbance of the cellular and humoral immunity. Prolonged exposure of radiation may lead to DNA mis-repair, chronic irradiation results in stable chromosome aberrations, increased incidence of micronuclei and point mutations in immune population [21].

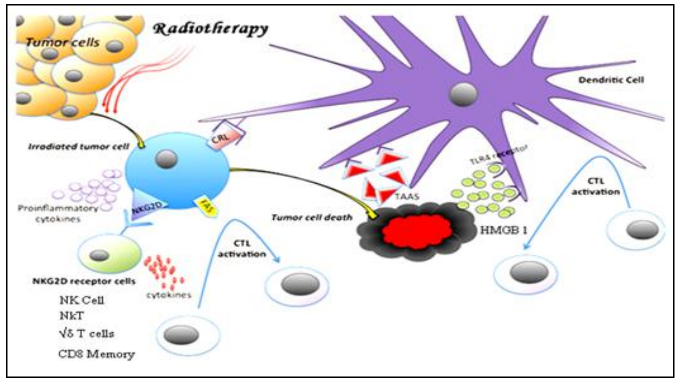

FIG. 3: RESPONSE OF IMMUNE SYSTEM ON IRRADIATION BY RADIOTHERAPY

Therapeutic / Protective Aspects: The usage of compounds to safeguard against the deleterious effects of radiation was endeavored following World War-II to protect humans from the military use of atomic weapons. The pre-treatment of amino-acid cysteine protected rats from the detrimental effects of X-rays was first demonstrated by Patt *et al*., [22]. Later on hundreds of synthetic compounds were screened for their radioprotective efficacy; the list of important synthetic compounds is shown in **Table 1**.

Chemical Compounds as Radioprotectants: The efficacy of any radioprotector is expressed in terms of dose modifying factor (DMF) or dose reduction factor (DRF). DRF is evaluated by plotting the percentage survival at the end of 30 days against different doses of radiation [23].

$$\frac{\text{DMF Radiation } LD_{50} \text{ in the presence of the protector}}{\text{DRF Radiation} LD_{50} \text{ in the absence of protector}}$$

Where, LD_{50} is the lethal dose of radiation causing 50% death in animals.

Although several compounds were screened and tested as radioprotective agents, they have some limitations and side effects and many of them have not fulfilled to be ideal for their effectiveness, availability, specificity and tolerance. In recent years, an array of immunomodulatory agents, hemopoietic growth and stimulating factors, synthetic chelating agents and natural antioxidants have been examined for their ability to ameliorate radiation-induced damage, however, the side effect profile of these agents necessitated the search for second-generation drugs that are more effective, less toxic and with more acceptable properties with respect to route and frequency of administration [14].

TABLE 1: LIST OF SYNTHETIC RADIOPROTECTANTS

Compounds	DRF	Dosage	Route	Reference
5-Aminosalicylic acid	1.43	25 mg/kg	i.p.	24
5-Hydroxytryptamine	-	3 mg/0.5ml	-	26
5-Hydroxyl tryptophan	1.2	200 mg/kg	-	14
2-Mercaptopropionyl-glycine	1.4	20 mg/kg	i.p.	27
Captopril	-	25 mg/kg	i.p.	28
Chromone-thiazolidine	1.48	790 mg/kg	i.p.	14
Cimetidine	1.61	15 mg/kg	i.p.	29
Cysteine	1.36	50 mg/day	i.m.	30
Dihydroxychromone	-	222 mg/kg	i.p.	31
WR-151327	1.46	200 mg/kg	i.p.	24, 25, 32
WR-2721	1.58	400 mg/kg	i.p.	24, 25, 33
WR-3689	1.51	455 mg/kg	i.p.	24, 25
WR-77913	1.58	1115 mg/kg	i.p.	24
Tempol-H (nitroxide)	1.3	325 mg/kg	i.p	34
Nimodipine	1.19	10mg/kg	i.p	32

Natural Product Based Radioprotectants: As an effective alternative, natural product based therapeutics are being increasingly explored as reliable alternative source for radioprotection. The availability of vast natural dietary and time tested medicinal resources in this planet is the motivation behind exploring the possibility of developing efficient, economically viable and clinically acceptable radioprotectors for human application from these resources. A good number of plants and herbs have been explored for their radioprotective activities. Some are categorized as 'Radio-protectors' because they can ameliorate the detrimental effects caused to the normal cells and reduce the side effects of radiation therapy and others are called as 'Radiosensitisers' since they augment the radiation induced cell death caused to the tumor, and thus curtail the dose of radiation treatment [35, 36].

