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Review article

Prospects in the development of natural radioprotective therapeutics with anti-cancer properties from the plants of Uttarakhand region of India

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ABSTRACT

Radioprotective agents are substances those reduce the effects of radiation in healthy tissues while maintaining the sensitivity to radiation damage in tumor cells. Due to increased awareness about radioactive substances and their fatal effects on human health, radioprotective agents are now the topic of vivid research. Scavenging of free radicals is the most common mechanism in oncogenesis that plays an important role in protecting tissues from lethal effect of radiation exposure therefore radioprotectors are also good anti-cancer agents. There are numerous studies indicating plant-based therapeutics against cancer and radioprotection. Such plants could be further explored for developing them as promising natural radioprotectors with anti-cancer properties. This review systematically presents information on plants having radioprotective and anti-cancer properties.

1. Introduction

1.1. Ionizing radiations

The harmful effects of radiation are familiar in today's world. The level of radiation is increasing day by day due to rapid technological advancement; therefore there is a need to protect human, animals, and even plants against such harmful effects of ionizing radiation. Radiations are present in our environment from the genesis of the Universe. Actually, radiation is the energy released in the form of particle or electromagnetic waves from radioactive isotopes. It can be terrestrial and cosmic (from outer space) ionizing radiations. Basically, ionizing radiations are of three types:

1. Alpha (α) radiation is emitted from radioactive isotopes and consists of alpha particles
2. Beta (β) radiation is emitted from radioactive nuclei and carries a high energy electron with a negative charge. It has high penetrating power in respect to alpha radiations
3. Gamma (γ) radiation is an electromagnetic radiation like visible light, radio waves, and ultraviolet (UV) light.

Alpha and beta radiations have got the capabilities to ionize the atom in ions. Radiation exposure can be accidental/unwanted or aimed. Radiations may be natural or man-made. The escalating consequence of undesirable radiation (radiography, nuclear, space flights, etc.) lays a demand of an effective radioprotector. Exposure to ionizing radiation causes threatening consequences to different organs such as lungs, reproductive system, gut, skin, and eyes, which can result in pathophysiological disorders [Fig. 1].

Devastating effects of radiation poses a need for radioprotectors for safeguarding different organs of our body and to avoid the lethality associated with these radiations.

1.2. Mechanisms of radiation damage

Ionizing radiations damage cells, tissues and organs through a cascade of molecular events that are triggered by free radical known as reactive oxygen species (ROS). As shown in Fig. 2, radiation exposure lead to DNA damage in terms of single- or double-strand breaks (DSBs), base damage and DNA—DNA or protein cross-links and is ultimately responsible for altered genomic expression, protein modification, cell death, senescence and

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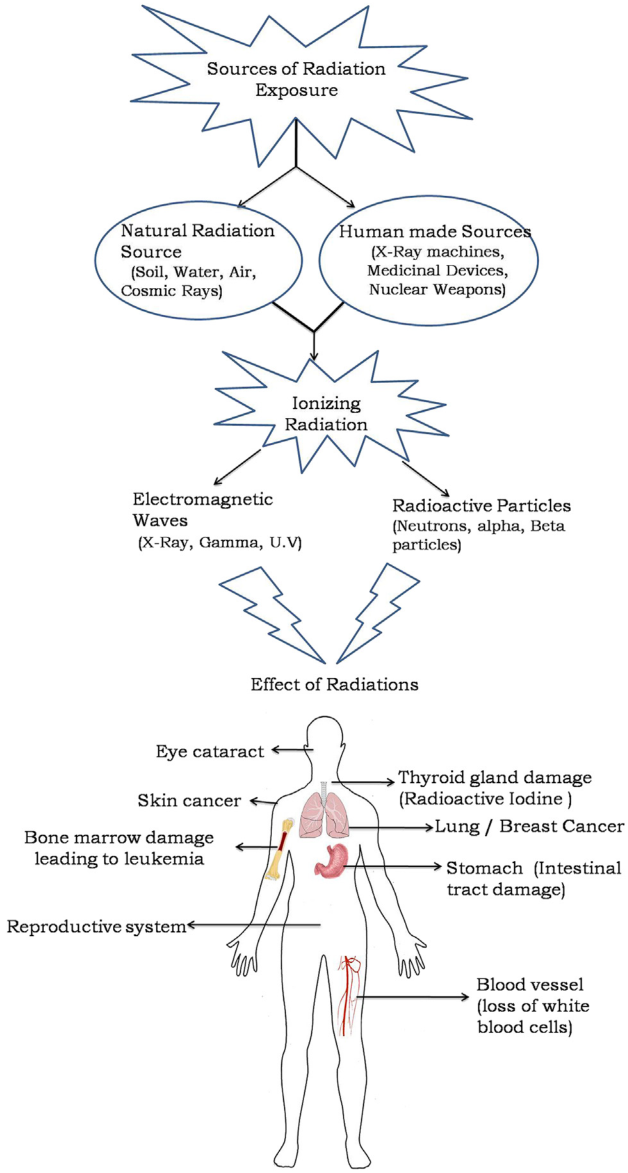

