Effects of traditional oriental medicines as anti-cytotoxic agents in radiotherapy (Review)

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Abstract. The primary goal of radiotherapy in oncology is to enhance the efficacy of tumor cell death while decreasing damage to surrounding normal cells. Positive therapeutic outcomes may be accomplished by improved targeting, precisely targeting tumor cells or protecting normal cells against radiation-induced damage. The potential for antioxidants to decrease normal tissue damage induced by radiation has been investigated in animal models for a number of decades. In attempts for radioprotection, certain synthetic chemicals are suggested as antioxidants and normal tissue protectors against radiation-induced damage, but they have exhibited limitations in pharmacological application due to undesirable effects and high toxicities at clinical doses. The present review focuses on the radioprotective efficacy of traditional oriental medicines with the advantage of low toxicity at pharmacological doses and how such treatments may influence various harmful effects induced by radiation *in vitro* and *in vivo*. In addition, medicinal plants and their active constituents with biological activities that may be associated with alleviation of radiation-induced damage through antioxidant, anti-inflammatory, wound healing and immunostimulatory properties are discussed.

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Abbreviations: CAT, catalase; CTA, conditioned taste aversion; GSH, reduced glutathione; GST, glutathione transferase; IL, interleukin; MDA, malondialdehyde; ROS, reactive oxygen species; SOD-1, superoxide dismutase 1; TGF-β1, transforming growth factor-β1; TNF-α, tumor necrosis factor-α; TOM, traditional oriental medicine

Key words: antioxidant, cancer, natural product, radiotherapy, radioprotector, reactive oxygen species, traditional oriental medicine

Contents

1. Introduction

Ionizing radiation is used as a primary treatment for a number of types of cancer. In total, >40% of patients with cancer depend on radiotherapy for the treatment of their disease (1). The major goal of radiotherapy in oncology is to enhance the cytotoxic effects on the tumor while minimizing injury to the neighboring normal tissues. In the last several decades, radiotherapeutic technologies have advanced by improvements in engineering and computing, resulting in the development of intensity-modulated radiotherapy, image-guided radiotherapy and stereotactic radiotherapy (1-3). In addition, spatial-localizing techniques and radiation-fractionated therapy have improved the rate of satisfactory therapeutic outcomes by enabling the repair of radiation-induced damage and regeneration of damaged and fresh cells. Positive therapeutic outcomes may be accomplished by the development of selective radioadjuvants, including radiosensitizers and radioprotectors (4-6). In spite of the improvement in radiotherapeutic modalities, surrounding normal tissues are also affected during radiotherapy, with local tissue damage, mucositis and general weakness occurring (7-9). These undesired side effects should be managed and minimized by treatments of adjuvant compounds. Various agents have been proposed owing to their radioprotective mechanisms and therapeutic effects (10-13). However, as numerous chemical compounds exhibit high toxicity, only a limited number have been investigated in clinical trials. Sulfhydryls have been considered the most promising radioprotectors. Among numerous sulfhydryl compounds, only amifostin (WR-2721, Ethyol®) has been approved by the US Food and Drug Administration for radiotherapeutic treatment of head and neck cancer (14,15). Further potential candidates for radiotherapeutic adjuvants are expected to decrease the harmful effects of radiation on normal cells.

Previous studies have been conducted to identify traditional oriental medicines (TOMs) that may serve as potent radioprotectors due to their safety and low toxicity, which have been confirmed by empirical testing and their clinical use in Asian countries (16-20). These compounds have been reported to have antioxidant properties, which may neutralize radiation-induced damage, including oxidative stress caused by reactive oxygen species (ROS). TOMs may regulate abnormal redox signaling by acting as proton donors, reducing agents and metal chelators, consequently exhibiting antioxidant activities. TOMs have also been reported to exhibit anti-inflammatory, pro-survival and anti-cytotoxic activities in animal systems, indicating that they have high potential to serve as radioprotectors. The present review attempts to evaluate the roles of TOMs in decreasing the radiological effects and summarizes the results of studies of radiation and medicinal plants, which may enhance the effects of radiotherapy by protecting normal tissues from radiation-induced damage.