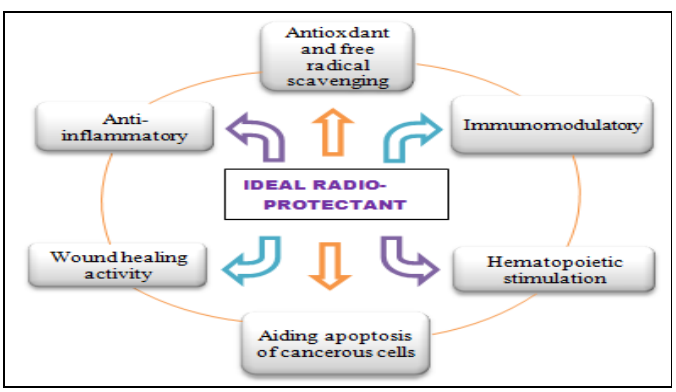

FIG. 4: BIOLOGICAL ACTIVITIES OF AN IDEAL RADIOPROTECTANT

However, their use as radioprotectors needs systematic assessment and scientific validation so as to label them successfully as potential alternatives in place of synthetic chemicals. Plant preparations have been classified variedly such as crude powders, plant extracts, fractions, poly-herbal formulations, pure compounds *etc*. The characteristic features of an agent to be considered as an ideal radioprotectant is shown in **Fig. 4**.

Several plants are rich sources of phytochemicals like alkaloids, saponins, polyphenols which include anthocyanins, flavonoids, stilbenes, tannins, lignins, *etc* [37]. Among these, several flavonoids (quercetin, orientin, myricetin-flavonol, luteolin-flavone and (−)-epigallocatechin gallate-flavanol, rutin, naringin, *etc*.), have been reported as potent antioxidants with radioprotective abilities [38, 39].

Scavenging of radiation-induced free radicals and elevation of cellular antioxidants might be foremost mechanism for radioprotection due to the presence of polyphenols. These polyphenols could up-regulate messenger RNA of antioxidant enzymes such as catalase, GSH transferase, GSHPx, superoxide dismutase (SOD) and hence counteract the oxidative stress-induced by ionizing radiations. Protection against radiation-induced damage is also conferred by the up-regulation of DNA repair genes, which bring about an error free repair of DNA damage. Certain extent of radioprotective activity is provided by the reduction in LPO and elevation in non-protein sulfhydryl groups. The plants and herbs may also inhibit activation of protein kinase C, mitogen activated protein kinase, cytochrome P-450, nitric oxide and several other genes that may be responsible for inducing damage after irradiation [37]. A variety of plant-derived materials such as polysaccharides, lectins, peptides flavonoids and tannins have been reported to modulate the immune system with potent good immunomodulatory activity.

Plants and Herbs as Radioprotectants:

***Withania somnifera* (Ashwagandha):** *Withania somnifera* is a short, tender perennial shrub that belongs to Solanaceae family. It occurs naturally in drier regions of Mediterranean, Middle East, Indian subcontinent and southern China. Ayurvedic system of medicine has been using this plant since centuries to increase longevity and vitality and western researchers also supported its versatile medicinal properties and its polypharmaceutical use. The roots are reported to contain alkaloids, amino acids, steroids, volatile oil, starch, reducing sugars, glycosides, hentriacontane, dulcitol, withaniol, an acid. The leaves and stem of the plant (Indian chemotype) are reported to contain about a dozen withanolides, alkaloids, many free amino acids, glycosides, chlorogenic acid, glucose, condensed tannins and flavonoids [40]. Withaferin A, a steroidal lactone is the most important withanolide isolated from the extract of the leaves and dried roots of *Withania somnifera*.