Fig. 1. Effects of radiation exposure on human body.

genomic instability. Genomic instability may also lead to mutations, cancer and birth defects. Among them, DSBs are considered to be an extremely lethal consequence of ionizing radiation.

Radiation affects the integrity and functionality of the cell through the following mechanisms:

1. Direct action: It involves absorption of radiation energy by macromolecules, like DNA or RNA, leading to molecular damage
2. Indirect action: If the molecule is not in reaction path, it can still become chemically altered indirectly via reactions with free radicals and ROS produced primarily from the radiolysis of water.

The rate at which energy is transferred from ionizing radiation to biological system/soft tissues is expressed in terms of linear energy transfer (LET) in kiloelectron volts per micrometer (keV/μm) of track length of soft tissue. Low LET radiation is less effective, whereas high LET radiation is highly efficient and much more effective in producing biological damage than low LET radiations [1].

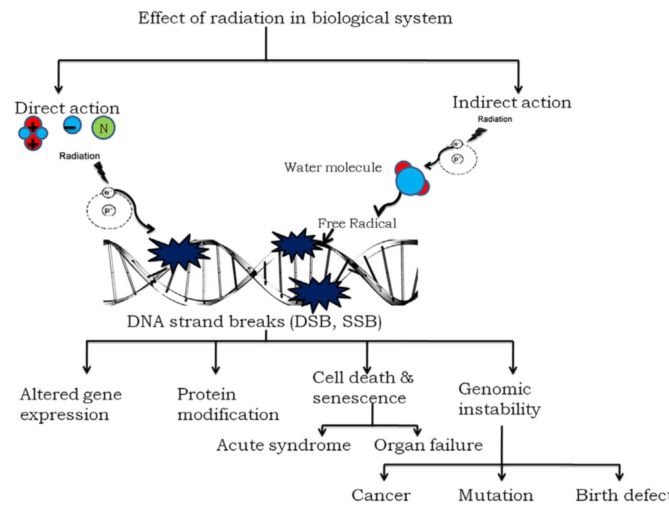

Fig. 2. Effect and mechanism of cellular damage by radiation.

According to the United States Nuclear Regulatory Commission fact sheet, biological effects of radiation on living cells may result in three outcomes: Injured or damaged cells, cell death and incorrect cell repair, resulting in biophysical alterations. The inappropriately repaired DNA breaks are the principal lesions in the induction of mutation, chromosome abnormality, and cancer.

1.3. Radiation and cancer

Radiation exposure is mundane to the people like professionals, handling radioactive materials or to the patients undergoing radio-diagnosis or radiotherapy [2]. According to a report, 22 million people in the world are cancer patients and 6 million die of the disease [3]. Though, indirectly, but radiations may trigger mutation in healthy cells, which further induces molecular alternation within the normal cells. In healthy cells, ionizing radiations generate free radicals from cytoplasmic water and ultimately induce lesions to the DNA content of nucleus. These DNA lesions may lead to cause cancer in normal and healthy cells. Thus, radiations are closely related to cancer.

