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Therapeutic Potential of Natural Plant Products and their Metabolites in Preventing Radiation Enteropathy resulting from Abdominal or Pelvic Irradiation

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Abstract

Purpose: Radiation-induced gastrointestinal injury or radiation enteropathy is an imminent risk during radiation therapy of abdominal or pelvic tumors. Despite remarkable technological advancements in image-guided radiation delivery techniques, the risk of intestinal injury after radiotherapy for abdominal or pelvic cancers has not been completely eliminated. The irradiated intestine undergoes varying degrees of adverse structural and functional changes, which can result in transient or long-term complications. The risk of development of enteropathy depends on dose, fractionation and quality of radiation. Moreover, the patients' medical condition, age, inter-individual sensitivity to radiation and size of the treatment area are also risk factors of radiation enteropathy. Therefore, strategies are needed to prevent radiotherapy-induced undesirable alteration in the gastrointestinal tract. Many natural plant products, by virtue of their plethora of biological activities, alleviate the adverse effects of radiation-induced injury. The current review discusses potential roles and possible mechanisms of natural plant products in suppressing radiation enteropathy.

Conclusions: Natural plant products have the potential to suppress intestinal radiation toxicity.

1. Introduction

Radiation is an integral part of multimodal cancer treatment and is used to treat approximately 50% of total cancer patients. International Agency for Research on Cancer (IARC) indicated that 14.1 million new cancer cases and 8.2 million cancer-associated deaths occurred in 2012 worldwide (Ferlay et al. 2015). Among these cancer patients, approximately 5.2 million patients were suffering from either abdominal or pelvic malignancies (Jemal et al. 2011). It is estimated that more than half of patients with abdominal or pelvic malignancies undergo radiotherapy (Delaney et al. 2005). The major limitation of abdominal or pelvic radiotherapy is the risk of developing enteropathy.

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Conflict of Interest

Authors declare no conflict of interest.

Enteropathy most commonly occurs following external beam radiation therapy, in which a beam is delivered from outside the body using an external low- linear energy transfer (LET) photon source, like X-rays or γ -rays. In clinical settings, an external beam is administered using various fractionation schedules, usually 1.8 to 2Gy fractions, for several weeks, depending on cancer nature and treatment objectives (Williams et al. 2006). The mechanisms of development of radiation enteropathy are highly complex and controversial (Hauer-Jensen et al. 2014; Kirsch et al. 2010; Paris et al. 2001).

Radiation-induced gastrointestinal tract injury during abdominal or pelvic radiotherapy may develop acute and/or delayed symptoms. Acute effects include nausea, abdominal pain, diarrhea and fatigue, while mucosal atrophy, vascular sclerosis and progressive intestinal wall fibrosis are the characteristics of delayed injury. All these adverse events can result in severe morbidity and mortality. A prospective cohort study was conducted on 59 patients with severe radiation enteropathy. It was reported that while a majority of those patients suffered from severe debilitating symptoms, almost 12% of those patients died due to radiation enteropathy (Larsen et al. 2007). New image-guided radiation delivery techniques have enhanced the precision and accuracy of radiation delivery to the target area to a great extent, but the risk of incidence of radiation enteropathy is still a serious challenge.

The management of radiation enteropathy is a global problem and yet, its successful mitigation has not been achieved. Several synthetic drugs offering a variety of potential biological activities have been tested for decades, but the range of their adverse effects and toxicities limit their use. On the other hand, plant-derived compounds have been used in numerous pathophysiological conditions because of their safety and efficacy profile. Clinical and pre-clinical studies have demonstrated that natural plant products may be a potential solution in suppressing radiation-induced gastrointestinal injury. For example, a clinical study reported that oral administration of a Japanese herbal medicine (2.5g, 3 times daily) improves radiation-induced abdominal distension in cervical cancer patients who underwent external-beam whole-pelvic radiotherapy (Takeda et al. 2008). Moreover, a preclinical study showed that oral gavage of a Chinese herbal medicine (PHY906) twice daily for 4 days considerably protects murine intestine from crypt loss, villi loss and crypt hyperplasia after exposure to 4 fractions of 2Gy of abdominal irradiation (Rockwell et al. 2013). However, the mechanisms of natural plant products-mediated radiation protection are not well understood. The most important bioactive compounds found in natural products are flavonoids, terpenoids, carotenoids and vitamins. All these compounds have shown to be protective against radiation-induced intestinal toxicity. In this review, we will discuss the efficacy of different natural plant products and their derivatives that may have the potential to ameliorate abdominal or pelvic radiotherapy-induced enteropathy.

Our literature search strategies involved seeking literature encompassing biological effects of different herbal products and extracts within the scope of our review article. The key words used were the names of the plant products considered in this article followed by “intestine” and “radiation”. The PubMed search engine was utilized as the primary source of our literature search and spanned from the year 1946 till present date.

