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Review

Application of Natural Products in Radiotherapy-Induced Dermatitis: A Comprehensive Review

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Abstract

Radiodermatitis (RD) is experienced by many cancer patients receiving radiotherapy. An increasing number of these patients demand alternative natural therapies. This study aimed to review the natural products application in cancer patients who experience RD.

A search of studies published from 1990 to 2020 in the databases including PubMed, Scopus, and Google Scholar was performed with the keywords relevant to "Radiotherapy","Dermatitis" and "Natural Products". Out of 73 papers obtained, 40 papers were excluded which described only protocols or were non-clinical, non-English language, or without full text. The obtained studies were discussed in detail according to the outcomes and potential mechanisms of action for each natural product. Clinically studied natural products were found to show several outcomes from non-effective to effective in diminishing various items of RD. Outcomes on the effectiveness of *Aloe vera* were diverse. Some trials suggest that *Silybum marianum*, *Boswellia*, *Nigella sativa*, olive oil, Lianbai, and *Hypericum perforatum* as well as some multi-ingredient products might be effective prophylactic treatments for RD. Potential mechanisms of these natural products included topical hydrating, anti-inflammatory, antioxidant, and wound healing activities. Results from this review shows that there are some promising natural product options for the prevention and treatment of RD via their multifactorial bioactivities. However, additional research is needed before any definitive conclusions. A larger sample size, optimum doses and duration of intervention as well as investigation of treatment effects in diverse populations and comorbid complications would also be essential in future studies.

Keywords: Herbal medicine; Phytochemical; Radiodermatitis; Radiotherapy; Radioprotective; Skin disorders

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Introduction

Radiation treatment is one of the most commonly used therapeutic strategies in cancer treatment [1]. Radiotherapy (RT) is very successful in various cancer treatments considering the rate of ailments. The efficiency and high success rate of RT made it one of the first choices of physicians in treating patients suffering from cancers. Presently it is known as one of the conventional cancer treatment strategies; however, RT causes many side effects like excessive hair loss, nausea, weight loss, and radiodermatitis (RD) [2]. RD refers to radiation-induced skin injury and following an inflammatory reaction. The use of radiation treatment often causes acute and chronic skin disorders such as itching, erythema, scratching, and pain, affecting patient life quality [3-5]. Radiodermatitis may affect the skin structure by thinning the epidermis, basal stratum atrophy, sub-epidermis inflammation and epidermis and superficial dermis necrosis. Clinical manifestations may include dry and inelastic skin, erythema and inflammation, pain, bleeding and infection [6]. Studies showed that patients receiving RT with breast cancer (almost 90%) [7] and head and neck cancer (up to 95%) [8] are affected by skin toxicity. Sometimes it is not convenient for patients to apply the treatment protocol because of RD [8]. Acute radiation-induced skin reactions occur 2-3 weeks following radiotherapy. Three main factors including radiation factors (e.g., dose of radiation, site of treatment, volume of tissue treated), genetic factors (e.g., genetic diversities, some genetic syndromes, radiosensitive diseases, sex) and personal factors (e.g., age, comorbidities that affect normal tissue response or repair, concurrent drug therapy, nutritional status, smoking, skin colour and condition, skin exposure to UV) contribute to severity of skin reactions [9]. Although there are no specific causes for RD, it is a possibility that RD is caused by free radicals producing double- and single-strand DNA breaks. During this inflammatory reaction, a wide variety of cytokines such as interleukin (IL)-1α, IL-1β, Tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β, IL-6, and IL-8 will be produced in irradiated skin cells. These pro-inflammatory mediators up-regulate the expression of intercellular adhesion molecule-1 (ICAM-1) in keratinocytes and endothelial cells. As a result, circulatory immune cells migrate to the irradiated skin. RT can also damage the sebaceous glands and hair follicles in the dermis, consequently skin dryness and epilation [10].

There is no standard treatment and management of RD [11-15], and the use of corticosteroid agents has remained controversial since it has no preventive effect [13]. Furthermore, skin thinning and skin atrophy may occur as an adverse effect during the use of topical steroids over 8 weeks.

Recently, an increase in complementary medicine for skin conditions has been reported [16,17]. Remarkably, there has been a 49% increase for alternative treatment of RD after 2000 in western countries [18]. Some studies showed the usage of natural products in RD treatment, such as *Aloe Vera*, which is commonly used in burn damages, and as a skin-soothing gel, which also has anti-inflammatory, antioxidant,

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and anti-bacterial properties [19,20]. *Calendula officinalis* [21] containing cream has also been investigated to treat radiation side effects on the skin. Moreover, preclinical studies are under progress on the protective and therapeutic effects of various natural products including *Ginkgo biloba* [22], *Centella asiatica*, *Withania somnifera* [23], and soybean seeds extract [24]. The underlying mechanisms for these herbal extracts are their antioxidant, anti-inflammatory, and wound healing activities, as well as protection of cells against the cytotoxic effects of ionizing radiation [25].

Because of the widespread application of RT in cancer treatment, the number of RD cases is increasing. More, alternative therapies and natural products are gaining attention recently to reduce the associated side effects of conventional cancer treatments. Thus, in this comprehensive review, we aimed to assess the effect of natural products on dermatitis caused by radiotherapy.

Methods

We searched studies that used natural products for treating radiation-induced dermatitis in cancer patients followed by radiation therapy from 1990 to 2020. All the authors performed the literature review and relevant data collection. The authors used PubMed, Scopus, and Google Scholar for searching relevant articles. The data was collected from articles only published in the English language. The used keywords for searching data were: "Radiotherapy", "Natural product", "Plant", "Extract", "Herb", "Dermatitis", "Radiodermatitis", "Skin Toxicity", and "Radiation". Every researcher independently conducted a literature evaluation as well as data extraction of each study that met the inclusion criteria. The obtained data were classified based on studies' detail and then each natural product was discussed separately.

Results

We recognized and screened 73 papers published in the years 1990-2020 by titles and summaries. We excluded 40 of the studies, which were describing only the protocol, not the clinical study, non-English language, and with no full text. Summary of the obtained studies on natural products used in patients with cancer undergoing radiotherapy is shown in Table 1 and some related molecular mechanisms are shown in figure 1. Studies on each natural agent have been explained more as follows:

Table 1. Summary of studies on natural products used in patients with cancer undergoing radiotherapy

Natural product	Year	Type of Cancer	Sample Size/design	Medium used	Intervention/ control	Dose, frequency and duration	Result/Outcome	Reference
AdlayBran (*Coix lacryma-jobi*)	2015	Breast	110/ Randomized, double-blind	Capsule	The ethanolic extract of bran part of seeds, Control: olive oil	500 mg, QID, from the first day of RT to 5-6 weeks	Reduced occurrence of severe acute RD (RTOG grade 2 or higher), No serious adverse effects	[94]