1.4. Need for radioprotector

Radioprotector is a group of measures, designed to ensure man and his environment protection against the harmful effect of ionizing radiations. They are effective to save our body from wanted or unwanted radiations such as β, γ, UV, or by radio nucleotides (e.g., americium-241, cesium-137. radium, radon, strontium-90, iodine-129 and 131, plutonium, tritium, thorium, and uranium). Hazardous radiations cause consequential injuries to biological systems; therefore, it is a necessity to formulate such pharmacologically dynamic radioprotector that can render protection to human against destructive and damaging outcome of ionizing radiation.

Cellular adaptations and mechanisms to counteract the lethal consequences of damage by radiation are depicted in Fig. 3. Similarly, radioprotectors ensure the elevation of nonprotein sulfhydryl groups, reduction in lipid peroxidation, upregulation of free radicals scavenging activity through transcription upregulation of antioxidant enzymes like glutathione transferase, catalase, superoxide dismutase, glutathione peroxidase. Radiation caused damage can also be neutralized by the upregulation of DNA repair activity.

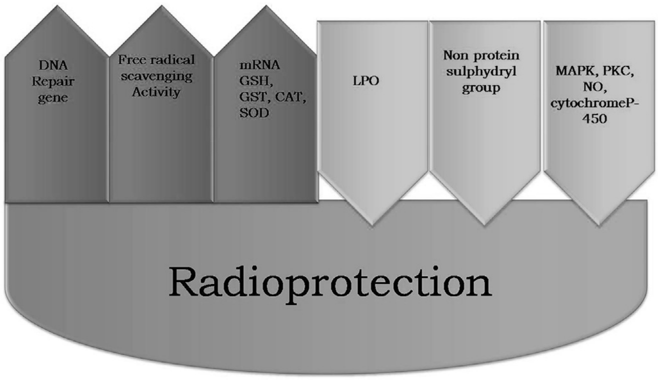

Fig. 3. Cellular mechanism of radioprotection (▮: Up-regulation; ▮: Down-regulation).

Other mechanisms, which help in radio-protection, are the inactivation of protein kinase (PK)-C, nitric oxide, mitogen-activated PK and down-regulation of several other effectors responsible for molecular damage [Fig. 3] [4].

Among the different radioprotectors, the one that has gone through a large number of clinical tribulations and is currently used in radiotherapy is amifostine. Amifostine is the only Food and Drug Administration (FDA) approved radioprotector being used clinically. Due to the limitations of cost and side effects, there is an urgent requirement of exploring safe, efficient and economic radioprotectors, especially of plant origin. Joshi et al., 2009 has defined the following criteria to develop an efficient radioprotective agent [1].

1. Efficient in providing multifaceted protection against undesired effects of radiation
2. No/minimal adverse effects on the majority of organs
3. Preferable route of administration either oral or intramuscular
4. It should reflect an effective time-window and acceptable stability profile
5. Compatible with the wide range of other drugs that will be made available during clinical care
6. The dose has to reach to all the organs and also to be able to cross the blood–brain barrier
7. It should have enough long shelf life, easily accessible and economically viable
8. Lastly, a radioprotector for emergency need should be effective in minimum period and efficacy should be maintained for a longer duration.

Radioprotective agents have potential to protect nontumor tissue from the cytotoxic effect of the ionizing radiation with a relevant impact in the therapeutic index of the radiotherapy treatment.

1.5. Types of radioprotectors

Radioprotectors may be classified as chemical, natural and plant derived.