2. Natural Products with the Potential to Suppress Radiation-induced Gut Injury

2.1. Vitamin E analogs

Vitamin E analogs are fat-soluble compounds, composed of an aromatic chromanol ring or head (that regulates antioxidant activity) and a 16-carbon side chain or tail. Structural differences in the side chain have broadly divided the vitamin E family into two subgroups, tocopherols (saturated side chain with no double bonds) and tocotrienols (unsaturated side chain with three double bonds). Each subgroup is further sub-divided into four isoforms (α , β , γ and δ) based on the number and position of methyl groups on the chromanol ring. Among the eight isoforms of vitamin E, α -tocopherol has been studied most extensively. However, tocotrienols have drawn much attention recently because of their numerous beneficial effects against various pathophysiological conditions. Studies by different groups have demonstrated tocotrienols have superior antioxidant properties compared to tocopherols (Kamal-Eldin and Appelqvist 1996). Tocotrienols can modulate target molecules through transcriptional, translational and post-translational modifications or by directly interacting with the target molecules (Khallouki et al. 2015). Tocotrienols' unsaturated side chain allows to suppress the activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR), an enzyme responsible for regulating cholesterol biosynthesis and conferring radiation protection through its so-called pleiotropic effects (Berbee et al. 2009). Tocopherols are unable to exert the similar functions because of their saturated side chain. However, antioxidant properties are observed in all isoforms of vitamin E. The antioxidant potency in different isoforms is determined by the number and the position of methyl groups in the chromanol ring. Because of their high potent antioxidant properties, investigators have tested the efficacy of vitamin E analogs in mitigating radiation-induced damage in biological systems (Singh et al. 2012; Singh et al. 2013b; Suman et al. 2013). Here, we will discuss only selected isoforms that have shown protective effects against radiation-induced intestinal toxicity. Plant sources of vitamin E include wheat germ oil, palm oil, rice bran, barley, sunflower oil, almonds and peanuts.

2.1.1. α -tocopherol—The vitamin E analog α -tocopherol is one of the major components of the cell membrane and its deficiency can cause structural damages in the membrane of intestinal cells affecting the rate of passive absorption (Meshali and Nightingale 1976). Preclinical research has demonstrated that dietary supplementation of α -tocopherol for 10 days or a single intraluminal dose 30 minutes before 11Gy exposure to low-LET radiation protects crypt cells, mucosal height and goblet cells (Felemovicius et al. 1995). Pre-clinical studies have also revealed that intraperitoneal administration of L- α -tocopherol (20mg/kg b. wt) once daily for 6 consecutive days, before exposure to 10Gy abdominal irradiation, renders protection to the gastrointestinal mucosal layer (Empey et al. 1992). Moreover, subcutaneous administration of α -tocopherol (400mg/kg b. wt.) 24hr before exposure to high dose of total body irradiation was shown to protect mice from gut injury by preventing apoptosis in jejunum, promoting regeneration of crypt cells and blocking inflammation in the intestinal villi (Singh et al. 2013a). The authors also proposed that tocopherol suppresses apoptosis induction in intestinal cells by inhibiting radiation-induced over-expression of BAX, caspase-3 and cleaved PARP after radiation exposure

(Singh et al. 2013a). Furthermore, when blood cells from tocopherol and AMD3100-treated mice were infused in lethally irradiated mice, significant intestinal protection was observed (Singh et al. 2012). Other studies have shown a causal association between radiation enteropathy and over-expression of miR-210. A recent clinical study has indicated that α -tocopherol in combination with pentoxifylline has the ability to down-regulate radiotherapy-induced over-expression of miR-210 in the intestinal samples obtained from cancer patients (Hamama et al. 2014). However, the mechanisms of action of α -tocopherol-mediated intestinal radiation protection are not clearly understood. The antioxidant property of α -tocopherol is thought to play a critical role in suppressing intestinal radiation damage.

2.1.2. γ -tocotrienol—Among tocots, γ -tocotrienol has the largest dose reduction factor discovered to date (Ghosh et al. 2009). Gamma-tocotrienol exerts its radio-protective effects primarily by virtue of its antioxidant properties and also by its ability to inhibit HMGCR, similar to the lipid lowering statin drugs. Inhibition of HMGCR is known to alleviate radiation-induced injury (Fritz et al. 2011). In addition, γ -tocotrienol-mediated induction of G-CSF and up-regulation of endothelial thrombomodulin was shown to play a critical role in radiation protection (Kulkarni et al. 2013; Pathak et al. 2015). Radio-protective efficacy of γ -tocotrienol was compromised when mice were treated with a G-CSF neutralizing antibody or in mice with thrombomodulin mutant gene (Kulkarni et al. 2013; Pathak et al. 2015). Moreover, systemic administration of recombinant thrombomodulin was shown to provide protection against radiation-induced intestinal toxicity (Geiger et al. 2012). In the intestine, γ -tocotrienol is absorbed by the Niemann-Pick C1 Like 1 (NPC1L1), a protein abundantly found in the small intestine and in the brush border membrane of enterocytes (Abuasal et al. 2010). Berbee et al (2009) demonstrated that a single subcutaneous dose of γ -tocotrienol (400mg/kg b. wt.) 24hr before irradiation improves intestinal crypt cell survival, mucosal surface area, plasma citrulline level (a biomarker of intestinal radiation injury) and also inhibits intestinal bacterial translocation to the liver (Berbee et al. 2009). A recent study has shown that γ -tocotrienol pre-treatment (200mg/kg b. wt.) promotes intestinal cell survival by preferentially up-regulating anti-apoptotic genes and down-regulating pro-apoptotic factors (Suman et al. 2013). Agents that are capable of scavenging ROS-mediated apoptosis induction are known to provide radiation protection, which could be one of the possible mechanisms of γ -tocotrienol-mediated radioprotection. However, γ -tocotrienol can exert radio-protective properties by numerous other mechanisms as discussed above.

2.1.3. δ -tocotrienol—Studies of comparative antioxidant activity of tocotrienols reveal that δ -tocotrienol has the highest antioxidant potency for scavenging free radicals generated by different oxidative sources (Palozza et al. 2006). Superior antioxidant activities of δ -tocotrienol compared to other isoforms of vitamin E are thought to be related to the least number of methyl groups in the chromanol ring, which allows the molecule to be easily incorporated in the membrane. Previous studies showed that δ -tocotrienol is a potent radioprotector with a dose reduction factor of 1.27 (Satyamitra et al. 2012; Satyamitra et al. 2011). However, the role of δ -tocotrienol in protecting radiation-induced intestinal damage has not been studied extensively. A previous study has shown that a single subcutaneous dose of δ -tocotrienol (75mg/kg b. wt.) protected CD2F1 mice from radiation-induced

intestinal injury by inhibiting inflammation, apoptosis and intestinal bacterial translocation (Li et al. 2013).