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Allantonin	2014	Breast, lung, or head and neck	174/ Randomized, double-blind	Emulsion	Oil-based emulsion containing allantoin, sweet almond oil, olive oil, rice bran oil, milk protein, *Aloe vera*, vitamin E, piroctone olamine, Control: aqueous cream	A thin layer of cream on the irradiated area, at the onset of RT, twice daily or more	Similar effects in managing skin toxicity, level of pain, itching, and skin-related quality of life in both groups	[67]
Aloe vera	1996	Breast	1: 194/ double blinded, placebo controlled, 2: 108/ randomized	Gel	1: *Aloe* gel Control: placebo gel 2: *Aloe* gel, Control: no treatment	-	No protection against RD, Rare contact dermatitis as side effect	[51]
Aloe vera	2001	Breast, Pelvic, Head and Neck	73/ randomized, blinded	Gel	100% *Aloe vera*	Applying the gel liberally, each day following RT	Prolonged the median time of any skin alteration (in high cumulative radiation dose), protective effect against RD	[58]
Aloe vera	2002	Breast	225/ randomized controlled	Gel	98% *Aloe vera*, Control: aqueous cream	Three times a day during RT and for two weeks after radiation completion	*Aloe vera*: No significant reduction in radiation-induced skin side effects, Aqueous cream: reduced dry desquamation and pain related to radiation therapy better than *Aloe vera* group	[20]
Aloe vera	2007	Breast	50/ non-blinded, non-randomized	Gel	*Aloe* barbadensis 97%, Control group: Essex lotion (palmitic acid, steric acid, cetyl alcohol, xanchan gum, magnesium aluminum silicate)	0.2 ml, Twice a day on every treatment day	No significant effect on the extent of erythema for both groups. No significant median differences were observed between groups	[57]
Aloe vera	2013	Breast, Pelvic, Head and Neck	60/ self-controlled	Lotion	*Aloe vera*, lanolin oil, diluted collagen, tocopherol, allantoin	On one half of the body. Twice daily from the beginning of RT and for two weeks after radiation	Protective effect against RD, more evident in patients undergoing radiotherapy with larger treatment fields and higher doses of radiation	[52]

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Aloe vera	2015	Breast	248/ randomized, placebo controlled	Cream	*Aloe* cream: processed *Aloe* (1000-5000 MW fraction) in placebo cream, Control: placebo base cream	2.5 ml, three times a day throughout radiation and for 1 month after RT	No reduction in RD in both test and control groups	[61]
Aloe vera	2017	Breast	100/randomized controlled	Gel	*Aloe vera*, pectin, Vitamin c, and Natamycin	1-2 mm of thickness on the radiation site. Twice a day in a minimum of 6 hours intervals throughout treatment	No positive effect on prevalence or severity of RD	[62]
Aloe vera	2017	Head and neck	60/ investigator-blinded, randomized	Cream	*Aloe* based cream (Elovera®), Control: Johnson's Baby Oil	-	Delay in the incidence of RD at week three, Reduced the incidence of Grade 1, 2, and 3 RD, Reduced average grade of dermatitis two weeks after the RT	[56]
Aloe vera	2018	Cervix	116/non randomized	Lotion	*Aloe vera* lotion containing 10% lidocaine	From the first day of treatment carried through 5 weeks till 2 weeks after treatment. Twice a day before RT and at night after RT	Effective in delaying the development of Grade 2 and 3 dermatitis	[63]
Alpha ointment (*Lawsonia inermis*)	2013	Breast	60/randomized controlled	Ointment-Control: hydrocortisone cream (1%)	Alpha ointment (natural Henna and unsaturated fatty acids),	Applying a thin layer of the topical agents twice a day, beginning on the day of the last session of RT and continuing every day for 3 weeks	More effective on the healing of RD than was topical hydrocortisone cream (1%). Decreased the patients' complaints (pain, pruritus, and discharge)	[118]
Boswellia	2015	Breast	114/ randomized placebo controlled	Cream	*Boswellia* cream 2%, Control: base cream	Twice daily: immediately after radiation and before bed time/in the morning and at night in days with no RT	Effective in reducing the use of topical corticosteroids, and the grade of erythema and the skin superficial symptoms, being well tolerated by the patients	[13]

Calendula officinalis	2004	Breast	254/ randomized controlled	Ointment	*C. officinalis* ointment, Control group: trolamine ointment	Twice a day until completion of RT	More effective in reduction of acute dermatitis (grade 2 or higher) than trolamine, Less frequent interruption of RT and radiation-induced pain in *Calendula* group	[21]
Calendula officinalis	2012	Breast	420/ randomized, blinded	Cream	extract of *C. officinalis* (10%), wool Fat, sesame oil, Control: aqueous ®cream (Essex)	Appling a thin layer of the assigned cream twice a day, starting at the onset of RT and continuing until two weeks after final RT session	Lower levels of skin related symptoms in both groups, No difference in severe acute radiation skin reaction (ARSD) between two groups	[43]
Centella asiatica, Cucumis sativus, Thunbergia laurifolia	2020	Breast	153/ randomized controlled	Cream	Cream 1: containing the *C. asiatica* extract (7% w/w), Cream 2: containing the *C. sativus* (cucumber) extract (20% w/w), cream 3: containing the *T. laurifolia* extract (5% w/w), Control: moisturizing	Once daily from their first radiotherapy session until 1-month post-irradiation.	No reduction of the severity or delay the onset of dermatitis with herbal creams. *C. sativus* cream helped with the skin recovery post-irradiation.	[158]
Matricaria recutita	1990	Breast	50/randomized controlled	Cream	Standardized extract of *M. recutita* flower, Control: Almond ointment	Twice daily, the first application 30 min before RT and the second before bed time throughout RT	No differences in skin reactions between treated areas in both groups, No preventive effect against skin reaction	[73]
Chamomile	2020	Head and neck	48/randomized controlled	Gel	8.35% chamomile, Control: urea cream	3 times a day (morning, afternoon and night) for the entire period of the radiation therapy.	Delayed onset of dermatitis, and onset of Grade 2 dermatitis in the chamomile group, Less report of itching, burning and hyperpigmentation in chamomile group	[74]

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Curcumin	2013	Breast	30/ randomized, double-blind, placebo-controlled	Capsule	(Curcumin c3 complex®): 25% curcuminoids (approximately 390 mg curcumin, 75mg demethoxy curcumin, 12.5 mg bisdemethoxycurcumin) plus excipients (20 mg microcrystalline cellulose, magnesium stearate, Silicone dioxide), Placebo: dicalcium phosphate, excipients and yellow food coloring	2 grams of curcumin or placebo orally three times per day (i.e., 6.0 grams daily) throughout their course of RT	No complete prevention of skin damage, Reduced moist desquamation, Improved quality of life during RT	[133]
Dead sea moisturizing cream product (Solaris®)	2007	Head and neck	54/randomized controlled	Cream	Isopropyl, (Hamamelis virginiana, Daucus carota seed oil, Simmondsia chinensis seed oil, Anthemis nobilis extract, Rosmarinus officinalis oil, Lavandula ngustifolia oil, sea salt, *Aloe* barbadensis gel, Lilium candidum, tocopherol, lecithin, isopropyl myristate, Dead Sea salt, and Thymus vulgaris oil, Control: *Aloe vera* or Biafine® (trolamine) creams	Three times daily, starting 1 week before, during and up to 2 weeks after the completion of RT	Reduction in skin toxicity in intervention group	[159]
Holoil (*Hypericum perforatum and Azadirachta indica*)	2014	Head and neck	28/ single-arm prospective observational	gel (for erythema and oedema) or oil formulation (for moist desquamation)	*H. perforatum* and *A. indica* oil	Twice a day, up to the end of RT and afterwards during follow up time, until complete recovery from acute skin toxicity	Partial wound healing after 2 weeks treatment, Complete wound healing with 2 weeks after the end of radiochemotherapy	[103]