1.5.1. Chemical radioprotector

This group of radioprotector includes thiazole, dithiocarbamates, aminothiols, tiourei derivative, aminosulphides, thiosulphur, thiophosphoric acid, some biogen amines, and their derivatives [5]. More than a century ago, the amino acid cysteine, containing sulfhydryl group was used *in vivo* for exploring a potent radioprotector [6]. From 1957, Walter Reed Army Research Institute synthesized and screened around 4500 compounds for developing a potent radioprotective agent, but among them only one compound showed the potential effect of radiotherapy [7]. This compound is amifostine (WR-2721), which is the only compound approved by FDA as a clinical radioprotective agent [8]. Amifostine is an organic thiophosphate prodrug [Fig. 4], the analog of cysteamine. Chemically, it is the ester of thiol and phosphoric acid [9]. The FDA has permitted the intravenous use of amifostine, whereas studies through subcutaneous administration have also been done [10,11]. The American Society of Clinical Oncology recommended intravenous administration of 200 mg/m^2 of amifostine daily, 15–30 min before radiotherapy [11]. It is also used by astronauts in space. Although it is useful as a radioprotective agent, but on the other side it has some side effects like cephalalgia, nausea, sickness, vomiting, etc. [12].

1.5.2. Natural radioprotectors

Several hormones and vitamins exhibit activity of radioprotection. β glucan and polysaccharide ginsan are considered to have multiple immune modulatory effects, but also shows radioprotection activity [6]. 5-androstenediol, a hormone produced by the human adrenal cortex is also studied for its potential radioprotective property [11]. Vitamins A, C and E also exhibit radioprotective properties [12,13]. The radioprotective activity is confirmed in Vitamin E and its water soluble derivative tocopherol monoglucoside [14]. There are several reports that supported the radioprotective ability of melatonin, as it is ROS scavenger and also scavenge peroxyl nitrite anions and peroxyl radicals [14]. In development of natural radioprotector several *in vivo* and *in vitro* tests have to be done.

1.5.3. Plant based radioprotectors

Unlike the synthetic compounds, herbal products are preferable due to being nontoxic, inexpensive and harmless to human. Polyphenols, flavonoids and a range of secondary metabolites are found in the different parts of the plant that are responsible for the radiation protection and anti-cancer properties. Several plants based natural products have been explored for its anti-cancer and radioprotective properties [15]. Over 60% of currently used anticancer agents are derived in one or another form of natural sources including plants. Taxol, vinblastine, vinca alkaloids, vincristine, and topotecan are anti-cancer agents of plant origin and are in clinical use all over the world [16,17]. Therefore, it seems pertinent to explore a plant-based safe, efficient, and low-cost radioprotector. There are several plants in the Uttarakhand region of India nested in Western Himalaya, which have shown promising radioprotective and anti-cancer activities.

2. Plants of Uttarakhand region having radioprotective and anti-cancerous properties

India has a rich history of using plants for healthcare in general and treatment of cancer without causing toxicity. As estimated,

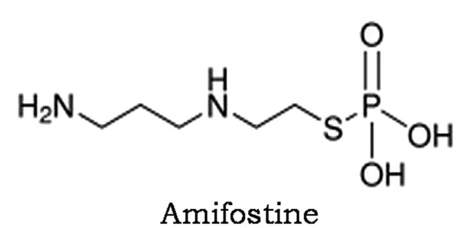

Fig. 4. Chemical structure of Amifostine.

India has about 15,000 species of plants with medicinal property. Presently, about 8000 of these are in use [18]. Contributions made by the Indian system of medicines and folk tradition have been acknowledged by the WHO as well. In India, Uttarakhand region is considered as one of the most important botanical realm of the world. The Uttarakhand region covers an area of 53,483 km^2 and it falls under Western Himalayan region. This region has a long history and tradition as well as the rich heritage of using medicinal and aromatic plants in health care.

Some plants of Uttarakhand region, which have exhibited significant radioprotective or anti-cancer properties, are shown in Table 1.