2.2. Genistein

Genistein, a soybean-derived isoflavone possessing strong tyrosine kinase inhibiting properties, is known to modulate functional activities in the intestine. Genistein was shown to stimulate secretion of chloride (Goddard et al. 2000) and bicarbonate (Tuo et al. 2011) in murine intestine, prevent endotoxin-induced intestinal inflammation (Paradkar et al. 2004), inhibit intestinal peristalsis by interfering with muscle excitation (Gharzouli and Holzer 2004), reduce rotavirus infectivity in the intestine and promote intestinal cell proliferation without affecting intestinal enzyme activity or nutrient transport (Donovan et al. 2009), suppress LPS-induced endothelial fractalkine expression in small intestine (Sung et al. 2010), block voltage-gated potassium channels in colonic smooth muscle cells (Li et al. 2006) and prevent colon pre-neoplasia in rats by suppressing carcinogen-induced WNT/ β -catenin signaling pathways (Zhang et al. 2013b). In addition, a large number of studies have reported that genistein blocks tyrosine phosphorylation of intestinal tight junction proteins induced by oxidative stress, inflammatory cytokines and enteric bacteria, thereby preserving intestinal barrier function (Rao et al. 2002; Schmitz et al. 1999; Wells et al. 1999). Because of all these potentially beneficial effects on the intestines, there is considerable scientific interest in evaluating the role of genistein in the prevention of radiation-induced intestinal damage. Son et al (2013) demonstrated that a single dose of genistein (200mg/kg b. wt.) 24hrs prior to abdominal irradiation (5 to 10Gy) considerably suppresses radiation-induced adverse structural changes in murine intestine and also attenuates tumor growth (Son et al. 2013). The authors also observed fewer apoptotic cells in the jejunal crypts when mice were pre-treated with genistein before exposure to 5Gy of abdominal irradiation (Son et al. 2013). Further, genistein pre-treatment was shown to enhance intestinal crypt cell proliferation in irradiated mice (Son et al. 2013). Derivatives of genistein were recently shown to enhance the efficacy of radiation in killing human colon cancer cells by modulating phosphorylation of epidermal growth factor receptors (Gruca et al. 2014).

2.3. Lycopene

Lycopene is the red pigment primarily found in tomatoes and watermelon. It is an open-chain carotenoid with strong antioxidant properties and plays a critical role in human health and disease. One case-control study conducted between 1985 and 1991 in northern Italy, showed that high intake of tomatoes minimized the risk of digestive tract cancers (Franceschi et al. 1994). A clinical study also indicated that patients suffering from digestive tract adenomatous polyps have reduced ability to absorb lycopene compared to their normal counterparts. The authors hypothesized that enhanced free radical activity in patients with adenomatous polyps dampens lycopene absorption in the colon (Nair et al. 2001). Lycopene also inhibits carcinogen-induced aberrant crypt foci formation in the colon (Arimochi et al. 1999; Wargovich et al. 2000). Chemical structure analysis revealed that lycopene has two isomeric forms, an *all-trans* isomeric form and a *cis*-isomeric form. *Cis*-isomeric forms were shown to have superior antioxidant potential and higher stability over *all-trans* forms. Although, the *all-trans* form is predominant in dietary sources of lycopene, it can undergo *cis*-isomerization in enterocytes (Richelle et al. 2010). However, other studies indicated that

the acidic environment of gastric milieu is responsible for *cis*-isomerization (Re et al. 2001). In the intestine, scavenger receptor class B type I (SR-BI) protein plays a critical role in the absorption of lycopene (Moussa et al. 2008). Lycopene, by virtue of its free radical scavenging property, suppresses radiation-induced reactive oxygen species generation. Sadaa et al (2009) demonstrated that oral administration of lycopene (5mg/kg b. wt.) for seven consecutive days protected the structural architecture of the small intestine in rats exposed to 6Gy of total body irradiation (Saada et al. 2010). Moreover, the authors observed that lycopene treatment significantly enhances SOD, catalase and GSH levels in intestinal samples, following total body irradiation, compared to an irradiated group without lycopene treatment. Lycopene supplementation also increases monoamines, such as epinephrine, norepinephrine, dopamine and serotonin levels in intestinal tissue of irradiated mice, suggesting lycopene prevents radiation-induced monoamine degradation in intestinal tissue (Saada et al. 2010).

2.4. Ascorbic acid

Ascorbic acid, commonly known as vitamin C, is a six carbon lactone and a potent water-soluble antioxidant, generally found in citrus fruits (oranges, grapefruits, limes and lemons). Ascorbic acid can potentially improve intestinal anastomotic healing (Cevikel et al. 2008), increase iron absorption from the small intestine (Wienk et al. 1997), suppress lipid peroxidation in human intestinal cells (Intra and Kuo 2007), protect structural damage to the intestine after ischemia-reperfusion injury in rats (Higa et al. 2007), improve neuronal density in the duodenum of diabetic rats (Pereira et al. 2006) and prevent jejunal autonomic dysfunction in rats subjected to cold ischemic preservation (Taha et al. 2004). Because of its powerful antioxidant properties, various groups have tested its efficacy in the suppression of radiation-induced injury to different organs including the intestine. Treatment with ascorbic acid was shown to protect radiation-induced adverse changes in brush border enzyme activities as well as in the intestinal structure (Anwar et al. 2013). An animal study revealed that a daily dose of 100 mg/kg b. wt. of vitamin C for 14 to 18 days protected intestinal goblet cells from the adverse effects of radiation (Kanter and Akpolat 2008). Pretreatment of ascorbic acid for three consecutive days (150mg/kg b. wt./day) followed by bone marrow transplantation after 24hr of 14Gy total body irradiation significantly suppressed radiation-induced DNA damage in the crypt cells and prevented denudation of the intestinal mucosa (Yamamoto et al. 2010). Combined pre- and post-treatment of ascorbic acid was found to be effective in protecting mice against radiation-induced gastro-intestinal damage (Ito et al. 2013). However, despite all of these promising effects, the clinical benefit was not statistically significant (Kim et al. 2004).