Holoil	2017	Head and neck	50/single-arm	Gel for erythema and edema, oil for moist desquamation	*H. perforatum* and *A. indica* oil	Twice a day until RT completion and during observation period	Lower toxicity profile, Decreased pain, Safe and effective in RD reduction	[105]
Lianbai	2007	Breast, Nasopharyngeal, Esophayeal, and Lung, and etc.	218/ randomized controlled	Liquid	Lianbai liquid (Rhizoma Coptidis, Cortex Phellodendri), Control 1 (prevention phase): No intervention Control 2 (treatment phase): norfloxacin	Prevention phase: externally applied on the skim after each time of RT, 3-4 times a day, until the end of treatment course; Treatment phase: 3-4 times a day for 2 weeks as a course of treatment.	Prevention in RD, Curative effect on grade III acute radiation dermal injury	[145]
Nigella Sativa	2019	Breast	62/ randomized, double-blind, placebo-controlled	Gel	5% *N. sativa* extract, glycerol, Polyacrilicacid Triethanolamine, Placebo: containing all of the aforementioned ingredients except the *N. sativa* extract	Twice daily during RT	Less frequency in acute RD, Prolonged incidence time of grade 2 and 3 of radiation toxicity, Delayed occurrence of moist desquamation and less pain in intervention group	[142]
NS-21	2019	Head and neck	39/ randomized controlled	Cream	Including *Calendula*, *Aloe vera*, Allantonin, Vitamin E, Betaglucan, Hydrolyzed soyprotein, grapeseed oil, zinc, Emu oil, Avacado oil, Jojoba oil, Rosehip oil, Urea,	Three times per day starting at the imitiation of RT and ending 2 weeks after the completion of RT	Effective for the keeping of skin moisture. no statistically significant reduction in the RD	[69]
Olive oil	2015	Breast	94/randomized controlled	Oil	Olive oil include oleic acid Phenolic constituents and squalene, Control: general skin care regimen	Twice daily for 7 weeks during chemoradiotherapy and for 2 weeks after	Reduced RD in test group	[15]

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Olive oil and Calcium hydroxide	2019	Breast	62/ randomized controlled	Emulsion	Emulsion of olive oil and calcium hydroxide,	Twice a day from the initiation of RT to 2 weeks after RT	Reduced RD and shown a better quality of life than control group	[119]
Olive oil, *Calendula* and Hypericum oils, Beeswax, and *Aloe* gel	2020	Breast, head and neck	59/ open label, non-randomized	Cream(RDC) Ointment(RDO) Gel(RDG)	RDC (*Aloe vera* gel, *Calendula officinalis* and Hypericum perforatum oil extracts) RDO (beeswax, Greek extra virgin olive oil, C. officinalis and *H. perforatum* oil extracts) RDG (*A. vera* gel, C. officinalis and H perforatum oil extracts)	RDC: 3 to 4 times daily RDO: before bedtime. The treated area was cleansed with the RDG and patted dry gently with a cotton towel. from the initiation of RT to 2 weeks after treatment	Reduced the intensity of RD, positively affected the quality of life of the patients	[123]
Punica granatum	2017	Head and neck	60/ randomized controlled double blind	Capsule	Each capsule contained 40% Polyphenols and 27% Punicalagin	300 mg, Each patient were given 2 capsules every day for a period of 6-7 weeks	Reduced acute skin toxicity	[108]
Silybum marianum	2011	Breast	101/ open label, nonrandomized	Cream	Leviderm® (silymarin 0.25%) Control group: standard of care (panthenol-containing creams)	Three times a day 2 weeks before begging, during and 2 weeks after the end of RT	Prolonged median time to toxicity in silymarin group	[78]
Silybum marianum	2019	Breast	40/ randomized double blinded	Gel	1% silymarin gel containing 80% silymarin flavonolignans, Placebo group: containing all ingredients of silymarin gel except silymarin and colored (with food coloring)	Once daily. Half fingertip unit of gel on the chest wall radiation field after treatment from the first day of RT for 5 weeks	Delay in RD development and progression in silymarin group	[79]
Vicco Turmeric	2013	Head and neck	50/ randomized	Cream	Composed of turmeric and sandal wood, Control: Johnson's(®) baby oil	2 grams every day until 2 weeks after the end of treatment	Reduced RD in test group	[136]

Boswellia spp.

The resin of the *Boswellia* species has traditionally been used to treat various diseases [26]. The genus *Boswellia* include about 25 species growing in dry regions of Asia and Africa [27]. However, studies on the anti-inflammatory activity of the genus *Boswellia* have been shown to be more related to *B. serrata* [28] and *B. carteri* [29]. Some *in vivo* studies have shown the anti-inflammatory activities of *Boswellia serrata* resin [30]. One clinical study on efficacy and safety of a *Boswellia*-based preparation for treatment of RD in mammary carcinoma patients showed that the degree of erythema was reduced in cases that used *Boswellia* cream in comparison with patients who were in the placebo group [13]. Also, the percentage of patients who used concomitant topical corticosteroids and the incidence of skin itching and burning sensation were significantly lower in the group receiving *Boswellia* cream. The authors suggested that patients receiving *Boswellia* cream might have lower superficial toxicity. Some evidence has indicated that the pharmacological activities of *Boswellia* are related to its boswellic acids (BAs) content. These phytochemicals have a steroid-like pentacyclic triterpene structure with an inhibitory effect on inflammatory pathways [13]. BAs inhibit 5-lipoxygenase and other targets such as proinflammatory cytokines (interleukins and TNF-α, leukocyte, and leukotrienes) [31-33]. Moreover, it has been indicated that d 3-O-acetyl-11-keto-β-boswellic acid interferes with mitogen activated protein kinases (MAPK), nuclear factor kappa B (NF-kB), and signal transducer and activator of transcription 3 (STAT3) pathways [34].

Calendula officinalis L.

Genus *Calendula*, include 15–20 species of plants in the Asteraceae family and occurs in temperate regions of Eurasia and North Africa [35]. The most studied species in this genus is *Calendula officinalis* L., which possess several pharmacological activities including antioxidant, antimicrobial, antioedematous, and wound healing effects, particularly due to the phytochemicals, such as polyphenols, flavonoids and carotenoids [36].

C. officinalis flower extract has been widely shown to have anti-inflammatory [37] and wound healing properties [38, 39]. It possessed an inhibitory effect on pro-inflammatory cytokines such as interleukin 6 (IL-6), interleukin 1 beta (IL-1β), tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN- γ) *in vitro*, and showed a mitigating effect on C-reactive protein (CRP) and cyclooxygenase-2 (COX2) levels in mice [37]. Among various phytochemical content of *Calendula*, triterpenoids have been shown to manifest anti-inflammatory and fibroblast stimulating activities [40], which are due to the inhibition of 5-lipoxygenase, COX2, and C3-convertase enzymes involved in inflammatory responses [39]. Moreover, *Calendula* contains many forms of flavonoids, having anti-inflammatory and anti-edematous properties [39]. *Calendula* alcoholic extract also showed other effects in various *in vitro* studies, such as proliferation and migration of human fibroblasts and keratinocytes, increased angiogenesis observed in the chorioallantois membrane

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model, and reduction in collagenase activity; these effects may contribute to activation of the phosphoinositide 3-kinase (PI3K) pathway in fibroblasts and NF-kB pathway in keratinocytes in the inflammatory phase of wound healing process [41]. A study on SKH-hr1 hairless mice used *Calendula* for preventing skin toxicity of ionizing radiation (IR). Each IR dose (10 Gy/day) was for 4 days. RD and inflammatory factors were assessed up to 15 days after radiation. The study showed that *Calendula* significantly inhibited inflammatory factors such as monocyte chemotactic protein-1 (MCP-1), Keratinocyte- derived chemokine and Granulocyte Colony-Stimulating Factor [42].