Besides reducing tumor cell proliferation, WS has demonstrated to increase overall animal survival time. Furthermore, by possibly alleviating undesirable side-effects it has been shown to augment the efficacy of radiation therapy. Without interfering with tumor reducing actions of the drugs, WS also decreases the side effects of chemotherapeutic agent’s cyclophosphamide and paclitaxel. WS treatment resulted in a major increase in heme oxygenase activity as well as a noteworthy reduction in reduced GSH content. Furthermore, the activities of antioxidant enzymes, including SOD and GSHPx in hepatic tissues were also reduced. Given its broad spectrum of cytotoxic and tumor-sensitizing actions, WS presents itself as a novel complementary therapy for integrative oncology care [41]. Administration of a 75% methanolic extract of the plant was found to significantly increase the total White Blood Cell (WBC) count in normal Balb/c mice and reduce leucopoenia induced by sublethal dose of gamma radiation (γ-GR). Major activity of WS seemed to be in the stimulation of stem cell proliferation [42].

***Aloe vera* (Gheekumari):** This is a stemless or very short-stemmed succulent plant, a member of Asphodelaceae family, and is cultivated around the world. It has escaped from cultivation and become naturalized in the Mediterranean, North Africa, the Indian subcontinent, South America and the Caribbean. Major components of *Aloe vera* include organic acids like isovaleric acid, pentanoic acid, lactic acid, furancarboxylic acid, threonic acid, malic acid, and polyphenolslike vanillic, gneissic, syringic, sinapic, caffeic, ferulic and p-coumaric phytosterols like campesterol, stigmasterol, *β*-sitosterol which support the radioprotective nature of this plant. *Aloe vera* extract is found to have damage resistant properties against radiation induced biochemical alterations in Swiss Albino mice. The remarkable radioprotective effect of the drug was also revealed by Bakuridze *et al*., [43].

***Pterocarpus santalinus* (Red Sandal Wood):** This is a light-demanding small tree of the family Fabaceae. It is popularly known as Red sanders and it is an endemic species confined to Southern parts of Eastern Ghats of India especially in Andhra Pradesh. It has been used as a folk remedy for the treatment of inflammatory conditions such as chronic bronchitis, chronic cystitis, fever, headache, mental aberrations, ulcers, cancers, *etc*. Phytochemical investigations of aqueous and ethanol extracts of stem bark revealed the presence of alkaloids, phenols, saponins, glycosides, flavonoids, triterpenoids, sterols, and tannins [44]. It is highly valued in East and South- East Asian Region especially in China and Japan.

Therefore, Red Sanders in various forms, shapes and sizes are being smuggled out of the country. The heart wood contains isoflavone glucosides and two anti-tumor lignans, *viz*., savinin and calocedrin. The previous phytochemical investigations of this plant revealed the presence of six sesquiterpenes, one isoflavone, two lignans, and two aurone glycosides. Literature shows that the methanol extract of the heartwood exhibited potent cytotoxicity (IC_{50} <20 lg/mL) against three cancer cell lines (HepG2, Hep3B, A549) and anti-inflammatory activity (IC_{50} <10 lg/mL) [45, 46, 47].

Syzygium cumini: It is an evergreen tropical tree in the flowering plant family Myrtaceae and native to the Indian subcontinent and adjoining regions of Southeast Asia. It is commonly known as black plum or jambu/Jambolan used as an important medicinal plant in various traditional systems of medicine. It is effective in the treatment of diabetes mellitus, inflammation, ulcers and diarrhoea and preclinical studies have also shown it to possess antineoplastic, chemopreventive and radio-protective properties [48]. The leaves are rich in acylated flavonol glycosides quercetin, myricetin, myricetin 3-O-alpha-L-rhamnopyranoside, esterase, galloyl carboxylase and tannin. The stem bark is rich in betulinic acid, friedelin, epi-friedelanol, β-sitosterol, eugenin and fatty acid ester of epi-friedelanol, quercetin, kaempferol, myricetin, gallic acid and ellagic acid, bergenins, flavonoids and tannins.