2.1. *Aegle marmelos*

Aegle marmelos belongs to *Rutaceae* family and is the only member of the monotypic genus *Aegle*. In an Indian traditional system of medicine, all parts of this the plant were used extensively to treat several diseases and disorders. The ethanolic extract showed anti-proliferative activity against several tumor cell lines and breast cancer cell lines [19,20]. The hydroalcoholic leaf extract of *Aegle* showed anti-cancer property at 400 mg/kg of concentration, when examined against *in vivo* mouse model injected with Ehrlich ascites carcinoma (EAC) cell lines [21]. The leaf extract of *A. marmelos* showed optimum radioprotective dose of 15 mg/kg of concentration against 10 gray (Gy) radiations when administered intraperitoneal in a mouse model [22]. The hydroalcoholic extract of fruit part at 20 mg/kg of concentration exhibited the radioprotective effect against gamma-irradiation in a mouse model [22]. The leaf extract also showed significant radioprotection in cultured human peripheral blood lymphocytes at 5 μg/ml of concentration [23].

2.2. *Allium sativum*

Allium sativum belongs to *Amaryllidaceae* family. This plant has high medicinal value and possesses antioxidant, antimicrobial, antitumor, anti-mutagenic, anti-inflammatory, antiviral and anti-ulcer properties. According to Jaiswal (1996), s-allyl cysteine sulphoxide, an active component of garlic oil extract exhibited radioprotective activity against 400 radian (rads) of irradiation in a rat model [24]. Another finding proves that some organosulfur compounds (s-allyl cysteine and s-allyl mercapto-L-cysteine) derived from aged garlic is responsible to retard the growth of tumors by increasing radical scavenging activity and hence can prevent cancer development [25]. Radioprotective activity of aqueous garlic extract has also been demonstrated in rat model at 0.5 mg/ml of concentration against 20 Gy of radiation [26].

2.3. *Andrographis paniculata*

It is a herbaceous plant in the family *Acanthaceae* and is native of India. *Andrographis paniculata* plant extract was found to have andrographolide, which have shown anti-proliferative activity against several tumor cell lines mediated through the induction of protein p27 and reduction of cyclin-dependent kinase 4, which result in cell cycle arrest at G0/G1 phase [27]. Further studies showed anti-cancer and immune stimulatory activity in the methanolic extract of *A. paniculata*. The fraction of methanolic extract in dichloromethane notably inhibited the proliferation of HT-29 cancer cells [28]. Its aqueous extract exhibited a potent antiradical activity against various path-physiological oxidants in rat liver subcellular organelle model system [29]. Varma et al., have also shown the possible application of the natural compound derived from *A. paniculata* in chemotherapy [30].

Table 1
Plants of Uttarakhand region with radioprotective and anti-cancerous properties.