Despite its known anti-inflammatory and wound healing effects, the evidence for *Calendula*'s effectiveness in treating radiation-induced skin toxicity is limited. A randomized clinical trial conducted in 2012 compared the effect of a *Calendula* cream with Essex cream (an aqueous cream without parabens, containing 5% urea) on severe acute RD in patients with breast cancer undergoing adjuvant RT, where they found no significant difference between the two studied groups [43]. Pommier et al., [21] evaluated the effects of a preparation containing *Calendula* (Boiron Ltd., Levallois-Perret, France) on acute RD in breast cancer patients in a randomized clinical study. They reported that cases treated with *Calendula* cream experienced a lower incidence of severe acute RD, pain, and treatment failure than the group treated with trolamine. Based on this observation, the study concluded that *Calendula* preparation might be an effective and safe medication for mild-to-severe RD [21].

The concentrations of topical *Calendula* preparations that are considered safe commonly contain 0.0001-0.8% for flower extract and 0.02-0.1% for flower oil [44]. Moreover, several studies approve that *Calendula* is not irritant in most patients and can be safely used in patients with eczema (32); therefore, *Calendula* could be considered a safe therapy that needs to be more evaluated in controlled trials for RD management.

Aloe vera (L.) Burm.f.

Aloe vera (Xanthorrhoeaceae), is commonly known for its therapeutic uses in several conditions like healing effects in skin inflammations and injuries through its anti-inflammatory and antioxidant activities [45, 46]. The number of species in *Aloe* genus is around 140, and most of them occur in South Africa [47]. Some studies have shown the wound healing and anti-erythema effects of several *Aloe* species such as *A. marlothii* and *A. ferox* and *A. vera*, specifically via their gel material [48, 49]. However, *A. vera* has been widely used and studied for its anti-inflammatory and wound healing applications [47,48].

Some studies have shown that the various pharmacological activities of *A. vera* are related to anthraquinones, glycoproteins like lectins, polysaccharides such as mannan, maloyl glucans, arabinan and arabinogalactan [50].

Experimental studies, *in vivo*, support the use of *A. vera* accelerating recovery from radiation-induced dermatitis [51,52]. It is assumed that COX2 inhibition might be the primary mech-

anism by which *A. vera* acts [53, 54]. Moreover, *A. vera* affects the leukocyte and platelet aggregation resulting in reduced vascular constriction, contributing to wound healing process [55]. In this regard, various *A. vera* preparations have been clinically evaluated for their effectiveness in preventing/attenuating radiation dermatitis [56]. One clinical study in 1996 showed that the severity of dermatitis in patients with breast cancer was not significantly different in groups receiving *A. vera* gel or an inert gel as a placebo [51]. Another trial in patients who received radiation therapy for breast cancer also reported that *A. vera* gel was not as effective as an aqueous cream on erythema, pain, itching, and dry and moist desquamation [20]. A study on a similar type of patients (breast cancer) receiving RT showed that *A. vera* gel could not reduce the intensity of erythema caused by radiation [57]. While another randomized, blinded trial evaluated the efficacy of *A. vera* gel in soap preparation in mitigating dermatitis in cancer patients undergoing RT. The results showed that soap formulation with *Aloe* gel had a protective effect only in increased cumulative dose (> 2,700 cGy) over time. There was no difference between patients in low cumulative dose levels less than or equal to 2,700 cGy [58]. Another randomized clinical study also showed that half of the patients routinely used *Aloe* gel as a prophylactic remedy [59]. Also, a self-controlled clinical trial evaluated the effect of *A. vera* lotion on preventing radiodermatitis in patients with various cancers. The mean grade of dermatitis was recorded from week 2-6 of RT and weeks 2 and 4 afterward. The results showed that the grade of dermatitis was significantly lower on the *Aloe*-treated areas of patients in weeks 4, 5, and 6 of RT and weeks 2 and 4 after radiation, showing that *A. vera* lotion had a prophylactic effect on the intensity of radiation-induced dermatitis [52]. Although several phytochemicals from *A. vera* like bradykinase, C-glycosyl chromone, and salicylic acid have been reported with anti-inflammatory and wound healing activities, the most important active ingredient in its gel is acemannan, the major polysaccharide of *A. vera* gel with potential skin protection and wound healing effects [60]. However, the clinical studies on *A. vera* gel are controversial. A three-arm trial study evaluating the effects of *Aloe* gel, moist cream, and a dry powder skin-care regimen on decreasing radio-dermatitis in breast cancer patients showed neither *Aloe* nor moist cream reduced dermatitis severity compared with the dry powder regimen [61]. In another randomized trial, *A. vera* gel lacked prophylactic effects when evaluated in cancer patients with radiodermatitis. Patients were enrolled in the treatment arm receiving the *A. vera* gel, and the control group did not receive the treatment. After five weeks of therapy, no significant effect on the severity of radiodermatitis was observed in the *A. vera* group compared to the control [62]. A recent study on Nigerian patients with cervical carcinoma receiving RT showed that *A. vera* lotion (*Aloe vera* and 10% lidocaine), when used as a prophylactic agent, effectively delayed the dermatitis development compared to the control group [63]. However, Richardson et al. (2005) concluded in their review that no evidence supported the effective-

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ness of *A. vera* in the prevention and treatment of skin problems and called for further extensive research by spotting methodology issues [64].

Allantoin

Allantoin, commonly known to be found in the herbal extract of comfrey, is available in many other plants such as sugar beet, chamomile, tobacco seed, and wheat sprouts [65]. A trial in 2014 assessed the effectiveness of several natural products in breast cancer patients comparing with aqueous cream as a placebo. The complex product was a combination of allantoin, vitamins, plant extracts, and many other natural-based elements that demonstrated little effectiveness in preventing RD after RT [66]. In a study, patients received two different formulations of allantoin, including cream 1 (contains allantoin) and cream 2 (contains no allantoin but aqueous cream). Several indicators, such as Common Terminology Criteria for Adverse Events and skin toxicity levels, were considered at different times. Results showed that patients who received cream 1 showed a significantly lower average level of adverse events at week 3 and had statistically higher average skin toxicity levels at weeks 7, 8, and 9. Almost the same results were obtained when skin toxicity was analyzed using grades. Once the pain was considered, patients in the cream 2 group had initially a significantly higher average level of the worst pain and itching at week 3; however, the differences were negligible at other weeks. The natural oil-based emulsion containing allantoin has been shown to possess the same effects for treating skin toxicity compared with aqueous cream, up to week 5. Notably, it was not effective at later weeks (week 6 and beyond) and no significant improvement in pain, itching, and skin-related quality of life were observed [67,68].