The presence of gallo-and ellagi-tannins may be responsible for the astringent property of stem bark. The flowers are rich in kaempferol, quercetin, myricetin, isoquercetin, myricetin-3-L-arabinoside, quercetin-3-D-galactoside, dihydromyricetin, oleanolic acid, acetyl oleanolic acid, eugenol-triterpenoid A and eugenol-triterpenoid B. The roots are rich in flavonoid glycosides and isorhamnetin 3-o-rutinoside. The fruits are rich in gallic acid, anthocyanins, delphinidin-3-gentiobioside, malvidin-3-laminaribioside, petunidin-3-gentiobioside, cyanidindiglycoside, petunidin and malvidin.

***Curcuma Longa* (Haldi):** It is a perennial shrub belonging to Zingiberaceae, found in almost all states of India, more abundantly in Bengal, Mumbai, Andhra Pradesh and Tamil Nadu where it is cultivated for commercial purpose. Widespread research in the last decade in cell culture and in rodents has shown that curcumin can sensitize tumors to different chemotherapeutic agents. Likewise evidence too demonstrates that this agent can sensitize a variety of tumors to γ-GR including glioma, neuroblastoma, cervical carcinoma, epidermal carcinoma, prostate cancer, and colon cancer. Earlier studies demonstrates that it down regulates several growth regulatory pathways and precise genetic targets including genes for nuclear factor kappa-light-chain-enhancer of activated B cells, signal transducer and activator of transcription 3, cyclooxygenase-2, Akt (also known as protein kinase B), anti-apoptotic proteins, growth factor receptors, and multidrug-resistance proteins [49]. While it acts as a chemosensitiser and radiosensitiser for tumors in some cases, curcumin has also been revealed to safeguard normal organs from chemotherapy and radiotherapy-induced toxicity.

The protective effects of curcumin seem to be facilitated by its ability to induce the activation and expression of antioxidant enzymes, directly quench free radicals, and inhibit p300 histone acetyl transferase (HAT) activity. These preclinical studies are expected to lead to clinical trials to prove the potential of this age-old golden spice for treating cancer patients and radiation effects [50]. Overall, *Curcuma longa* exerted a beneficial radioprotective effect against radiation-induced oxidative stress in male rats by alleviating pathological disorders and modulating antioxidant enzymes [51].

Tinospora cordifolia: Known as guduchi is a member of Menispermaceae family. It is a large, glabrous, perennial, deciduous, climbing shrub of weak and fleshy stem distributed throughout the tropical Indian subcontinent and China. Berberine, palmatine, tembetarine, magnoflorine, choline, tinosporin, isocolumbin, palmatine, tetra-hydro-palmatine, magnoflorine, β-sitosterol, hydroxyl ecdysone and ecdysterone are some of the potent bioactive constituents of this plant [52]. Its aqueous extract showed antioxidant activity and inhibited radiation mediated 2-deoxyribose degradation in a dose dependent fashion. The radiosensitization activity of TC extract may be due to depletion of GSH and GSH-S-transferase (GST), accompanied by elevated levels of LPO and DNA damage of tumor cells. Thus, TCE may offer an alternative treatment strategy for cancer in combination with gamma radiation (γ-GR) [53, 54].

***Ocimum sanctum* (Tulsi):** It is an herb belonging to family Lamiaceae, widely distributed in tropical and warm temperate regions. Ocimum genus contains about 130 species of herbs and shrubs from the tropical regions of Asia [55, 56].

Several *Ocimum* species are regularly used for the treatment of inflammation, stress, diarrhoea and as an antioxidant drug in the Indian ethnic system of medicine. The stem and leaves of tulsi contain a variety of constituents that may have biological activity, including saponins, flavonoids, triter-penoids, tannins eugenol, urosolic acid, carvacrol, linalool, limatrol, caryophyllene, methyl carvicol, rosmarinic acid, apigenin, cirsimaritin, isothymusin and isothymonin.

The antimelanoma and radioprotective activity of Ocimum was demonstrated in C 57 BL and Swiss Albino mice. The aqueous extract of Ocimum caused a substantial decline in tumor volume, increase in average body weight, and survival rate of mice. Ocimum extracts exhibited modulatory effect against radiation-induced chromosomal damage, caused increase in reduced GSH level and GST activity. Two flavonoids of this plant resulted in protection against death from gastrointestinal syndrome as well as bone marrow syndrome when injected intraperitoneally. These findings demonstrate Ocimum as one of the potential sources for plant-based pharmaceutical products.