Name of plant	Common name	Distribution range (m)	Active components/chemical constituents	Part used	Experimental system
Aegle marmelos	Bael	Up to 1200	Skimmianine, luvangetin, psoralen, marmin, marmelide, aurapten, marmelosin, lupeol, aegelin, marmrsinin, eugenol, and coumarin [62]	Fruit, leaves, seed, bark	Mice, MCF-7 cell line, T-lymphoid and B-lymphoid cells HPBLs[a], [19–23]
Allium sativum	Garlic	Up to 2400	Allicin, flavonoids, phenol [63,64]	Bulb	Mice [24–26]
Andrographis paniculata	Kalmegha	Up to 500	Diterpenes, lactones, flavonoids, kalmeghin [65]	Whole plant	HPBLs[a], mice, HT-29 cancer cells [27–30]
Centella asiatica	Pennywort	Up to 2500	Titerpene, flavonoid, phenolic acid, sterols, acetylenes [66]	Leaves, root, stem	Cell lines (MK-1, HeLa, B16F10), mice [31–33]
Curcuma longa	Turmeric	Up to 1800	Cucurminoids, cucurmine (I, II, III) [67]	Root	Human lung cancer cell lines, mice [34–40]
Emblica officinalis	Indian Gooseberry	500–1500	Tannins, alkaloids, quercetin, emblicanin A and B, and ellagotannin [68]	Fruit, seed, leaves, root, bark, flower	L929 cell line, mice [41,42]
Hippophae rhamnoides	Sea Buckthorn	2000–3000	Flavonoids, carotenoids, vitamins, tannins, titerpenes, stearic, and oleic acid [69]	Fruits, leaves, bark	Cell lines (P388, S180, SGC7901, lymphatic leukemia), mice [43–46]
Hypericum perforatum	Basanti	900–2700	Acyl phloroglucinols, flavonoids, xanthones, and n-alkanols [70]	Flowers	Mice [47]
Mentha arvensis/ *Mentha piperita*	Field mint/ Peppermint	Up to 1800/ Upto1200	Alkaloids, flavonoids, phenols, tannins, saponins, diterpenes, and monoterpenes [71,72]	Leaves, stem, roots	Mice [48,49]
Nelumbo nucifera	Sacred Lotus	Up to 300	Sesquiterpenes, flavonoids, riterpenes, and alkaloidsa [73]	Flower, seeds, leaves, rhizomes	Human peripheral blood mononuclear cells, mice [50,51]
Ocimum sanctum	Tulasi	Up to 1800	Alkaloids, tannin, saponin, steroid, terpenoid, flavonoid, cardiac glyceride, orientin, vicenin, eugenol, and arsenic acid [54]	Leaves	Lung cancer cell lines, mice [52–55]
Podophyllum hexandrum	Himalayan May Apple	Above 2800	Epipodophyllotoxin, podophyllotoxone, aryltetrahydronaphthalene lignans, and flavonoids [74]	Root and underground stem	Mice, rat [56–61]

[a] HPBLs: Human peripheral blood lymphocyte.

2.4. Centella asiatica

Centella asiatica is the member of *Apiaceae* family. It is commonly used in the Indian traditional system of medicine to treat several diseases. Babu et al., has reported the anti-tumor property of the methanolic extract of *C. asiatica*. The acetone fraction of methanolic extract at 17 and 22 μg/ml of concentration have shown 50% inhibition of EAC and Dalton's lymphoma ascites tumor cells, respectively, whereas 8 μg/ml of extract concentration showed anti-proliferative activity against mouse lung fibroblast (L-929) [31]. Several bioactive components in the methanolic extract of *C. asiatica* were found to possess anti-proliferative activity against several cell lines [32]. The aqueous extract of *C. asiatica* exhibited radioprotective activity at 100 mg/kg body weight in a rat model against the maximum radiation dose 8 Gy [33].

2.5. Curcuma longa

It is a member of *Zingiberaceae* family and is used in Indian history from a long back ago for the treatment of different ailments and diseases. *Curcuma longa* roots contain an active compound curcumin, which exhibit anti-cancer activity against several cancer cells, such as cancer of murine skin, intestine, liver, and stomach. In a clinical phase-1 trial, 8000 mg/day uptake of curcumin is found to be nontoxic [34]. Turmeric extract at 0.4 mg/ml of concentration had potency to inhibit the growth of Chinese Hamster Ovary cell line and was cytotoxic to lymphocytes and Dalton's lymphoma cells. Initial experiments indicated that turmeric extract and curcumin reduced the development of animal tumors [35]. It showed the anti-proliferative activity against A549 human lung cancer cell lines (IC_{50}: 8 μg/L) and several others, mediated through apoptosis [36–39]. Radioprotective and radio-sensitization nature of curcumin has also been revealed in a mouse model at a concentration of 1% (wt/wt) against 3 Gy of radiation [40].

2.6. Emblica officinalis

It is commonly known as amla in India and belongs to *Euphorbiaceae* family. Aqueous extract of *Emblica officinalis* was found to be cytotoxic to L929 cells, and further results suggest cell cycle regulation as a result of antitumor activity of *E. officinalis* [41]. Along with this study, the fruit pulp aqueous extract of *E. officinalis* exhibited radioprotective activity at 100 mg/kg body weight against sub lethal gamma radiation (9 Gy) in Swiss albino mice [42].