2. Side effects of radiotherapy and need for radioprotectors

Ionizing radiation generates electrically charged ions and possesses energy to induce ionization. This energy passes through the cells in the tissues, and may destroy cancer cells or induce damage to the genome, resulting in cell death. Cells may be affected by ionizing radiation directly or indirectly (21). The radiation is able to directly damage biological macromolecules leading to protein malfunction, lipid peroxidation and genetic alterations, including mutations, base lesions and DNA strand breaks. The radiation also causes the formation of ROS including $OH^•$, $H^•$, $^1O_2$, H_3O^+ and H_2O_2 through the interaction with water molecules (19,22). When these ROS interact with biomolecules, secondary free radicals may be produced, leading to cytotoxic events (23,24).

The majority of radiation-induced DNA damage results from short-lived primary free radicals produced by radiation and secondary free radicals produced by the interaction between primary radicals and biomolecules. In addition, ROS may act as signaling molecules to activate various cellular signaling pathways, including pro-inflammatory, pro-survival and pro-apoptotic responses (22,25,26). Exposure of cells to ionizing radiation results in oxidative stress and DNA damage, with subsequent activation of p53 and ataxia telangiectasia mutated involved in damage-response signaling and cell death signaling. In addition, ROS may induce loss of mitochondrial membrane potential, which consequently leads to the release of mitochondrial pro-apoptotic proteins, including cytochrome *c*, second mitochondria-derived activator of caspases and apoptosis-inducing factor (25,27,28). These pro-apoptotic proteins may subsequently translocate into the cytoplasm and the nucleus to activate mitochondria-dependent apoptosis signaling. Radiation-induced inflammation is regarded as a critical side effect.

Various free radicals may stimulate an inflammatory response through the induction of cytokines and chemokines, which generates long-lived free radicals, leading to chronic damage (26,29). Various cytokines including transforming growth factor-β1 (TGF-β1), tumor necrosis factor-α (TNF-α) and interleukins (e.g. IL-1α, IL-1β, IL-6 and IL-12) that are upregulated by radiation exposure cause radiation-induced inflammation in normal tissues. Chronic inflammation occurring as a late effect of radiation is primarily responsible for the induction of fibrosis, which is an irreversible disease (29-31). In this setting, sufficient amounts of antioxidants as radioprotectors may neutralize the toxic effects of these free radicals and protect normal tissues against ROS-induced damage during radiation exposure (Fig. 1). Positive therapeutic outcomes may be accomplished by scavenging ROS in normal tissues and/or increasing the cytotoxic activities of these free radicals in tumors.

3. Traditional oriental medicines

TOMs are typically multi-plant formulas that have long been used to treat diseases in Asian countries (32-34). These natural herbal products have developed through practical testing and improvement over thousands of years. Numerous people around the world currently depend on TOMs for improving their quality of life. In addition, investigation of TOMs provides fundamental knowledge essential for modern drug development. However, a major problem associated with TOMs is limited understanding of their underlying molecular mechanisms of action, which has restricted their widespread application to public healthcare. TOM products are frequently used to treat various symptoms without considering their action mechanisms or disease-causing mechanisms. Therefore, numerous researchers have focused on how each TOM acts in a biological system and what signaling pathways are associated with these phytochemicals. Investigations to elucidate the underlying molecular mechanisms of TOMs have led to the establishment of proper medication protocols and development of promising drugs with decreased side effects. A number of medicinal plants utilized for the treatment of a number of ROS-related diseases including rheumatoid arthritis, cancer, aging and other inflammatory diseases have been identified to exhibit antioxidative, anti-inflammatory, antimicrobial and immunostimulatory activities (16-20). These results indicate that plants may include specific compounds that may protect against radiation-mediated damage as well, which is closely associated with ROS-induced damage.

As a number of types of TOM essentially consist of a multi-plant formula, these compounds may exert synergistic effects that single-active ingredients do not. Such multi-formula medicines may potentiate multi-target approaches to treat complex diseases including cancer caused by abnormal signaling pathways associated with a number of key molecules at the same time (35-37). Their functions may result from an isolated single constituent as well as a combinational effect from crosstalk of a number of constituents in the same plant or multiple plant complexes. For synergistic effects, considerable toxicity produced by major active ingredients of a certain plant may be neutralized by other ingredients in the plant without disrupting therapeutic activities. Therefore, the focus has been on the evaluation of radioprotective efficacy from whole extracts of a plant to isolated constituents based on the anti-cytotoxic activity against radiation-induced damage.