***Adhatoda vasica*:** It is a small evergreen plant of the family Acanthaceae. This shrub grows on the plains of India and in the lower Himalayas up to a range of 1000 meters above the mean sea level and it can be cultivated too in other tropical areas. It grows well in low moisture areas and dry soils also. Oral administration of *A. vasica* leaf extract prior to whole body irradiation showed a noteworthy increase in GSH content, decrease in LPO level and ultimately demonstrated significant protection in terms of hematological parameters. Likewise, a major drop in level of acid phosphatase and increase in alkaline phosphatase level were observed. *A. vasica* pre-treatment significantly prevented radiation-induced chromosomal damage in bone marrow cells and also showed significant radioprotective effects on testis that merits additional systematic studies designed at ascertaining the role of key constituents in the extract [57, 58].

The vast variety of pharmacological uses of Adhatoda is believed to be the result of its rich concentration of alkaloids like vasicine, l-vasicinone, deoxyvasicine, maiontone, vasicinolone and vasicinolin leaves and roots. Research indicates that these chemicals are responsible for Adhatoda's pharmacological effects.

***Amaranthus paniculatus*:** This is a short-lived herb of Amaranthaceae family that grows mostly in the temperate and tropical regions. Radio modulatory effect of *A. paniculatus* leaf extract against 6, 8 and 10 Gy γ-GR has been assessed by 30day survival of Swiss Albino mice. Animals of control groups exhibited diarrhoea, rufled hairs, epilation, facial edema and consistent decrease in body weight [59].

However, in experimental groups treated with Amaranthus extract these signs were less severe / absent. The pharmacological activity could be due to beta carotene, ascorbic acid, folate, phenolic acids like ferulic acid, vanillic acid and syringic acid are present in Amaranthus in addition to alkaloids and saponins [60].

***Allium sativum* (Garlic):** *Allium sativum* is a bulb belonging to Amaryllidaceae family typically grow in a temperate climate like central Asia and in the northern and southern hemispheres. Garlic is reported in traditional medicine to be effective to regulate vascular pressure and elasticity of blood vessels. Experiments on the bone marrow micronucleus revealed that pre-treatment with garlic extract showed a significant reduction in the sulphydryl content and GST activity and it was effective in reducing γ-GR-induced chromosomal damage. Important phytochemicals that are seen in *A. sativum* are quercetin, alliin, allicin, allyl alcohol, diallyl disulfide, ajoene, S-Allyl cysteine, alliinase, allixin, allistatin-I, allistatin-II, β-phyllandrene [61].

***Emblica officinalis* (Amla):** It is a small to medium sized deciduous tree distributed throughout India. The fruit pulp of this plant is an important drug used as a tonic for many diseases in Indian systems of medicine including Triphala. It contains several phytoconstituents like tanins, alkalods, phenolic compounds, amino acids, carbohydrates, Vitamin C, flavanoids, ellagic acid, chebulinic acid, quercetin, chebulagic acid, emblicanin-A, gallic acid, emblicanin-B, puni-gluconin, pedunculagin, citric acid, ellagotannin, trigallayl glucose and pectin as the major constituents [62]. The extract increased the survival time and reduced the mortality rate of mice significantly. Moreover, body weight loss in amla administered irradiated animals was significantly less in comparison with animals who were given radiation only [63].

Aegle marmelos **(Bael):** This is a deciduous tree belongs to Rutaceae family and distributed throughout Southeast Asia as a naturalized species. *Aegle marmelos* extract (AME), commonly known as bael, is used to treat diseases resulting from oxidative stress from ancient times. The radio protective effect of AME was investigated in mice exposed to different doses of γ-GR. In an experiment on mice, pre-radiation treatment of mice with AME caused a significant depletion in LPO followed by a significant elevation in GSH concentration in the liver of mice 31 days after irradiation [64]. Treatment of mice with AME before irradiation reduced the symptoms of radiation sickness and delayed death compared with the irradiated control mice given sterile physiological saline.