2.5. Resveratrol

Resveratrol (3,5,4'-trihydroxystilbene) is a plant-derived polyphenol with anti-inflammatory, anti-tumorigenic, anti-diabetic and anti-oxidant properties. Moreover, resveratrol was shown to reduce the risk of cardiovascular diseases and increase the lifespan in lower-organisms. Polyphenol possess the ideal chemical structure for scavenging free radicals more efficiently than other natural products, like tocopherols and ascorbate. The major dietary source of resveratrol is red wine. A number of studies have shown that resveratrol has very low bioavailability and undergoes extensive metabolism in humans, thus

limiting the bioavailability of the parent molecule at organs remote from the site of absorption. Therefore, it is expected that resveratrol will exert most of its beneficial effects in the gastrointestinal tract. Indeed, a cornucopia of resveratrol-mediated positive effects on intestine have been reported. Resveratrol has been reported to decrease gastrointestinal inflammation (Lozano-Perez et al. 2014), inhibit collagen-I synthesis in intestinal fibroblast in a colitis rat model (Li et al. 2014b), improve gut microbiota dysbiosis induced by high fat diet (Qiao et al. 2014), suppress sub-acute intestinal ischemia-reperfusion injury (Dong et al. 2013) and protect the intestinal mucosal barrier in rats with severe acute pancreatitis (Jha et al. 2008). Because of so many beneficial effects of resveratrol on intestine, studies have been conducted to determine the efficacy of resveratrol in attenuating radiation-induced gastrointestinal damage. Resveratrol treatment (10mg/kg b. wt./day) for 10 days before and for 10 days after 8Gy of total body irradiation significantly suppressed radiation-induced intestinal toxicity by preventing the reduction of glutathione levels as well as by promoting malondialdehyde levels, myeloperoxidase activity and collagen content in ileal tissue (Velioglu-Ogunc et al. 2009). Moreover, the study also revealed that resveratrol reverses radiation-induced suppression of Na-ATPase activity and an increase in apoptotic cell numbers in ileum (Velioglu-Ogunc et al. 2009). Another preclinical study conducted in mice provided additional evidence on protective properties of resveratrol. A 40 mg/kg b. wt. dose of resveratrol was administered via gavage 1 day prior to radiation and 5 days after partial body irradiation. It was reported that the treatment group showed elevated levels of SOD2, a protective factor against oxidative injury. Moreover, proliferation of crypt cells was maintained along with a reduction in the number of apoptotic cells. Alongside, it was also reported that resveratrol might have been successful in activating Sirtuin 1 (Sirt 1), a strong factor involved in deacetylation of various transcription factors involved in triggering DNA repair systems, cell cycle progression and prevention of apoptosis (Zhang et al. 2017).

2.6. Berberine

Berberine is a yellow-colored isoquinoline alkaloid with many therapeutic efficacies, which includes anti-diabetic, anti-inflammatory, anti-tumorigenic, anti-malarial and anti-fungal activities. Animal studies reported that berberine modulates a number of intestinal functions, such as cholesterol absorption (Wang et al. 2014), glucose metabolism (Zhang et al. 2014), barrier dysfunction (Li et al. 2014a), tight junction injury (Gu et al. 2013), polyp growth (Zhang et al. 2013a) and jejunal motility (Chen et al. 2013). Berberine was also shown to enhance the susceptibility of various cancers to radiation, including cancers of the digestive system (Liu et al. 2011; Park et al. 2012; Yang et al. 2013). Other studies have also confirmed the radio-protective potential of berberine (Liu et al. 2008). A clinical study showed that berberine treatment for 6 weeks significantly suppresses radiation-induced lung injury in non-small cell lung cancer patients by improving pulmonary functions as well as by suppressing markers of endothelial dysfunction (Liu et al. 2008). Radiation-induced endothelial dysfunction is one of the major causes of radiation enteropathy (Wang et al. 2007). Therefore, it is not surprising that berberine will have some positive effects on the intestine, particularly after radiation exposure. In mice, intra-gastric gavage of berberine (20mg/kg b. wt.) before 1 to 12hr of abdominal irradiation (0 to 16 Gy of acute or fractionated dose) significantly suppresses inflammation, lipid peroxidation, mucosal injury and crypt cell apoptosis in intestinal tissue (Li et al. 2010b). Clinical studies demonstrated

that oral intake of berberine (300mg) three times daily from the third week to the fifth week after abdominal radiotherapy significantly reduces the incidence and the severity of radiation-induced acute intestinal symptoms in human subjects (Li et al. 2010a).