4. TOMs as radioprotectors

A variety of TOMs have been reported to contain antioxidant phytochemicals and to have the potential to function in a

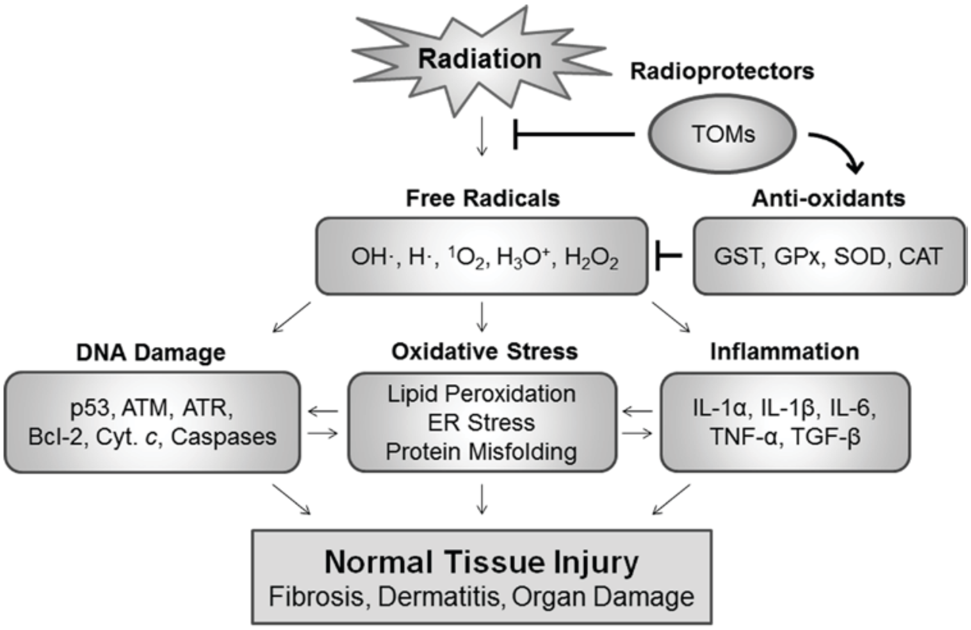

Figure 1. Proposed mechanism for the radioprotective effects of TOMs. Radiation induces formation of free radicals in the cells, which subsequently stimulates DNA damage response, oxidative stress response and inflammation. These events act as major causes for normal tissue injuries including fibrosis, skin dermatitis and organ damage. TOMs exhibiting radioprotective and anti-cytotoxic activities may decrease radiation-induced free radicals through their ROS-scavenging activities and upregulation of endogenous antioxidants, consequently leading to protection of normal tissues against radiation-induced damage. TOM, traditional oriental medicine; GST, glutathione transferase; GPx, glutathione peroxidase; SOD, superoxide dismutase; CAT, catalase; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia- and Rad3-related; Bcl-2, B cell lymphoma 2; Cyt. *c*, cytochrome *c*; ER, endoplasmic reticulum; IL, interleukin; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor β.

radioprotective role in various systems (16-20). The most appropriate approach to screening candidates as potential radioprotectors is to assess whether an active constituent or a number of compounds with synergistic effects have antioxidative, anti-inflammatory, antimicrobial or immunostimulatory activities. Table I presents a summary of TOMs that exhibit radioprotective activities.

Angelica sinensis. *A. sinensis* has been used for thousands of years in China to treat a number of symptoms including inflammation, pain, menstrual disorders and amenorrhea (38,39). Pharmacological studies have demonstrated that the compounds purified from *A. sinensis* root have antioxidant, antitumor, immunomodulatory, neuroprotective and radioprotective activities (39,40). The root extracts of *A. sinensis* serve a radioprotective role through inhibiting radiation-induced lung damage, including pulmonary fibrosis (41,42). These studies have demonstrated that administration of *A. sinensis* extracts led to the protection of normal lung tissues by decreasing radiation-induced TNF-α and TGF-β1 overexpression, which are considered to be responsible for the induction of pulmonary fibrosis. In addition, acidic polysaccharides including *A. sinensis* polysaccharide (ASP) 1 and ASP3 were identified to be the major constituents of the root extracts, which were reported to alleviate radiological damage and to promote hematopoiesis in bone marrow through the increase in the thymus and spleen index and activation of the phosphoinositide 3-kinase/protein kinase B-mediated survival pathway (43-45). ASP3 may also enhance the expression levels of superoxide dismutase 1 (SOD-1) in liver cells, and inhibit radiation-induced micronuclei formation and apoptosis in liver and bone marrow (46).