2.7. Hippophae rhamnoides

Hippophae rhamnoides belongs *to Elaeagnaceae* family and its extract (25–35 mg/kg body weight) was found to provide around 80% protection against the exposure of 10 Gy to the mice [43]. Goel et al., 2003 reported significant radioprotective activity of *H. rhamnoides* in a mouse model at a dose of 30 mg/kg body weight [44]. The aqueous-alcoholic extract of berries of *H. rhamnoides* increased life span and rendered 82% survival when administered to mice 30 min before ^{60}Co-Gamma irradiation [45]. Patel et al., reported that *H. rhamnoides* can kill both cancer cells and lymphatic leukemia [46].

2.8. Hypericum perforatum

Hypericum perforatum belongs to *Hypericaceae* family and is traditionally used in several countries for healing wounds, nervous disorder, and many more diseases. In India, it is used as anti-helminthic and emmenagogues. *H. perforatum* aqueous extract gives a reliable result in protecting bone marrow and intestinal Mucosa against X-ray in concentration and time dependent manner [47].

2.9. Mentha arvensis/Mentha piperita

They both belong to *Lamiaceae* family and are aromatic plant with diverse usage. *Mentha arvensis* was reported to provide the best protection against radiation in a mouse model after being administered orally at a dose of 10 mg/kg body weight. The chloroform extract of Mentha was found to reduce the severity of symptoms of radiation sickness [48]. The aqueous leaf extract of *Mentha piperita* (1 g/kg body weight) showed efficient protection against chromosomal damage in bone marrow of swiss albino mice after exposure to 8 Gy of radiation [49].

2.10. Nelumbo nucifera

It belongs to *Nelumbonaceae* family. Ethanolic extract of *Nelumbo nucifera* was detected to prevent the proliferation of primary human peripheral blood mononuclear cell, *in vitro* [50]. Acetone-water extract from lotus seed pod was found to possess *in vivo* radioprotective activity against whole body gamma radiation in swiss albino mice at a concentration of 200 mg/kg body weight [51].

2.11. Ocimum sanctum

Ocimum sanctum belongs to *Lamiaceae* family and has diverse medicinal values. The aqueous-ethanolic extract of *O. sanctum* was reported to have a radioprotective effect against gamma radiation in albino mice [52]. The optimal dose for protection was reported to be 50 mg/kg body weight while the acute LD_{50} was 6 g/kg body weight. Ranga et al., reported that along with anti-cancer and chemo-preventive effects of Ocimum, it also has fewer side effects [52]. Further, radioprotective activity was investigated in the leaf extract (10 mg/kg body weight) of *O. sanctum* in combination with WR-2721 (100–400 mg/kg body weight) on bone mouse marrow. Synergism resulted in enhanced protective activity, by the increasing protection factor by the two-fold (PF = 6.68) as compared to that of WR-2721 alone at a dose of 400 mg/kg body weight [53]. Scientific evidence are available for *O. sanctum* to have anti-carcinogenic and radioprotective properties. In a comparative study in a mouse model, Ocimum flavonoid, orientin and FDA approved amifostine were found to exhibit the similar radioprotection at the doses of 50 μg/kg body weight and 150 mg/kg body weight respectively, upon irradiation with 2 Gy-gamma radiation whereas vicenin showed lesser activity [54]. The chemical structure of orientin and amifostine is shown in Figs. 4 and 5. Orientin and vicenin were also reported to reduce chromosome damage in cultured human peripheral lymphocytes at a concentration of 17.5 μM against 4 Gy of gamma irradiation [55].