Phytochemicals present in new alkaloids from the leaves of *A. marmelos* were reported *viz.*, O-3,3-(dimethylallyl) halfordinol, N-2-ethoxy-2-(4-methoxyphenyl) ethylcinnamamide, N-2-methoxy-2-[4-(3',3'-dimethylallyloxy)phenyl] ethylcinnam-amide, N-2-methoxy-2-(4-methoxyphenyl) ethyl-cinnamamide and marmeline. The essential oil of *A. marmelos* leaves were studied very much extensively in India by various workers since 1950. α-phellandrene was found to be the common constituent of the essential oil from leaves, twigs and fruits. Limonene (82.4%) was reported as the main constituent from *A. marmelos* leaves and it was shown that limonene is characteristic marker for identification of *A. marmelos* oil samples.

Mentha piperita **(Pudina):** It is an aromatic herb belonging to Lamiaceae family, found indigenous to Europe and the Middle East, is now widespread in cultivation in many regions of the world. Detailed investigations have also shown that the aqueous extract of *M. piperita* protected the vital radiosensitive organs like testis, gastrointestinal and hematopoietic systems in mice against radiation induced damage. Previous studies suggest that, phenolic compounds, flavonoids and flavonols of *M. piperita* leaf extract may be held responsible for radioprotective effect due to their antioxidant and radical scavenging activity [65, 66]. The protective effects of leaf extract of *M. piperita* against radiation induced hematopoietic damage in bone marrow may be attributed to the maintenance of Erythropoietin (EPO) level in Swiss Albino mice [67]. The major constituent reported is volatile oil of which the principal component is usually menthol, together with menthol stereoisomers such as neomenthol and isomenthol. Other monoterpenes include menthone, menthyl acetate, menthofuran, cineol and limonene.

Zingiber officinale **(Ginger):** It is an herbaceous perennial flowering plant, indigenous to south China, spreaded eventually to the Spice Islands and other parts of Asia and subsequently to West Africa. The rhizome of *Z. officinale* commonly known as ginger (Sunthi/Ardraka) has widely been used as a spice and condiment in different societies since antiquity. That ginger possesses chemo-preventive and antineoplastic properties has been documented by numerous preclinical studies. Side-effects of γ-GR, doxorubicin and cisplatin have been effectively reduced by *Z. officinale*. In addition, it is also reported to inhibit the efflux of anticancer drugs by P-glycoprotein and to possess chemosensitizing effects in certain neoplastic cells *in-vitro* and *in-vivo* [34].

Preclinical studies carried out in the last decade have shown that ginger and its phytochemicals dehydrozingerone andzingerone possess radio protective effects in laboratory animals and in cultured cells *in-vitro*. Mechanistic studies have indicated that free radical scavenging, antioxidant, anti-inflammatory and anti-clastogenic effects may contribute towards the observed protection. Additionally, studies with tumor bearing mice have also shown that zingerone selectively protects the normal tissues against the tumoricidal effects of radiation [33]. Major compounds found in *Zingiber officinale* are cineole, camphol, cycloisosativene, α curcumen, α gingiberene, α fernesene, gingerol, β-pinen and zingiberenol.

Azadirecta indica **(Neem):** It is a fast growing tree of the family Meliaceae, native to India and the Indian subcontinent including Nepal, Pakistan, Bangladesh and SriLanka. Radiosensitization by neem oil was studied using mice/3T3 cells and severe combined immunodeficiency cells. neem oil enhanced the radiosensitivity of the cells when applied both during and after X-ray irradiation under aerobic conditions. The cytofluorimeter data showed that neem oil treatment before and after X-irradiation reduced the G2/M phase, thus inhibiting the expression of the radiation induced arrest of cells in the G2 phase of the cell cycle [70].

Phytochemical compounds of neem include isoprenoids (like diterpenoids and triterpenoids containing protomeliacins, limonoids, azadirone and its derivatives, gedunin and its derivatives, vilasinin type of compounds and C-secomeliacins such as nimbin, salanin and azadirachtin) and nonisoprenoids, which are proteins or amino acidsand carbohydrates, sulphur compounds, polyphenolics such as flavonoids and their glycosides, dihydrochalcone, coumarin and tannins, aliphatic compounds, *etc*.,[71]. Nimbidin, a major bitter component of seed kernels oil of *Azadirachta indica* demonstrated several biological activities. From its crude some tetranortriterpenes, including nimbin, nimbinin, nimbidinin, nimbolide and nimbidic acid have been isolated and reported for their biological activity [71].