Curcuma longa. The Indian spice plant *C. longa* is well-known for containing turmeric in its rhizome, which also contains curcumin. This compound has been used in Ayurvedic medicines for a number of centuries. A variety of studies have demonstrated that the extracts of *C. longa* and curcumin have antioxidant, anti-inflammatory, antiseptic, antitumor and radioprotective activities in a large number of *in vitro* and *in vivo* systems (47-51). Additionally, a previous study identified that aqueous extracts of *C. longa* exerted beneficial effects on radioprotection against radiation-induced oxidative stress by modulating antioxidant systems (52). In the present study, administration of *C. longa* extracts to rats prior to and following whole-body treatment with 6.5 Gy γ-irradiation resulted in alleviation of transaminase disorders, a decrease in lipid abnormalities, decreased lipid peroxidation, decreased release of inflammatory cytokines including IL-6 and TNF-α, recovery of reduced glutathione (GSH) levels, and increased expression of antioxidant enzymes, including SOD-1 and peroxiredoxin-1, in rat liver. Previous studies have identified that curcumin may serve a radioprotective role in normal cells, although it may enable cancer cells to be sensitized to radiotherapy (53,54). Curcumin exhibits antioxidant potential to improve therapeutic efficacy through the induction of expression of antioxidant genes including SOD-1, catalase (CAT) and glutathione peroxidase, leading to decreased ROS levels and DNA damage (55-57). A study in which curcumin was administered to mice prior to application of γ-irradiation to the thorax demonstrated that curcumin enhanced the expression levels of heme oxygenase 1 to protect against radiation-induced ROS production, and suppressed acute lung injury, inflammation and pulmonary fibrosis induced by radiation exposure (58). These results were consistent with those of

Table I. Radioprotective functions of TOMs and their active constituents.

TOM origin	Major active constituents	Radioprotective functions	(Refs.)
Angelica sinensis	ASP1, ASP3	Decreasing TNF-α and TGF-β1 expression, leading to inhibition of radiation-induced pulmonary fibrosis Decreasing radiation-induced micronuclei formation and apoptosis in bone marrow Improving hematopoietic function of $CD34^+$ cells Inducing SOD-1 expression in liver	(41-46)
Curcuma longa	Curcumin	Alleviating radiation-induced transaminase disorders and lipid peroxidation, increasing SOD-1 and peroxiredoxin-1 expression, and decreasing IL-6 and TNF-α expression in rat liver Increasing HO-1 expression in lung, and inhibiting inflammation and pulmonary fibrosis Reducing TBARS level and γ-H2AX foci in irradiated skin of mice Increasing SOD-1, CAT and GPx expression to inhibit radiation-induced oxidative stress in human lymphocytes	(52-59)
Gingko biloba	EGB-761	Relieving radiation-induced skin dermatitis through inhibition of lipid peroxidation and recovery of GSH levels Reducing radiation-induced oxidative stress responses (increase in MDA level, myeloperoxidase activity, collagen contents, LDH level and TNF-α level) in lung, liver, kidney and ileum tissues Improving memory, mood and quality of life in patients with brain tumors that had been irradiated	(62-64)
Hippophae rhamnoides	RH-3	Decreasing corticosterone and serotonin level, and alleviating radiation-induced CTA in rats Decreasing lipid peroxidation and DNA damage, and maintaining mitochondrial membrane potential through ROS scavenging	(69-74)
Ocimum sanctum	Orientin, vicenin	Increasing body weight, survival rate and GST activity in irradiated mice Scavenging free radicals and inhibiting xanthine oxidase activity to suppress radiation-induced oxidative stress Reducing lipid peroxidation and DNA damage to protect against cell death in liver and bone marrow	(79-84)
Panax ginseng	Ginsan, ginsenosides	Inhibiting COX-2 overexpression to suppress radiation-induced inflammatory response in the thymus and spleen of mice Enhancing proliferation of bone marrow cells, and increasing release of hematopoietic growth factors and cytokines (IL-1, IL-2, IL-4, IL-6, IL-12, interferon-γ and TNF-α) in irradiated mice Increasing survival rate and life expectancy, recovering antioxidants (GST, CAT and SOD-1), and inhibiting radiation-induced lipid peroxidation, sickness and weight loss in mice	(90-96)
Syzygium cumini	α-pinene	Inhibiting micronuclei formation to protect against radiation-induced DNA damage in lymphocytes Suppressing gastrointestinal damages (decrease in villus height and crypt number, and increase in goblet and apoptotic cells) in mice Scavenging free radicals to suppress radiation-induced lipid peroxidation and DNA damage in the brain and spleen of mice	(100-106)
Zingiber officinale	Zingiberene, gingerol	Enhancing spleen weight, proliferation of splenocytes, humoral immunity and secretion of cytokines (IL-1β and IL-3) in the spleen of mice Decreasing lipid peroxidation and recovering GSH level in irradiated mice Scavenging free radicals to protect against radiation-induced CTA in rats	(113-117)