NS-21

NS-21 is a cream formulation marketed by Plunkett Pharmaceuticals, Ltd., Sydney, Australia. This product comprises of natural ingredients such as *Calendula*, *A. vera*, allantoin, vitamin E, beta-glucan, emu oil, urea, honey, Zn-Cu, and several herbal oils including grape seed oil, soybean oil, avocado oil, jojoba oil and rose hip oil. Using NS-21, a randomized control trial study has been performed in patients with head and neck cancer undergoing RT. RT is resulted in inflammatory response, impaired stratum corneum hydration and consequently acute radiation dermatitis. However, NS-21 increased skin moisture and integrity through epidermal barrier repair, wound healing improvement, antioxidant and anti-inflammatory effects due to the presence of above-mentioned components. The results showed that NS-21 was useful for retaining skin hydration. However, there was no statistically significant reduction in the RD [69].

Chamomile

Genus *Matricaria*, belonging to the family Compositae, includes 22 species, which are grown in temperate regions of Asia, Europe, Africa, and America. Several pharmacological activities such as anti-inflammatory, antioxidant, and anticancer effects have been shown by the plants of this genus. However, chamomile (*M. chamo-*

milla) is one of the most studied species of this genus. Their bioactivity is mainly due to their main phytochemicals including terpenoids and flavonoids, particularly α-bisabolol, apigenin and quercetin [70]. *Matricaria chamomilla* L. flower has anti-inflammatory and anti-allergic effects, which are due to the presence of flavonoid and coumarin components. The inhibitory effect of chamomile on the content of prostaglandin E2 (PGE2) and nitric oxide (NO) concentrations has been proven [71, 72]. However, in a 1990 double blind randomized trial, the effect of almond and chamomile were evaluated in RD and results showed that chamomile was not effective in preventing RD in breast cancer patients [73]. While, a randomized trial study in 2020 compared chamomile gel with urea cream in prevention of acute RD in head and neck cancer patients (n=24 per group). Results demonstrate a delayed onset of dermatitis, with onset of Grade 2 dermatitis at 5.1 (1.3) weeks in the chamomile group and 4.5 (1.3) weeks in the urea group (effect size of 0.46) and indicates a potential efficacy of the chamomile in reducing or delaying the occurrence of RD than the urea cream. Itching, burning and hyperpigmentation were more frequently reported in the urea group [74].

Silymarin

Another well-known herb with various pharmacological properties is Milk thistle (*Silybum marianum* L.), which belongs to the Compositae family. A study based on chemical composition analysis showed that *Silybum marianum* contains silybin (50%), silychristin (20%), silydianin (10%), isosilychristin (5%), and between 10% and 30% unidentified chemicals like polymeric and oxidized polyphenolic compounds [75]. Some studies showed that silymarin increases the glutathione content and superoxide dismutase (SOD) activity, which explains its antioxidant, and lipid peroxidation inhibitory properties. Also, the study by Gharagozloo et al., represented that silymarin inhibits T cell proliferation and reduces the secretions of interleukin (IL)-4, and IL-10 and IFN-γ. By acting on NF-κB pathway, silymarin also suppresses T-cell activation, neutrophil migration, and also inhibits COX2 and lipoxygenase-5 (Lox-5) expressions [76]. More, silymarin has been shown to inhibit neutrophil accumulation induced by irritants which attract neutrophil and adhesion molecules, including ICAM-1 [77].

One nonrandomized clinical study on breast cancer patients with RT reported significantly prolonged skin reaction and lower incidence of RD in patients treated with silymarin-based cream (Leviaderm(®); 0.25%) compared to their local standard care (5% dexpanthenol cream) [78]. Moreover, a recent randomized, double-blinded, placebo-controlled trial showed that topical application of silymarin (80% silymarin flavonolignans) 1% gel lowered the severity, prolongation, and progression of RD in patients compared to placebo formulation [79]. Silymarin-based cream might cause antioxidative effect when the skin is exposed to irradiation [80,81].

Numerous studies indicated the antioxidant effect of silymarin. The mechanism of action is probably through increasing the cellular glu-

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tathione content, inhibiting lipid peroxidation, and acting as reactive oxygen species (ROS) scavenger. Karimi et al. reported that it could increase RNA and protein synthesis resulting in faster repair of tissue damages [82]. A study by Kren and Walterovera showed the immunomodulatory and anti-inflammatory activities of silymarin by inhibiting T-cell proliferation via inhibition of the activation of NF-κB pathways, COX2, and decreasing inflammatory cytokines serum levels (e.g., IL-1, IL-6, IL-8, and TNF-α) [83]. Finally, it has been shown that the topical administration of silymarin is more effective than oral administration [84].

Adlay Bran

Adlay (*Coix lacryma-jobi* L. var. ma-yuen Stapf) is mainly known in Far East Asia countries such as China, Japan, and India. The adlay seed has four different layers known as hull, testa, bran, and endosperm. The cereal crop is used in traditional Chinese medicine and as a food supplement. Some recent studies investigated the pharmacological properties of this plant [85, 86]. Adlay bran is known to have anti-inflammatory [85, 87, 88], antioxidant [89-91], and anticancer properties [92, 93]. A prospective, randomized, double-blind study was performed in 2015, assessed the effect of adlay bran extract in reducing RD after RT in patients with breast cancer. The study showed that in patients who received adlay bran, RD was significantly reduced compared to the placebo group (olive oil) [94]. Adlay bran mainly contains neutral oil (25% of the dry weight)[95], mostly composed of fatty acids, including oleic acid, linoleic acid, palmitic acid, and stearic acid. It is also reported that the bran part contains phytosterols, phenolic compounds, and flavonoids [90]. Some studies have also indicated that phenolic compounds and flavonoids contribute to the antioxidant and anti-inflammatory actions of adlay bran [85, 88, 91]. The mechanism of action of these compounds is through suppression of COX2 expression [87] and inhibition of nitric oxide production [88]. Other mechanisms are also supposed to have some roles, such as manifesting antioxidant activity by scavenging superoxide anion radicals [91]. However, a definite understanding of the mechanisms of bran compounds requires further investigations.

Hypericum perforatum L.

The genus *Hypericum* (Hypericaceae) is one of the 100 largest genera including over 500 species distributed worldwide [96]. However, the most widely studied species in this genus is *H. perforatum* [97]. *H. perforatum* (St John's wort) is known with anti-bacterial, anti-carcinogenic and anti-proliferative properties. Moreover, *H. perforatum* has remarkable wound healing and anti-inflammatory activities [98]. Several phytochemicals have been reported in *Hypericum* species such as naphthodianthrones, phenolic acids, phloroglucinols, flavonoids, tannins, xanthones, and triterpenes [97]. Among them, compounds like amentoflavone, hypericin, hyperforin dicyclohexylammonium (DHCA) salt and adhyperforin have been shown to be responsible for potent anti-inflammatory activity in *H. perforatum* [99].

Hyperforin is known for its anti-inflammatory,

anti-bacterial, and antioxidant activities. It has been reported to reinforce the skin barrier function [100]. *H. perforatum* has been shown to reduce LPS-induced PGE2 and nitric oxide (NO) production in RAW 264.7 macrophages [101]. *H. perforatum* has been indicated to act as anti-inflammatory agent through down- regulating the expression of COX2, IL-6, and inducible nitric oxide synthase (iNOS), and inhibiting the PG synthesis via pseudohypericin and hyperforin [102]. Studies on a commercially available product, Holoil, which contains *H. perforatum* flower and *Azadirachta indica* oil, demonstrated the anti-inflammatory effect of Holoil. It has been suggested to be used as a safe and effective treatment of RD for patients with head and neck cancer [103]. *Azadirachta Indica* (Neem) oil also has cicatrizing, antiphlogistic and anti-inflammatory characteristics [104,105].