2.7. Curcumin

Curcumin is the yellow-pigmented most active ingredient of turmeric (*Curcuma longa* or *Curcuma domestica*), which has long been used as a traditional herbal medicine in India and China against a variety of diseases, including digestive disorders. A large body of pre-clinical studies established the fact that curcumin treatment potentially protects the gastrointestinal tract from various insults through its anti-inflammatory and anti-oxidant properties. The anti-inflammatory effect of curcumin is believed to be exerted by its ability to down-regulate the NF- κ B pathway. Thus, curcumin was shown to improve colitis in rats by suppressing NF- κ B (Zeng et al. 2013). However, a recent animal study demonstrated that curcumin could also exercise its anti-inflammatory functions by inhibiting STAT3 signaling pathways (Liu et al. 2013). The study indicated that curcumin treatment significantly inhibits inflammatory markers such as TNF α , IL-1 β and myeloperoxidase (MPO) in a murine model of colitis. Other studies demonstrated that curcumin plays a major role in alleviating chemotherapy-induced intestinal toxicity. A previous study has shown that intra-peritoneal administration of the chemotherapeutic drug 5-fluorouracil (5-FU, 100mg/kg b. wt. for 6 days) causes mucosal atrophy, loss of villi, epithelial cells necrosis and induction of apoptotic proteins in the small intestine of rats. However, intra-gastric curcumin treatment (20mg/kg b. wt.) for 3 days after initiation of 5-FU exposure considerably improves mucosal morphology, villus structure, intestinal cell viability and organization (Yao et al. 2013). In addition, curcumin was shown to suppress radiation-induced intestinal damage. Abdominal irradiation with single or double doses of 5Gy ^{60}Co γ -rays results in depletion as well as morphological changes in epithelial cells, atrophic mucosa, shortened villi and decrease in goblet cell numbers in rat intestine; oral administration of curcumin (100mg/kg b. wt./day) for 10 to 14 days before to 4 days after irradiation reversed all the adverse morphological changes in the intestine (Akpola et al. 2009). However, the authors observed that the severity of damage was more intense after two doses of irradiation than single exposure. Curcumin was also shown to inhibit radiation-induced apoptosis in human intestinal microvascular endothelial cells via modulating Akt/mTOR and NF- κ B pathways (Rafiee et al. 2010).

2.8. Tea extracts

Health benefits of different tea extracts, particularly green tea extract, have been well-established for at least three decades by various groups. The bio-potent polyphenolic compounds present in tea extracts play a critical role. It has been found the content of bioactive phenolic compounds such as flavanols, epigallocatechingallate, epicatechingallate, epigallocatechin, epicatechin and flavandiol is significantly higher in green tea than in black tea (Lee et al. 2002). However, the relative efficacy of different tea extracts in promoting health benefits necessitates additional research studies. The chemistry of tea is quite complicated. Various forms of tea are produced through different types of processing. Several groups have claimed that green tea is healthier than black tea because of its higher content of bioactive polyphenols (Liu et al. 2018; Saeed et al. 2017). Among different

polyphenols found in green tea, epigallocatechin gallate (EGCG) is the most potent compound. Experimental evidence indicates that polyphenols can modulate a plethora of gastrointestinal functions. However, its bioavailability is very poor because the dietary polyphenols are not completely absorbed from the gastrointestinal tract. Moreover, gut microflora metabolize the dietary polyphenols. Polyphenols, in turn, can also modulate the intestinal bacterial population. Tea polyphenols were shown to inhibit the growth of pathogenic bacteria, without severely affecting the beneficial commensals and prebiotics in the intestinal microenvironment (Lee et al. 2006). Enhanced prebiotic activity and decreases in the pathogenic bacteria population in rat intestine was observed after oral administration of selenium containing green tea extract daily for 6 days (Molan et al. 2010). In addition, tea extract was shown to attenuate disruption of colonic structure and to enhance production of inflammatory cytokines and over-expression of adhesion molecules in a rat colitis model induced by intracolonic instillation of dinitrobenzene sulphonic acid (Mazzon et al. 2005). Green tea drinking also suppresses 1,2-dimethylhydrazine (DMH)-induced aberrant crypt foci formation (Jia and Han 2001). The authors suggested that the observed decrease in aberrant crypt foci formation may be due to ras-21-mediated suppression of cell proliferation in the intestinal crypts. Another group of researchers showed that green tea drinking attenuates DMH-induced DNA damage in colonic mucosa (Inagake et al. 1995). Tea extracts are also known to be effective in suppressing digestive cancers (Hu et al. 2013; Shimizu et al. 2008; Yamane et al. 1996). However, the role of tea extract in preventing radiation-induced intestinal damage is not well documented. Lee et al. (2008) demonstrated that pre-administration of different polyphenolic compounds in green tea promoted intestinal crypt survival and suppressed apoptosis in crypt cells in irradiated mice (Lee et al. 2008). The author also revealed that among different polyphenolic compounds, epicatechin gallate and epigallocatechin gallate are the most potent compounds to prevent radiation-induced crypt cell apoptosis (Lee et al. 2008). A randomized controlled clinical trial with 42 patients undergoing pelvic or abdominal radiotherapy (50Gy) showed intake of green tea tablets (450mg/day) for five weeks prevented diarrhea and vomiting (Emami et al. 2014).