TOM, traditional oriental medicine; ASP, *Angelica sinensis* polysaccharide; TNF-α, tumor necrosis factor α; TGF-β1, transforming growth factor β1; CD34, cluster of differentiation 34; SOD-1, superoxide dismutase 1; IL, interleukin; HO-1, heme oxygenase 1; TBARS, thiobarbituric acid-reactive substances; γ-H2AX, phosphorylated histone H2AX; CAT, catalase; GPx, glutathione peroxidase; EGB-761, Ginkgo biloba extract 761; GSH, reduced glutathione; MDA, malondialdehyde; LDH, lactate dehydrogenase; RH-3, *Hippophae rhamnoides* preparation 3; CTA, conditioned taste aversion; ROS, reactive oxygen species; GST, *glutathione transferase*; COX-2, cyclooxygenase 2.

another study that demonstrated that treatment with curcumin combined with radiation exposure to local areas of the skin or the whole body of mice exhibited radioprotective effects via a decrease in thiobarbituric acid-reactive substances and phosphorylated histone H2AX foci, indicating decreased lipid peroxidation and DNA damage, respectively (59).

Gingko biloba. G. biloba (Cycadaceae), a popular herb in East Asia, has been reported to exhibit beneficial biological activities including antioxidant, anti-inflammatory, anti-aging and cardioprotective properties (60). *G. biloba* extract 761 (EGB-761) is a mixture of standardized *G. biloba* leaf extracts composed of flavonoids, terpenoids, organic acids and other constituents with antioxidant properties that has been developed and widely utilized as a dietary supplement and herbal therapy (61). The plant contains ~300 compounds including ginkgolides, bilobalide, ascorbic acid, carotenes, quercetin, myricetin, ginkgetin, coumarins, catechins, rhamnetin and tocopherol. The majority of these constituents exhibit radioprotective activities. A previous study identified that EGB-761 serve a protective role in radiation-induced dermatitis (62). As the skin is primarily affected, regardless of the organ targeted by radiotherapy, skin damage including dermatitis may be caused by radiation-induced oxidative stress, lipid peroxidation and redox imbalance. In the present study, administration of EGB-761 to irradiated rats resulted in reduction of radiation-induced malondialdehyde (MDA) levels, an indication of lipid peroxidation, and recovery of GSH levels to normal status, indicating that increased oxidative stress by radiation exposure was significantly suppressed (62). Furthermore, dermatitis caused by radiation was markedly alleviated when EGB-761 was applied. Another study demonstrated that administration of whole-body radiation to Sprague-Dawley rats increased MDA levels, myeloperoxidase activity, collagen contents, lactate dehydrogenase levels and TNF-α levels in lung, liver, kidney and ileum tissues, whereas these oxidative responses were significantly inhibited by administration of *G. biloba* extracts (63). In addition, the extracts of *G. biloba* resulted in improvement of memory, brain-related symptoms, mood and quality of life in patients with brain tumors that had been irradiated (64). The results of these studies suggest that *G. biloba* extracts serve a protective role against radiation-induced oxidative damage in tissues and organs.