Punica granatum L.

Punica granatum L., pomegranate (Punicaceae), a well-known fruit in the Mediterranean region and Iran, is extensively used for therapeutic formulations, cosmetics, and food processing. Pomegranate has shown antioxidative, anti-tumor and anti-bacterial as well as anti-inflammatory effects. It has been indicated that its hydrolysable tannins including punicalagin, punicalin, strictinin A, and granatin B inhibited NO production and iNOS expression in RAW 264.7 cells and had the PGE2 inhibitory activities in the *in vitro* and *in vivo* studies [106]. *P. granatum* has a protective property against the toxicity effects of RT [107]. Pomegranate extracts contain antioxidant ingredients, mainly phenolic compounds. A prospective clinical double-blind study performed in 2017 evaluated the effect of capsules contain the whole pomegranate extract (40% polyphenols and 27% punicalagin) in patients with head and neck cancer under RT. Pomegranate extract was shown to be effective in preventing RD [108].

Alpha ointment

The Alpha® ointment is a mixture of *Lawsonia inermis* (Natural Henna) and unsaturated fatty acids. It is commonly used in the treatment of burning wounds. *L. inermis* is known to possess anti-inflammatory, analgesic, anti-microbial, antioxidant, and burn wound healing effects [109-113]. The main phytochemicals of henna are lawsone (2- hydroxy-1:4 napthaquinone), phenolic compounds like gallic acid, and other constituents such as terpenoids, sterols, xanthones, coumarins, alkaloids, and fatty acids [114]. The alkaloids of *L. inermis* seeds have been indicated to inhibit the lipo-oxygenase enzyme via diminishing the nitric oxide (NO) production and decreasing the prostaglandins biosynthesis [115]. Also, lawsone has been demonstrated to activate the aryl hydrocarbon receptor (AhR) which controls the regulation of skin homeostasis. Lawsone exposure affected the differentiation and proliferation of keratinocyte, and controlled the inflammation of skin. Lawsone was shown to upregulate the expression of the antioxidant enzyme NAD(P)H dehydrogenase (quinone1), which is also controlled by the nuclear factor erythroid 2–related factor 2 (Nrf2). More, topical exposure of lawsone showed a reduction of IL-17 expression [116].

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Also, *L. inermis* extract has been shown to promote the wound healing process *in vivo* via enhancing glucose uptake by up-regulating the expression of glucose transporter-1 (Glut-1) and insulin-like growth factor I (Igf-1) [117]. A randomized clinical study showed that alpha ointment was significantly effective on the healing of RD in patients with breast cancer. Alpha ointment significantly reduced the patients' complaints including pain, pruritus, and discharge in comparison with topical hydrocortisone (1%) [118].

Olive oil

Olive oil has a long history of traditional use for skin disorders. The main ingredients of olive oil consist of oleic acid, phenolic constituents, and squalene. This natural oil is used in atopic dermatitis, acne, psoriasis, and also has antioxidant, and anti-inflammatory effects. Olive oil significantly reduces the level of reactive oxygen species-induced 8-hydroxydeoxyguanosine generation which is a biomarker of oxidative stress and carcinogenesis [119]. Some studies indicated that polyphenolic compounds of olive oil increase the activity of SOD, catalase, glutathione peroxidase, glutathione reductase, and glutathione S-transferase, which explains its antioxidant activity [120]. Olive oil might help to wound healing via affecting inflammation, and stimulation of dermal reconstruction [121]. Its fatty acids can act as activators of peroxisome proliferator-activated receptor-alpha (PPAR-α), which increase keratinocyte proliferation and lipid synthesis[121]. Also, phytochemicals of olive oil exert potent anti-inflammatory effects. Its phenolic compounds have been indicated to reduce responses of human keratinocytes and inhibit key epidermal cytokines, such as thymic stromal lymphopoietin (TSLP) [122]. These compounds prohibited inflammatory responses via countering IL-1- and Toll-like receptors (TLR3-l) induced formation of TSLP. Also, they could diminish the expression of various genes such as IL-8, TNF-, IL-6, and COX2. Olive oil chemicals can moderate the NF- B pathway and increase the levels of nuclear p65 along with decrease in the cytosolic I-B-levels [122].

A 2015 prospective study in nasopharyngeal carcinoma patients under RT showed that olive oil was effective in decreasing RD [15]. Another study on olive oil in 2019 indicated that olive oil and calcium hydroxide reduced RD and showed a better quality of life than the control group in post-mastectomy patients who received RT [119]. In 2020, one clinical study evaluated the protective role of 3 herbal formulations against the incidence of RD in either breast or head and neck cancer patients undergoing RT. A total of 59 patients participated in the study. An herbal product, consisting of olive oil, beeswax, Calendula and Hypericum oils and Aloe gel, were daily being used by the patients during RT and 2 weeks after the end of treatment. The application of this novel multi-component natural product proved to be effective in decreasing the intensity of RD, and improving the quality of life of the patients [123].

Turmeric

Curcuma longa (turmeric) has been known to be traditionally useful in the treatment of various skin conditions such as inflammation, ec-

zema, wounds, urticaria, psoriasis, etc. [124]. Researches carried out during the past three decades have indicated that turmeric and its major phytochemical curcumin have wound-healing, anti-aging, anti-psoriatic properties as well as relieving activity against UV-induced skin damage in cancer patients when applied topically [125-127]. Curcumin, also has antioxidant and anti-inflammatory properties [125, 128-131]. In an animal study, topical administration of curcumin resulted in enhancement of epithelial cell survival and improvement in irradiated skin, via decreasing the expression of COX2 and NfkB [132]. In 2013, one study showed that oral curcumin decreased RD severity in cancer patients, reduced moist desquamation and improved the quality of life during RT [133]. However, in subsequent larger trial oral curcumin did not reduce RD severity in comparison with placebo [134], probably due to its low bioavailability. Another multi-center, randomized, blinded trial on 191 breast cancer patients evaluated the effect of topical administration of curcumin gel (known as Psoria-Gold® Curcumin, contains 4% curcumin) on reducing RD and associated pain compared to HPR Plus™ (a moisturizer cream that contains free fatty acids, hyaluronic acid, and ceramides), or placebo. Results showed that curcumin has no significant effects on the overall population of the treatment group, but in subgroup analysis it might have effective prophylactic treatment for reducing skin reactions and pain for patients with the worst skin reactions [135].

More, in 2013 a double-blinded study indicated that vicco turmeric cream (VTC) has beneficial effects in preventing RD in patients with head and neck cancer undergoing RT and it also reduced the incidence and occurrence of Grade 3 dermatitis. Vicco turmeric cream (VTC) has been often prescribed in the treatment of acne and it is composed of turmeric and sandal wood oil, which are two main skincare plants in the traditional medicine of India [136]. Both sandal wood oil and its main chemical α-santalol have been shown to have healing effects on the skin, and to protect against chemical and UV-induced skin carcinogenesis [137].

Nigella sativa L.