2.9. Garlic

Garlic (*Allium sativum*) products are one of the major best-selling herbal supplements in the United States containing more than 2000 bioactive compounds. Experimental evidence indicates that the sulfur and non-sulfur compounds in garlic act independently or synergistically to prevent various ailments. Garlic was shown to be effective in preventing inflammation, osteoporosis, diabetes, infection, oxidative stress and cardiovascular diseases (Majewski 2014). Efficacy of garlic in suppressing disorders of the gastrointestinal system has been extensively studied. A study reported that a garlic-supplemented diet decreases intestinal lipid abortion in mice (Mohammadi et al. 2013). The authors also showed that a garlic-supplemented diet resulted in a decrease in the expression of the npc111 gene and an increase in the expression of ATP-binding cassette transporter genes in intestinal tissue that may play a critical role in the efflux of cholesterol back into the intestinal lumen. Further, garlic treatment reduces cholesterol and triglycerides in hypercholesteromic mice by overexpressing the cholesterol regulatory protein, called the liver X receptor α (LXR α) protein in intestinal cells (Mohammadi and Oshaghi 2014). Garlic, like γ -tocotrienol, can also inhibit HMGCoA reductase activity (Gebhardt 1991), suggesting lipid lowering and

radiation protection properties. *In vivo* studies also revealed that garlic modulates enteric pathogenic bacteria (Peinado et al. 2012). The sulfur-containing compounds of garlic were shown to suppress endotoxin-induced intestinal damage in rats (Lee et al. 2012). Moreover, garlic was shown to attenuate oxidative stress-induced intestinal damage by various agents, including chemotherapeutic compounds (Li et al. 2009; Rajani et al. 2008). It has long been misunderstood that the organosulfur compound allicin, responsible for garlic's characteristic smell, is the active compound exerting all the health benefits. However, allicin was found to be extremely unstable and does not exert beneficial effects inside the body. Experiments were also performed to investigate the effects of garlic on intestinal damage after exposure to radiation. Treatment with Diallyl sulfide (200mg/kg b. wt.), a major flavor component of garlic, 3hr prior to total body irradiation provided protection against radiation-induced colonic injury, nuclear damage and cellular proliferation in mice (Baer and Wargovich 1989). However, the safety and efficacy of garlic is yet to be determined clearly, as others have described adverse effects of garlic on the gastrointestinal tract, such as abdominal pain, bloating, loss of appetite, particularly in patients suffering from acute gastroenteritis.

2.10. Ginkgo biloba extracts

An extract from the *Ginkgo biloba* tree was shown to improve biological functions under various pathological conditions (Tchantchou et al. 2007; Wang et al. 2013). The flavonoid and the diterpene terpenoids (ginkgolides and bilobalide) in *Ginkgo biloba* extract are considered to be the active compounds responsible for conferring health benefits. In addition, its role in modulating gastro-intestinal functions is also well-documented. *Ginkgo biloba* extract was shown to protect the intestinal mucosa against ischemic damage (Otamiri and Tagesson 1989), restrict intestinal pathogenic bacteria population (Lee and Kim 2002), improve mucosal healing in rats with duodenal ulcer (Chao et al. 2004), attenuate mucosal damage in a rat model of ulcerative colitis (Mustafa et al. 2006), enhance intestinal barrier functions (Harputluoglu et al. 2006) and augment the functional activity of mesenteric plexus in aged rats (Schneider et al. 2007). Further investigations revealed its radioprotective efficacy. A phase-II study of *Ginkgo biloba* extract in irradiated brain tumor patients showed substantial improvement in their quality of life and cognitive function (Attia et al. 2012). Intraperitoneal administration of the *Ginkgo biloba* extracts at a dose of 100mg/kg b. wt./day for five consecutive days before exposure to 36Gy total body irradiation with both the hind-legs shielded, protected rats from radiation-induced dermatitis (Yirmibesoglu et al. 2012). Oral supplementation of *Ginkgo biloba* extract was shown to attenuate radiation-induced lens injury in rats (Okumus et al. 2011). *Ginkgo biloba* extract also potentiated radiation effects to effectively eradicate tumors (Ha et al. 1996). In a clinical trial, *Ginkgo biloba* extract neutralized genetic damage in Graves' disease patients treated with radioiodine (Dardano et al. 2007). Despite all these abovementioned beneficial activities of *Ginkgo biloba* extract, studies of its role in suppressing intestinal damage after irradiation were seldom undertaken. Sener et al. (2006) demonstrated that intraperitoneal administration of 50mg/kg b. wt./day *Ginkgo biloba* extract significantly prevents radiation-induced apoptosis, epithelial cell loss and inflammatory cell invasion in the lamina propria of rat intestine (Sener et al. 2006). The author also reported that pre-treatment with *Ginkgo biloba* extract enhanced GSH level, reduced MDA level and MPO activity and suppressed DNA fragmentation in intestinal tissue following irradiation (Sener et al. 2006).

2.11. Podophyllum hexandrum extracts

Himalayan mayapple (*Podophyllum hexandrum*) is a high altitude perennial herb found mainly in the Alpine-Himalayan belt. A resin found in the rhizome and root of the species contains various lignans, among which podophyllotoxin is most important bioactive compound with anti-tumorigenic, anti-viral, anti-inflammatory and anti-proliferative activity. Further, *in vivo* and biochemical studies demonstrated that rhizome also has a strong antioxidant capacity (Ganie et al. 2011; Ganie et al. 2013; Li et al. 2012). Because of high free radical scavenging activity, various investigators tried to determine whether the plant extract could mitigate the adverse radiation effects in biological systems. A large number of published articles indicated that *Podophyllum hexandrum* significantly attenuates radiation-induced hematopoietic aplasia (Verma and Gupta 2015), chromosomal aberration (Dutta and Gupta 2014), lethality (Sankhwar et al. 2011), immunosuppression (Goel et al. 2007), apoptosis (Kumar et al. 2005), neuronal damage (Sajikumar and Goel 2003) and decline in blood cell counts (Gupta et al. 2010). Moreover, various other groups have proved the efficacy of *Podophyllum hexandrum* in reducing radiation-induced intestinal injury. Salin et al (2001) showed that 2h pre-administration of *Podophyllum hexandrum* extract before radiation considerably increased the number of surviving crypts, enhanced villus cellularity and attenuated crypt cell apoptosis (Salin et al. 2001). Another study reported results on intestinal levels of superoxide dismutase (SOD), an enzyme capable of scavenging oxidative stress-induced superoxide anions. Intraperitoneal injection of *Podophyllum hexandrum* extract before 2h of 10Gy total body irradiation revealed an elevation in the levels of intestinal superoxide dismutase (Mittal et al. 2001). A recent study has shown that treatment with a formulation using three bioactive compounds, found in the rhizome of *Podophyllum hexandrum* (G-002M) significantly blocked radiation-induced intestinal toxicity by protecting villi, crypts, and the mucosal layers (Dutta et al. 2015). The study also demonstrated that G-200M pre-treatment considerably reduced free radical generation, lipid peroxidation, protein carbonylation and cell death in mouse intestine after 9Gy of total body irradiation. The authors hypothesized that G-200M exerts its radioprotective efficacy by activating redox-sensitive transcription factor (Nrf2), which in turn upregulates heme oxygenase-1 and SOD-1 (Dutta et al. 2015).