Hippophae rhamnoides. H. rhamnoides has been used in India and Tibet for a number of centuries to treat dyspepsia, wound healing, cardiovascular disorders and hepatic disorders. The plant has been reported to have antioxidant, anti-inflammatory, antimicrobial and immunostimulatory properties (65-67). *H. rhamnoides* berries contain polyphenolic compounds, including rhamnetin, quercetin, and kaempferol, carotenes, vitamins, folic acids and tannins (68,69). These bioactive constituents are responsible for the biological activities that contribute to radioprotection through free radical scavenging. A previous study demonstrated that the alcoholic extracts of *H. rhamnoides* berries resulted in a significant decrease in radiation-induced cytotoxicity via inhibition of radiation-induced ROS in the cytoplasm and mitochondria, as well as through maintenance of the mitochondrial membrane potential (69). The administration of *H. rhamnoides* leaf extracts prior to whole-body radiation in rats partially increased antioxidant systems, whereas it decreased corticosterone levels in plasma and serotonin levels in jejunum and plasma, leading to the prevention of behavioral changes including conditioned taste aversion (CTA) in rats. Since CTA in rodents is regarded as a similar behavior to nausea and vomiting in humans, the extracts could be a promising candidate for the suppression of radiation-induced behavioral effects (70). In addition, the extracts of *H. rhamnoides* have been reported to have the capacity to mitigate lipid peroxidation, genomic DNA damage and mitochondrial DNA damage (18,71,72). These extracts also possess the ability to induce chromatin compaction to protect against radiation-induced DNA strand breaks (73,74).

Ocimum sanctum. O. sanctum, which is also known as Tulsi or Indian holy basil, is a medicinal herb used in Ayurvedic, Greek, Roman, Siddha and Unani treatments. *O. sanctum* has been utilized for a number of therapeutic treatments including the common cold, vomiting, malarial fever, asthma, bronchitis, hepatic disorders, cardiac disorders and skin diseases (75,76). This medicinal plant reportedly has antioxidative, antibacterial, antifungal, anti-inflammatory, antitumor and immuostimulatory properties. *O. sanctum* contains a number of constituents including apigenin, caffeic acid, cirsilineol, eugenol, luteolin, orientin, rosmarinic acid, vanillin and vicenin, the majority of which are contained in the leaves and stem (77,78). Studies have been conducted to investigate the radioprotective role of *O. sanctum* since Uma Devi and Ganasoundari (79) first reported its radioprotective properties. It was reported that administration of *O. sanctum* leaf extracts along with radiotherapy resulted in increased body weight, survival rate and glutathione transferase (GST) activity in mouse models with reduced chromosomal damage and tumor volume of melanoma (80). In addition, polysaccharides isolated from *O. sanctum* were reported to prevent lipid peroxidation and DNA damage against oxidative stress induced by γ-radiation through scavenging free radicals and inhibiting xanthine oxidase activity (81). Among a number of constituents, the flavonoids orientin and vicenin are considered to be the major active components responsible for radioprotective function. These two components may increase the survival rate of mice when administered 30 min before whole-body exposure to γ-radiation (82). The two flavonoids may also reduce radiation-induced lipid peroxidation through their activities to scavenge free radicals in the liver and protect against chromosomal aberrations and stem cell death in bone marrow (83,84).

Panax ginseng. P. ginseng is a well-known medicinal herb containing multiple bioactive constituents that is extensively used in China and Korea. The plant has a variety of beneficial activities including antitumor, antioxidant, anti-aging, antifungal, anti-inflammatory and neuroprotective properties (85-90). Ginseng contains various types of ginsenosides (major active components), kaempferol, caffeic acids, acidic polysaccharides and palmitic acids in its stem, leaves and roots. The majority of the evidence for the radioprotective properties of ginseng has been accumulated over the last several decades (90-93). For example, the administration of ginseng extracts resulted in suppression of radiation-induced inflammatory response through inhibition of cyclooxygenase-2 overexpression, as well as recovery of spleen and thymus damage induced by radiation exposure in mouse models (94). In addition, whole ginseng extracts increased colony-forming capability and reduced apoptotic cell death in the spleen and intestine of irradiated mice (95). Another study reported that the protective effects of ginsan, an acidic polysaccharide of ginseng, led to enhanced cell proliferation of bone marrow and spleen, and increased production and release of hematopoietic growth factors and various cytokines, including IL-1, IL-2, IL-4, IL-6, IL-12, interferon-γ and TNF-α, in irradiated mice (90). These cytokines may be necessary for recovery of the hematopoietic system and induction of the immune system to protect against radiation exposure. Furthermore, oral administration of ginseng root extracts to albino mice prior to whole-body exposure to γ-radiation increased survival rates and life expectancy, restored the levels of a number of endogenous antioxidants, including GST, CAT and SOD-1, and inhibited radiation-induced sickness and weight loss (92). These extracts also significantly decreased the increased level of radiation-mediated lipid peroxidation (92,96).