Nigella sativa is used as a traditional medicine for headache, inflammation, asthma, and etc. [138]. Some animal and human studies have shown the anti-inflammatory, antioxidant, and analgesic effects of *N. sativa* mainly because of thymoquinone content in its essential oil [139-141]. In a randomized trial, cancer patients undergoing RT were administered the *N. sativa* 5% gel, and the treated patients showed significantly less RD compared to the placebo group. Moreover, the incidence time of grade 2 and 3 of radiation toxicity (RTOG/EORTC: Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer) and the onset of moist desquamation was prolonged with *N. sativa* gel. Also, the occurrence of moist desquamation was delayed with *N. sativa* gel compared to the placebo, where the mean score of the experienced pain in the placebo group was higher than that in *N. sativa* gel group at week 3. However, *N. sativa* gel showed no significant effect on the self-reported quali-

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ty of life (SRQOL) of participants at any week [142]. A clinical trial study conducted on breast cancer evaluated the effectiveness of *Nigella sativa* in RD. The observations demonstrated that *Nigella sativa* significantly decreased acute RD [142].

Several studies have shown different anti-inflammatory mechanisms for thymoquinone (TQ), an active component of *Nigella sativa*. The effect of TQ on NF-κB signaling pathway has been comprehensively studied, where results cover a range of possibilities. Such as, inhibition of LPS-induced NF-κB signaling by preventing the translocation of p65 to the nucleus, increasing the nuclear levels of NF-κB p50 homodimer, decreasing the nuclear levels of NF-κB p65:p50 heterodimer [143], and dose-dependent inhibition of angiotensin II-triggered NF-κB activation and IL-6 expression in human proximal tubular epithelial cells [144]. It is also reported that TQ may inhibit the expression of proinflammatory mediators such as IL-1β, TNFα, MCP-1, and COX2. Suppression of AGE (advanced glycation end products)-induced NF-κB activation and IL-6 expression and inhibition of LPS-induced TNFα generation in the rat basophil cell line (RBL-2H3) have also been indicated. In another study, TQ prevented LPS-induced activation of p38 mitogen-activated protein kinase (MAPK), ERK1/2, and NF-κB, which lead to suppression of IL-1β, TNFα, matrix metalloproteinase 13 (MMP-13), COX2, and prostaglandin E2. These studies show that TQ's anti-inflammatory effects are entangled with many signaling pathways, and a definite understanding of its action calls for more targeted studies. Another significant finding in this regard is establishing a connection between TQ and PPARγ signaling. Active PPARγ has been shown to suppress the expression of a wide variety of proinflammatory genes, and TQ may enhance the transcriptional activity of PPARγ [140].

Lianbai

The Lianbai liquid, a preparation contains Huang Lian (Rhizoma Coptidis) and Huang Bai (Cortex Phellodendri) [145], was evaluated in a clinical study for its effect on RD in patients with cancer. Results showed that Lianbai liquid effectively prevented radiation dermatitis and was influential in treating grade III acute radiation dermal injury. Lianbai liquid has anti-inflammatory and itching-relieving properties. In this study, 75 cases externally received Lianbai liquid since the first RT, 51 cases were only given advice, 54 cases with grade III acute radiation-induced dermal injury externally received Lianbai liquid, and finally, similar 38 cases (with grade III injury) treated by norfloxacin. The results demonstrate the effectiveness of Lianbai liquid in prevention of radiation dermatitis and treatment of grade III acute radiation dermal injury [145]. Coptidis rhizoma is the rhizome of some Coptis species (Ranunculaceae), which contains protoberberine-type alkaloids, such as berberine, palmatine, coptisine, epiberberine, jatrorrhizine and columamine, as the principle bioactive phytochemicals [146]. The bark of *Phellodendron amurense* Rupr (CPA) or *P. chinense* (Rutaceae), chemical markers include phellodendrine, palmatine, berberine, magnoflorine, obacunone, menisperine, and obaculac-

tone [147]. Cortex Phellodendri is a traditional medicine widely used for the treatment of different inflammation-related conditions. The effects of CPA were evaluated in an *in vivo* mice model of LPS-induced endotoxemia and LPS-stimulated macrophage RAW 264.7 cells. The results of *in-vivo* studies showed CPA significantly attenuated LPS-induced IL-6, IL-1β, and MCP-1 in serum. It also inhibited iNOS and activation of NF-κB. Furthermore, CPA diminished phosphorylation of mitogen-activated protein kinases (MAPKs), extracellular signal-regulated kinase (ERK) 1/2, and Jun N-terminal kinase (JNK). *In vitro* studies also confirm the anti-inflammatory effects of CPA through dose-related down-regulation of LPS-stimulated NO, iNOS, and proinflammatory cytokines expression [148]. It is assumed that berberine is the active compound of CPA, which manifests its anti-inflammatory properties by inhibiting the NF-κB pathway. The *in vivo* and *in vitro* studies of berberine had been comprehensively reviewed, showing it acts through many mechanisms such as reducing TNF-α, IL-6, and IL-1β cytokines and regulation of LPS-stimulated IL-10/IL-1β and Concanavalin A-stimulated IL-10/TNF-α [149].

Several other mechanisms are detailed through which berberine manifests its anti-inflammatory properties. For instance, it inhibits the expression of COX2 by the regulation of activator protein 1 (AP-1). Besides, berberine interferes with phosphorylation of Ik-Ba and following the production of TNF-α and IL-1β. In another study, Berberine improved myeloperoxidase activity, which is considered as a proinflammatory marker [150]. The study of *Takahara* et al., [151] also confirmed that berberine suppressed the production of TNF-α, IFN-γ, and IL-17 proinflammatory mediators. Moreover, berberine mechanism of action may involve antigen-presenting cells (APCs) including dendritic cells. The inhibition of NF-κB activity and consequent reduction of CD80 and CD86 on APCs results in proinflammatory cytokines such as IL-6, IL-12p40, and IL-23p19 in APCs. Berberine can increase apoptosis in dendritic cells and decrease their longevity, and eventually, it reduces antigen delivery performance [152].

Cucumis sativus L.

Cucumber (*Cucumis sativus*) is a member of the family Cucurbitaceae. It is widely used in traditional medicines. Cucumber fruit consists mostly of water and makes remarkable hydration. It is believed that its regular consumption or topical usage on skin helps in decreasing the skin aging process, boosting metabolism, and immunity improvement [153]. It exhibits various pharmacological effects like antioxidant, anti-carcinogenic, anti-hyaluronidase, anti-elastase, anti-inflammatory, anti-hyperglycemic, diuretic, amylolytic, antimicrobial, and analgesic effects. Cucumber has high amounts of polyphenols, steroids, terpenoids, glycosides, resins, flavonoids and tannins [154]. In addition, it contains antioxidants such as ß-carotene, α-carotene, vitamin C, vitamin A, zeaxanthin and lutein that these compounds have protective effects against both reactive oxygen species and reactive carbonyl species by free radical scavenging activity [155]. *Cucumis sativus* has been

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shown to inhibit phospholipase A2 and prostaglandin synthase activities [156]. Its aqueous extract has also been shown to decrease the production of IL-6 [157]. In a 2020 study, the protective effect of three herbal topical formulations containing *Centella asiatica*, *Cucumis sativus*, and *Thunbergia laurifolia* extracts, as well as a commercial cream was evaluated on the skin reaction in patients with breast cancer undergoing RT. The patients were instructed to use the creams once daily from their first RT session until 1-month after irradiation. The results showed that the use of the herbal creams or the commercial cream could not decrease the severity or delay the onset of dermatitis in comparison with the control group. Nevertheless, despite the limited benefits protection, the *Cucumis sativus* cream was indicated to be helpful in the skin recovery after irradiation [158].