2.12. Aloe Vera

Aloe vera has become increasingly popular in recent decades because of its medicinal properties. *Aloe vera* contains a myriad of vitamins, minerals, anti-oxidants and anti-inflammatory fatty acids. A systematic review of clinical trials indicate that *Aloe vera* treatment suppresses radiation toxicity in various organs (Ferreira et al. 2017; Nair et al. 2016). However, literature on its beneficial effects in the intestine remains sparse. One randomized clinical trial, conducted on patients with acute radiation proctitis reported further evidence of anti-inflammatory properties of *Aloe vera*. The symptoms documented in the patients enrolled in the study were either a combination of any two or more of the following: rectal bleeding, abdominal/rectal pain, diarrhea or fecal urgency. A symptom index was calculated based on the severity of the symptoms pre- and post-treatment of the intervention group with 1g ointment with 3% *Aloe vera*, twice daily for 4 weeks. A significant number of patients in the intervention group experienced improvement in

symptom index in comparison to the placebo group (Sahebnaasagh et al. 2017). However, the exact underlying mechanisms of protection are yet to be identified.

3. Summary and Future Perspective

Abdominal or pelvic radiotherapy-induced gut injury can be chronic, progressive, irreversible, and even lethal. Therefore, strategies are required to minimize the toxicity of intestinal normal tissue, not only to improve the effectiveness and outcome of therapeutic radiation, but also to enhance the quality of life for patients after radiation treatment. Sophisticated radiation delivery techniques have substantially reduced the risk of normal tissue injury compared to conventional radiotherapy, but the possibility of radiation toxicity has not been completely eliminated. Several pharmacological compounds have been tested in order to reduce the incidence and severity of radiation enteropathy; however, the adverse side-effects and toxicities caused by these compounds limit their use. On the contrary, natural plant products have been found to be very safe to use and have minimal to no toxic effects. Moreover, a diverse range of bioactive molecules present in plant extracts are expected to exert health benefits by modulating various signaling pathways. Emerging data from clinical trials suggest that natural products have considerable potential to prevent chronic gastrointestinal diseases that occur in patients after radiation therapy and also improve patients' quality of life (Takeda et al. 2008). Although the mechanisms and efficacies are diverse, plant extracts exert their beneficial effects by scavenging ROS and by regulating a variety of molecular signaling pathways. ROS scavenging activity of natural compounds depends on the number of the hydroxyl groups present on aromatic rings (phenolic rings). However, a better understanding of the molecular mechanisms involved in natural products-mediated protection against radiation enteropathy is warranted to identify the critical targets.

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Table 1.

Effects of natural products in modulating intestinal radiation toxicity as observed in preclinical and clinical studies.

Products	Radiation dose and mode of delivery	Duration and dose of natural products/ supplementation	Effects in the intestine	Citation
α-tocopherol	11 Gy, segmented intestinal irradiation	Single intraluminal administration of 5mg/ml or 250 IU of vitamin E enriched food for 10 days prior to radiation exposure	Increase in crypts per circumference and increase in mucosal height was noticed	Felemovicious et al. 1995
L-α-tocopherol	10 Gy, abdominal irradiation	Intraperitoneal administration of 20mg/kg daily for 6 days	There was no significant change in intestinal fluid absorption rate, histologic or morphometric appearance in comparison to the physiologically normal control group	Empey et al. 1992
α-tocopherol	11 Gy, total body irradiation	Single subcutaneous administration of 400 mg/kg 24 hours prior to radiation exposure	Prevented apoptosis in jejunum and promoted regeneration of crypt cells	Singh et al. 2013a
γ-tocotrienol	8.5 Gy total body irradiation	Single subcutaneous administration of 400 mg/kg 24 hours prior to radiation exposure	Reduced radiation-induced intestinal injury, enhanced hematopoietic recovery and accelerated the recovery of endothelial function biomarkers	Berbee et al. 2009
	11 Gy total body irradiation	Single dose administration of 200 mg/kg 24 hours prior to radiation exposure	Anti-apoptotic gene upregulation and intestinal crypt survival was noticed	Suman et al. 2013
δ-tocotrienol	10 – 12 Gy total body irradiation	Single subcutaneous administration of 75 – 100 mg/kg 24 hours prior to radiation exposure	Protected intestinal tissue by reducing apoptotic cells and inhibited gut bacterial translocation	Li et al. 2013
Genistein	5 – 10 Gy, abdominal irradiation	Single dose administration of 200 mg/kg 24 hours prior to radiation exposure	Inhibited intestinal inflammation, apoptosis and gut bacterial translocation	Son et al. 2013
Lycopene	6 Gy, total body irradiation	5 mg/kg oral administration for 7 days via gavage	Improved oxidant/ antioxidant ratio, significantly enhanced small intestine regeneration and improved monoamine levels	Sadaa et al. 2009
Ascorbic acid	5 Gy, abdominal irradiation	Daily dose of 100 mg/kg administered over 14 days	Antioxidant properties provided protection from radiation-induced intestinal injury	Kanter & Akpolat 2008
		Daily dose of 100 mg/kg administered over 18 days		
Ascorbic acid	< 12 Gy, total body irradiation	Pretreated with oral 150 mg/kg/day for 3 days followed by bone marrow transplant 24 hours after irradiation	Pretreatment reduced radiation-induced DNA damage in crypt cells and prevented denudation of intestinal mucosa	Yamamoto et al. 2010
Resveratrol	8 Gy, total body irradiation	Pretreatment with 10 mg/kg/day for 10 days before and 10 days after radiation exposure	Reversed biochemical indices and histopathological changes in the intestine due to radiation-induced injury	Velioglu-Ogunc et al. 2009