Syzygium cumini. *S. cumini*, known as jamun, is used in traditional Indian systems of medicine. The bark, leaves, seeds and fruits of *S. cumini* are used for medicinal applications to treat diabetes, splenopathy, bacterial infection, constipation, stomachache, fever, gastropathy and dermopathy (97,98). This plant has been reported to contain flavonoids and phenolic acids, including ellagic acid, quercetin, kaempferol and myricetin. The bioactive constituents of the plant have various biological functions including antioxidant, anti-inflammatory, antibacterial, antidiabetic and cardioprotective properties (99,100). A number of previous studies demonstrated the radioprotective role of *S. cumini* in the *in vitro* and *in vivo* systems (101-104). Administration of *S. cumini* leaf extracts resulted in suppression of radiation-induced micronuclei formation and protection of lymphocytes against DNA damage (102). Extracts of *S. cumini* leaves and seeds also exhibited radioprotective effects to lessen radiation-mediated sickness and mortality in mouse models (100,103). Another previous study demonstrated that gastrointestinal damage, including a decrease in villus height and the number of crypts, and an increase in goblet and apoptotic cell numbers, was induced by exposure of whole-body g-radiation to mice, and this damage was prevented and reversed by pre-treatment with leaf extracts of *S. cumini* (105). In addition, the *S. cumini* extracts have ROS-scavenging activities as do other medicinal herbs. Results from a further study demonstrated that administration of the leaf extracts decreased the formation of free radicals, including hydroxyl radicals and superoxide anion radicals, leading to the suppression of radiation-induced lipid peroxidation and DNA damage in the brain and spleens of mice (106).

Zingiber officinale. *Z. officinale*, commonly known as ginger, is consumed extensively as a spice and flavoring herb worldwide. The rhizomes of ginger have been used for medicinal purposes in traditional Ayurvedic medicines to treat dyspepsia, asthma, cough, diarrhea, cardiac disorders, nausea, vomiting and inflammation (107-109). Ginger, or its extracts, contains limonene, cymene, cineole, zingiberene, terpenoid, geraniol, shogaol and gingerol, among other constituents, which demonstrate diverse pharmacological properties including analgesic, anti-inflammatory, antitumor and antioxidant activities (110-112). Previous studies have attested to the radioprotective potential of ginger (113,114). One study demonstrated that the extracts of *Z. officinale* administered to mice with γ-radiation exposure enhanced the spleen weight, splenocyte proliferation, humoral immunity and secretion of cytokines including IL-1β and IL-3 in the spleens of mice, indicating alleviation of radiation-induced immunosuppression (113). In addition, hydroalcoholic extracts of ginger rhizomes have been reported to decrease lipid peroxidation and recover GSH levels through their free-radical-scavenging activities in irradiated mice (114,115). The administration of ginger rhizome extracts prior to 2 Gy γ-radiation in rats also resulted in inhibition of lipid peroxidation and ascorbate ion stress via increased scavenging ability for ROS removal, which contributed to neurobehavioral protective effects against radiation-induced CTA (116,117).

5. Conclusions

It is clear that a number of TOMs exhibit a variety of biological activities with respect to radioprotective roles. However, only a limited number of TOMs have been studied, and clinical trials of the majority of TOMs have not yet been conducted. Although these medicinal plants have been utilized in numerous Asian countries, validation of their quality, chemical contents and underlying molecular mechanism of action is imperative prior to initiating clinical trials for application to current therapeutic systems. Indiscreet variations composed of similar agents have appeared due to a lack of regulation of these plant products. As environmental factors including soil content, water, temperature and acidity differ, different specimens of the same plant species frequently have differential amounts of the bioactive ingredients, leading to inconsistent outcomes of biological activities. Further studies are required to identify the bioactive constituents in TOMs responsible for specific properties including radioprotection. For preclinical assays and clinical application, it is important that the exact formula of TOMs or their active constituents be determined with specified preparation methods and that they be tested with strict validation and verification in accordance with modern scientific standards. Overall, further intensive studies of these medicinal plants are necessary to verify their potential for use as radioprotectors and application in further clinical trials.

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