***Piper betle* (Betel Leaf/Pan):** It is a tropical shade-loving perennial evergreen plant of Piparaceae family, native to central and eastern Malaysia and was taken into cultivation throughout Malaysia and tropical Asia. Oral administration of *Piper betle* leaf extract (PBL extract) an hour before irradiation in mice considerably enhanced radiation abated antioxidant potential of plasma and GSH level in all the observed organs. Treatment with PBL extract effectively lowered the radiation induced lipid peroxidation in the selected group treated with the extract. Frequency of radiation induced micronucleated cells declined significantly at 24h post-irradiation interval by *P. betel* extract administration.

The radioprotective and antioxidant activity of *P. betle* can be related to a variety of phytochemicals present in it. Chavibetol, allypyrocatechol, chavibetol acetate, eugenol, piperitol, quercetin, luteolin, β-sitosterol, hydroxychavicol, α-terpineol, allyl catecol Eugenol methyl ether, D-limonene, 2-noanone, 4-allyl phenyl acetate, piperlonguminine, α-cadinol, ocimeme, N-decanal, 2-undecanone, myrcene, stearic acid, 2-mono palmitin, alloocimene, cavacrol, cymene, terpinolene, α-myrcene, limonine, vanillin, thymol, Cis-piperitolterpinolene, procatechuic acid, *etc*., are the major bioactive components observed in *P. betle* [72].

***Moringa oleifera* (Drumstick Tree/Sahjan):** It is a slender softwood tree of Moringaceae family that is native of India, occurring wild in the sub-Himalayan regions of Northern India and now grown world-wide in the tropics and sub-tropics. Protective effect of *Moringa oleifera* leaf extract (MoLE) against radiation-induced lipid peroxidation has been well reported. It was observed that, treatment with Moringa extract prevented radiation induced lipid peroxidation in liver and inflammation and restored GSH in the liver.

Phytochemical analysis showed that Moringa possess various phytochemicals such as ascorbic acid, phenolics (catechin, epicatechin, ferulic acid, ellagic acid, myricetin) *etc*., which may play the key role in prevention of hepatic LPO by scavenging radiation induced free radicals. Mice treated with *Moringa* extract prior to irradiation demonstrated an increase in SOD, catalase, GSH and fluorescence recovery after photobleaching. Its activity can be augmented by the presence of well-known compounds like 4-(4'-O-acetyl-a-L-rhamno-pyranosyloxy) benzyl isothiocyanate, 4-(a-L-rhamnopyranosyloxy) benzyl isothiocyanate, niazimicin, pterygospermin, benzyl isothiocyanate, and 4-(a- L- rhamnopyranosyloxy) benzyl glucosinolate [73].

***Centella asiatica* (Brahmi):** It is a small, herbaceous, frost-tender perennial flowering plant belongs to Apiaceae family and is native to wetlands in Asia (*C. asiatica*). Administration of the extract prevented a radiation-induced decline in antioxidant enzyme levels. This suggests that radioprotection by *C. asiatica* extract could be mediated by mechanisms that act in a synergistic manner, especially involving antioxidant activity [74]. The primary active constituents of *C. asiatica* include asiaticosides, in which a trisaccharide moiety is linked to the aglycone asiatic acid, madecassoside and madasiatic acid. These triterpene saponins and their sapogenins are mainly responsible for the wound healing and vascular effects by inhibiting the production of collagen at the wound site. Other components isolated from *C. asiatica*, such as brahmoside, brahminoside and centelloside and its derivatives may be responsible for CNS, utero relaxant and in the treatment of veinous hypertension. In addition, the total plant extract contains plant sterols, flavonoids, and other components like tannins (20-25%), phytosterols (campesterol, sitosterol, stigmasterol), mucilages, resins and free aminoacids (alanine, serine, aminobutyrate, aspartate, glutamate, lysine and treonine).

Aphanamixis polystachya **(Rohitak/ Pithraj):** It is a tree species of Meliaceae family commonly called as Rohituka, found in Indo-Chinaregion. Jagetia and Venkatesha[75] investigated the effect of ethyl acetate fraction of *Aphanamixis polystachya* (EAP) on the radiation-induced chromosome damage in the bone marrow cells of Swiss Albino mice exposed to various doses of γ-GR. EAP treatment also reduced LPO in bone marrow cells in a concentration dependent manner. Thus EAP 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 LPO [76].