Products	Radiation dose and mode of delivery	Duration and dose of natural products/ supplementation	Effects in the intestine	Citation
	7 Gy, partial body irradiation	40 mg/kg via gavage every day for 1 day prior to radiation exposure and 5 days post-radiation exposure	Increased defensive biomarkers (SOD2) against oxidative stress, reduced apoptosis and maintained intestinal regeneration	Zhang et al. 2017
Berberine	Experiment 1: 3, 6 and 12 Gy; Experiment 2: 16 Gy, whole abdominal irradiation in both groups	Experiment 1: 20 mg/kg via intra-gastric gavage at 12 hours, 4 hours and 1 hour before irradiation Experiment 2: 20 mg/kg via intra-gastric gavage at 12 hours, 4 hours and 1 hour before irradiation and for 8 hours after irradiation until killed for examination	Pre-treatment and post-irradiation treatment with berberine increased mean survival time and attenuated intestinal injury indicated by a reduction in interleukins and cytokines and apoptotic proteins	Li et al. 2010b
	Fractionated 36 Gy dose to iliac artery lymph node areas and 46 Gy to pelvis.	300 mg oral administration thrice daily from week 3 to week 5 post-irradiation (Eighteen patients with seminomas and lymphomas received a fractionated dose of 36 Gy and 21 patients with cervical cancer received a fractionated dose of 46 Gy to the whole pelvis)	Intensity and incidence of radiation-induced acute intestinal symptoms (anorexia, nausea, vomiting, colitis, proctitis, unintentional weight loss and diarrhea) were significantly reduced	Li et al. 2010a
Curcumin	5 Gy, abdominal irradiation	100 mg/kg oral administration daily once via gastric intubation (2 treatment groups: 1. Curcumin treatment for 10 days pre- and 4 days post-irradiation for single-dose irradiation group and 2. Curcumin treatment for 14 days pre-irradiation and 4 days post- second dose of irradiation. Radiation doses were 4 days apart)	Free radical interception resulted in an increase in the number of protective mucin-producing goblet cells in the intestine	Akpolat et al. 2009
Tea extracts	12 Gy for jejunal crypt assay; 2 Gy for apoptosis assay	50 mg/kg of green tea polyphenols administered via single intra-peritoneal injection 24 hours before irradiation	Significantly increased the number of surviving crypts and decreased the number of apoptotic cells	Lee et al. 2008
Garlic	0.5 Gy, 1 Gy, 6 Gy and 10 Gy	200 mg/kg administration of diallyl sulphide (major constituent of garlic) via gavage 3 hours prior to radiation exposure	Reduced radiation-induced nuclear aberration, reduced overall colonic injury and promoted cellular proliferation in all 4 experimental groups	Baer et al. 1989
Ginkgo biloba extract	36 Gy, partial body irradiation	100 mg/kg/day via intraperitoneal injections for 5 consecutive days before radiation exposure	Biomarkers of oxidative stress were significantly reduced resulting in protection against radiation-induced dermatitis	Yirmibesoglu et al. 2012
	8 Gy, total body irradiation	50 mg/kg/day pretreatment via intraperitoneal injections for 15 days before radiation exposure	Biomarkers of oxidative stress were significantly reduced resulting in protection against radiation-induced oxidative organ injury	Sener et al. 2006
Podophyllum hexandrum extracts	10 Gy, total body irradiation	200 mg/kg pretreatment via intraperitoneal injections 2	Number of surviving crypts in jejunum and cellularity were increased	Salin et al. 2001

Products	Radiation dose and mode of delivery	Duration and dose of natural products/ supplementation	Effects in the intestine	Citation
		hours before radiation exposure	while the number of apoptotic bodies in the crypts were reduced	Mittal et al. 2001
			Biomarkers of oxidative stress were significantly reduced resulting in protection against radiation-induced oxidative organ injury	
	9 Gy, total body irradiation	2.5 mg/kg pretreatment via intramuscular injections 1 hour before radiation exposure	Biomarkers of oxidative stress and free radical generation were significantly reduced, as evidenced by reduced damage to villi, crypts and mucosal layers in jejunum	Dutta et al. 2015
<i>Aloe vera</i>	4.5 Gy, total body irradiation	1000 mg/kg aloe vera leaf extract 15 days before radiation exposure	Antioxidant effects attributed to radical scavenging properties were reported	Dadupanthi 2015
	46 – 72 Gy external beam irradiation	1 gm of 3% Aloe vera gel twice daily for 4 weeks for 20 consecutive patients with pelvic malignancies	Symptom index score improved for any two or more of the following symptoms: rectal bleeding, abdominal/rectal pain, diarrhea or fecal urgency	Sahebnaasagh et al. 2017