2.12. Podophyllum hexandrum

It belongs to *Berberidaceae* family and is native of the Himalaya. It is known as Himalayan May apple or Indian May apple. The plant is poisonous, but after processing, it turns into therapeutic. The root and rhizome of the plant have been widely used in India, for over 2000 years to cure a several diseases and disorders. A report on *Podophyllum hexandrum* depict that it acts as an efficient anti-tumor, which was tested against mice carrying solid tumors developed by transplanting Ehrlich ascites tumor [56]. Podophyllotoxin, a natural product of *P. hexandrum* has anti-tumor activity and it is also used as starting compound for the synthesis of anti-cancer drug etoposide and teniposide [57]. Effect of

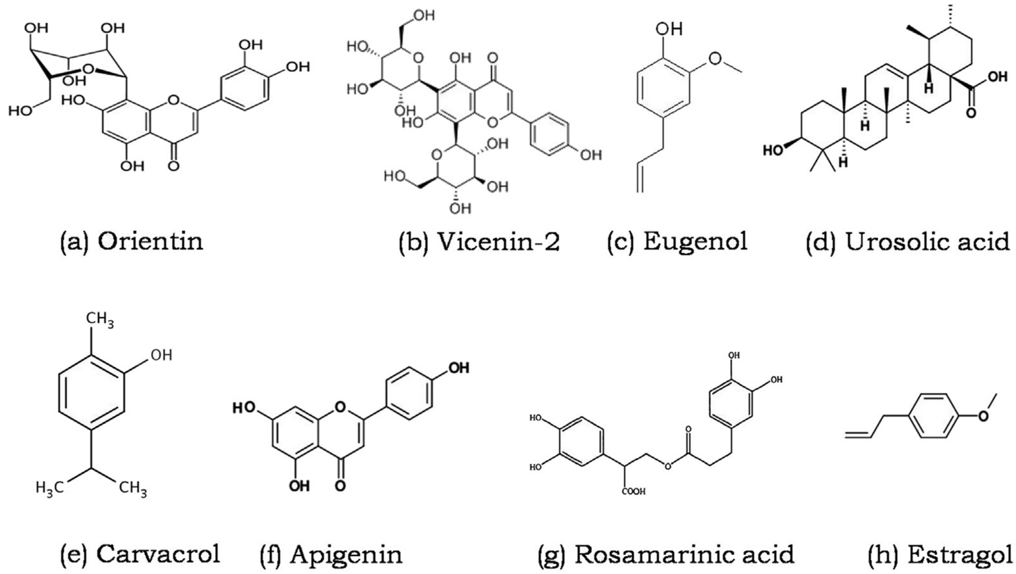

Fig. 5. Structure of some important active components of *Ocimum sanctum*.

P. hexandrum (200 mg/kg body weight.) was studied in rats, which were irradiated (2 Gy) *in utero* [58]. Aqueous extract of *P. hexandrum* rendered protection against irradiation damage in hemopoietic, gastrointestinal and male germinal tissue in a mouse model [59]. The aqueous-ethanolic extract of high altitude *P. hexandrum* was reported to have *3-o-β-*D-galactoside, which renders radio-protection by protecting lipids, proteins in neural and renal model against supra-lethal gamma radiation [60]. The aqueous extract of *P. hexandrum* has also shown a potential to be developed as an anti-cancer drug [61]. It is apparent that *P. hexandrum* has got the promising radioprotective and anti-cancer activities.

3. Conclusion

Most of the plant extracts have shown appreciable anti-cancer and radioprotective properties. Different classes of phenolics and flavonoids are the most abundant phytoconstituents those are already known for radioprotective and anti-cancer properties. Orientin, a flavonoid isolated from *O. sanctum*, has shown radioprotective properties comparable to amifostine and is currently undergoing preclinical trials for its radioprotective efficacy. Extract from *P. hexandrum* has also shown potent radioprotective properties. Likewise, there are several plants with anti-cancer and radioprotective potentials. In conclusion, Western Himalayan region at Uttarakhand, India is an abode for several plants of medicinal importance due to their special phytoconstituents.

This review is attempted with an aim to enlist the key plants of Uttarakhand region, which have got the potential of being developed as an effective and safe natural radioprotective as well as anti-cancer therapeutics.

Source of support

Nil.

Conflicts of interest

None declared.

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