Phytochemical constituents of *Aphanamixis polystachya* are aphanamixinin, aphanamixolin, aphanamixolide, aphananin, aphanamixol, amo-orinin, prieurianin, amooranin, *β*-sitosterol, stigmasterol and sometannins. Fruit shell contains triterpenesaphanamixin. Bark contains tetra nortriterpene, aphanamixinin. Leaves contain diterpene, alcohol, aphanamixol and b-sitosterol. Seed yield a limonoid, rohitukin, polystachin, alkaloid, a glycoside and a saponin, a chromone and three flavonoid glycosides.

Polyherbal Formulations: There are some polyherbal formulations that show radioprotective effects. Abana, cystone, geriforte, mentat, triphala are the major polyherbal formulations and their active ingredients and mode of action were pointed out in the **Table 2**.

TABLE 2: LIST OF HERBAL FORMULATIONS

Name of the poly herbal formulation	Ingredients	Mode of radioprotection
Abana	*Terminala arjuna, Centella asiatica, Withania somnifera*	Good radioprotective agent, protects mouse bone marrow against radiation-induced micronuclei formation, enhance the survival of mice after exposure to γ-radiation [77-83]
Cystone	*Rubia cordifolia, Didymocarpus pedicellata, Saxifrago ligulata, Cyperus scariosus, Achyranthes aspera, Tinospora cordifolia*	Delayed the onset of mortality and reduced the symptoms of radiation sickness [84]
Geriforte	*Chyavan-prash, Withania somnifera, Emblica officinalis, Mucuna urens*	Protects against GI and bone marrow death upon γ-radiation exposure [85]
Mentat	*Bacopa monniera, Centella asiatica, Adoxa moschatellina, Terminalia arjuna*	Delayed the onset of mortality and reduced the symptoms of radiation sickness [86]
Triphala	*Terminalia chebula, Phyllanthus emblica and Terminalia bellerica*	Reduces the symptoms of radiation sickness upon exposure to γ-radiation and provides protection to gastrointestinal and hematopoietic deaths [87-90]

Semi-natural Compounds and Other Plant Species as Radio-protectors: There is some semi synthetic and many natural phytochemicals that show radioprotective effects are cited in the literature. Ascorbic acid, caffeine, chlorophyllin, ferulic acid, glutathione, glycyrrhizic acid, troxerutin, vanillin, Vitamin E and its derivatives, alpha-tocopherylandits derivatives [91]. Other plants that are reported to show radioprotection include *Asparagus racemosus* (Shatavari), *C. aurantium* var. amara, *Panax ginseng*, *Phyllanthus amarus*, *Rubia cordifolia*, *Terminalia chebula*, *Ageratum conyzoides* Linn., *Allium cepa* Linn, *Aloe arborescens* Mill., *Angelica sinensis* (Oliver) Diels, *Archangelica officinalis* Hoffm, *Biophytum sensitivum* (Linn.), *Coronopus didymus* Linn., *Ginkgo biloba* Linn, *Glycyrrhiza glabra* Linn., *Hippophae rhamnoides* Linn, *L. chinense* Mill., *Mentha arvensis* Linn, *Podophyllum hexandrum* Royle, *Tephrosia purpurea* (Linn.), *Piper longum*

Linn, *Pilea microphylla* (Linn.) *etc*.,[92-96]. Evidence also has been documented for the radioprotective potential of *Rhodiola imbricate* (Roseroot) [97-99], *Podophyllum hexandrum* [100], *Grewia asiatica* [101, 102], *Olea europaea* Linn. (Olive tree / Jaitun), *Rosemarinus oficinalis* (Rosemary).

CONCLUSION: This review highlighted the increased exposure of humans to various sources of radiation and their ill effects to cellular level. It summarized various synthetic, semi-synthetics and natural product based drugs/formulations used for radioprotection or that augment chemo / radio-therapy. This review offers a platform for researchers to work develop novel formulations/ drugs that are cost effective and can protect or mitigate radiation-induced damage.

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