Discussion

In this review, we tried to present a brief discussion of the clinical studies performed on natural products to treat RD. According to the studies discussed in this review, varieties of topical or oral dosage form preparations derived from natural compounds might be beneficial for RD. Among the studied natural products, *Aloe vera*, Calendula, *Hypericum perforatum*, and olive oil were respectively the most studied agents both in mono- and multi-component formulations. Although various preparations of *Aloe vera* including its gel or extract were the most studied agents, its effectiveness in the management of RD is not clearly known. *In vivo*, *Aloe vera* has been shown to improve wound healing, reduce inflammation and affect the platelets and leucocytes as well as inhibit vasoconstriction [20]. But, clinical evidence for the effects of *Aloe vera* is varied, and no complete conclusion about its effectiveness can yet be made. The lack of consistency of research results is likely due to the diversity in the type of the extracts and concentrations used in studies, and also small sample sizes in some trials. In some cases, such as breast cancer, it does not affect RD [20, 57, 61]. On the other hand, some studies conducted on patients with other varieties of cancers such as pelvic, head, and neck showed the protective effects of *Aloe vera* against RD [52, 58]. These conclusions are consistent with a review by Farrugia et al. (2019) who concluded that there is contradictory evidence for the use of *Aloe vera* in regards to its effectiveness in the prophylaxis and treatment of RD [53].

Remarkably, greater effects were reported in the studies when multi-component products were used. Multi-component preparations containing *Aloe vera* have shown good efficacy. It seems that combined formulations such as RDC, and the Dead Sea cream, containing several natural products including *Aloe vera*, *Calendula, Hypericum perforatum*, olive oil, emu oil, etc., might have the potential to prevent or treat radiation-induced skin damages [159]. Nevertheless, large sample size studies are needed for a definitive conclusion. Also from another aspect, with complex of several natural products, there might be interactions with inflammatory responses that may contribute to damage skin tissue [160]; this probable alteration should also be considered in these studies.

Herbal products including *Boswellia*, *Nigella sativa*, *Lawsonia inermis*, and *Silybum marianum* were all shown to be effective in delaying RD development and progression, the occurrence of moist desquamation and less pain and erythema. Topical products containing these herbal preparations are worth further study in this area, according to their known anti-inflammatory activities. Inflammation is one of the most acute side effects of radiotherapy [161, 162]. More, it is worth mentioning that there should be more focus on ionization characteristics in these types of studies. Because, skin reaction to ionizing radiation is a complex issue, which may vary depending on the characteristics of the radiation, patient, and treatment-related factors. It seems that this process is very intricate, and it may be concerned with the dose of radiation on the radiated area. When the cumulative dose is in more than 20 Gy, the basal layer cells are destroyed; consequently, the functions of sweat and sebaceous glands are declined, which leads to dry skin desquamation [163]. The doses of 45 to 60 Gy might result in dermis damage as well as moist desquamation. Also, the age of the patient and size of the field radiated affect the development of RD.

Although topical treatments remain a key area of RD prevention or treatment, among the products studied, there are two oral products including *Punica granatum* (pomegranate) extract [108] and curcumin; pomegranate extract was shown to be effective in reducing skin toxicity caused by RT. While, curcumin was shown with no complete prevention of skin damage, and it only caused to reduced moist desquamation as well as improvement of quality of life during RT. Nevertheless, the bioavailability of these agents in various formulations should always be considered when it comes to oral administration. Some of curcumin formulations with higher bioavailability might be potentially more effective [164]. So, more studies are needed to conclude about these two oral products.

It is also of importance that study on herbal products should be carried on using standardized extracts due to variation in quality and potency. This might be potentially one of the factors affecting the inconsistent results on *Aloe vera*. Recognizing optimum doses and duration of intervention would also be essential in future trials. An investigation of therapeutic effects in diverse populations based on gender, age, RD staging, and comorbid complications would be helpful to recognize patients most likely to benefit from an herbal product. Also, the efficacy and safety of multi-component herbal formulations may also be considered. This could enhance therapeutic effect due to more mechanisms by combination products.

From a mechanistic view, the cutaneous hydration and the anti-inflammatory effects of natural products could be useful in RD, such as *Nigella sativa*, *Lawsonia inermis*, *Silybum marianum*, *Boswellia*, *Calendula*, *adlay bran*, and *Hypericum perforatum*. Also, immunomodulatory, antioxidant, and wound healing activities of natural products could be considered in alleviating RD (Figure 1).

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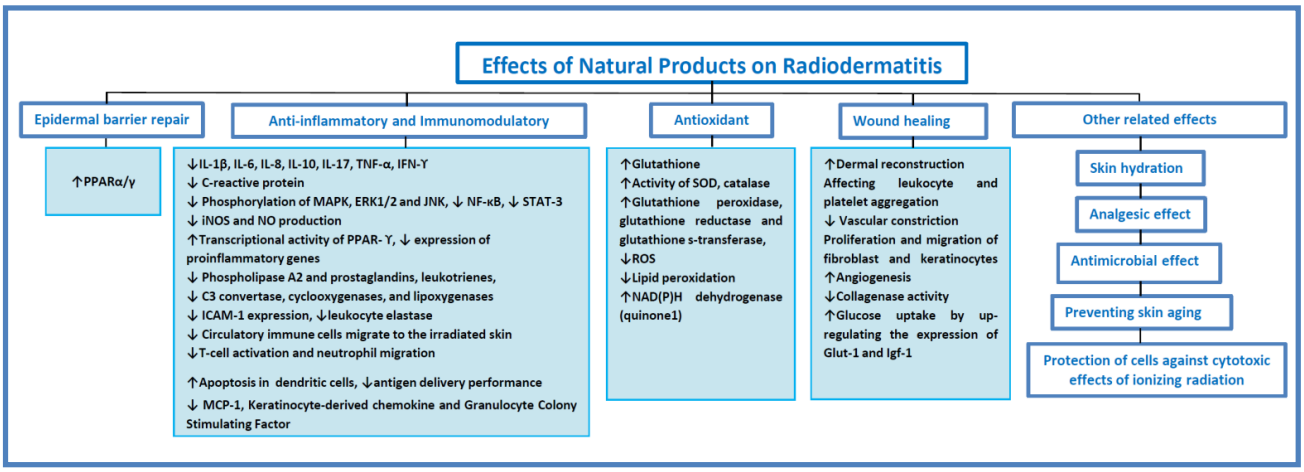
Figure 1. Some molecular mechanisms related to natural products' effects in radiodermatitis



Conclusion

Results from this review shows that there might be some promising natural product options for the prevention and treatment of RD via their multifactorial bioactivities. However, various limitations impede the strength of the conclusion. Among reviewed studies, we could not recognize a specific treatment, as the strongest evidence for the prevention or treatment of RD in patients undergoing RT. Findings on the therapeutic effects of *Aloe vera* are controversial. Preliminary outcomes from studies suggests that *Silybum marianum*, *Boswellia*, *Nigella sativa*, olive oil, Lianbai, and *Hypericum perforatum* as well as some multi-ingredient products may be effective prophylactic treatments for RD. Promising findings were recognized from both topical preparation and an oral dosage form of pomegranate extract. However, further research on the effect of natural/herbal products for RD is needed before any definitive conclusions. It is essential to note that full taxonomic validity of the natural materials, a larger sample size of the study, optimum doses and duration of intervention, and investigation of treatment effects in diverse populations and comorbid complications would also be crucial in future studies.

Conflict of Interest

The authors declare that there is no conflict of interest.

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