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Aloe vera for prevention of radiation-induced dermatitis: A systematic review and cumulative analysis of randomized controlled trials

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Background: Aloe vera were frequently reported to reduce the risk of radiation-induced dermatitis (RID), but the quantitative results from all the relevant studies were not presently available. This study sought to conduct a cumulative analysis to better clarify the preventive effects of aloe vera in RID.

Methods: MEDLINE (PubMed), Cochrane, EMBASE, PsychINFO, Web of Science, China National Knowledge Infrastructure (CNKI), and Wan Fang Database were utilized for identifying the eligible randomized controlled trials (RCTs) without language restrictions, up to March 2022. The pooled incidence of RID was conducted by the Relative risk (RR) with its 95% confidence interval (CI) through the STATA software under a random-effects model. This systematic review and cumulative analysis were registered on PROSPERO (ID: CRD42022335188).

Results: Fourteen RCTs met our predefined inclusion criteria, enrolling 1,572 participants (mean age: 46.5−56 years). The cumulative results revealed that patients pretreated with aloe vera were associated with a significantly lower risk of RID compared to those without aloe vera usage (RR = 0.76, 95% CI: 0.67−0.88, $p < 0.001$; heterogeneity: $I^2 = 79.8\%$, $p < 0.001$). In the subgroup analysis, the pooled incidence of Grade 2−4, Grade 2, and Grade 3 RID was also dramatically lower in the group of aloe vera as compared to the placebo group [RR = 0.44 (0.27, 0.74), 0.58 (0.36, 0.94), and 0.27 (0.12,

0.59) in Grade 2–4, Grade 2, and Grade 3, respectively]. However, in regard to Grade 4 RID, the combined RR indicated that the incidence of RID was comparable between aloe vera and the control group (RR = 0.13, 95% CI: 0.02–1.01, p = 0.051; heterogeneity: I^2 = 0.0%, p = 0.741). The sensitivity analyses showed that there was no substantial change in the new pooled RR after eliminating anyone of the included study.

Conclusion: The current cumulative analysis revealed that patients pretreated with aloe vera were less likely to suffer from RID than the controls without using aloe vera. Based on this finding, the prophylactic application of aloe vera might significantly reduce the incidence of RID, especially in Grade 2 and Grade 3 RID. Further large-sample multicenter RCTs are still warranted to confirm these findings and for better clinical application.

Introduction

Cutaneous disease is a global public health concern and brings immense health and economic burden on society because of its increasing prevalence. Since the worldwide population are rapidly ageing, the prevalence and the profile of skin diseases are growing, leading it to becoming a public health problem entailing an enormous socio-economic burden (Yew et al., 2022). Of the cutaneous manifestations of the disease, dermatitis has attracted great attention because of its global prevalence, and can be caused by endogenous and exogenous, including atopic dermatitis (AD), radiation dermatitis, contact dermatitis, and allergic contact dermatitis (Woo et al., 2019). It is difficult to determine the aetiological factors due to the similar skin changes of radiation dermatitis, atopic dermatitis, irritant dermatitis, and allergic contact dermatitis.

Approximately 50% of diagnosed cancer patients will receive radiotherapy alone or in combination with surgery or chemotherapy (Zhang et al., 2022). Radiation dermatitis is a common side effect of radiotherapy, affecting up to 95% of patients receiving radiation for cancer (Liao et al., 2019). As is well known, radiotherapy, a widely employed treatment for various cancers, inevitably involves exposing the skin to ionizing radiation. When the skin receives a relatively high dose of radiation, the epithelial cells of the skin can undergo a series of changes, which can lead to skin damage such as erythema dry or moist desquamation, and even ulceration or necrosis (Chitapanarux et al., 2019). Ionizing radiation contributes to DNA double-strand breaks by producing free radicals, and then causes acute inflammatory reactions in the skin (Kasmann et al., 2020; Tang et al., 2021). Additionally, progressive stenosis of the vasculature can be induced by radiation, leading to local ischemia and hypoxia, which exacerbates skin damage (Liao et al., 2019; Wang et al., 2021). The above studies indicate that the combined action of multiple factors results in the occurrence of radiation dermatitis. Although various treatments have been proposed to control dermatitis-associated symptoms of certain patients, including antihistamines and topical corticosteroids for atopic dermatitis, and steroidal, non-steroidal, and topical preparations and dressings for radiation dermatitis, several side effects remain, such as osteopenia and cataracts (Fallah et al., 2018; Choi et al., 2020; Umehara et al., 2020). In general, topical formulations, showing minimum side effects, are generally preferred. A previous study has demonstrated that the anionic polar phospholipid (APP) skin cream, a novel oil-in-water emulsion, has a preventive effect against radiation dermatitis (Merchant et al., 2007). Recently, mounting studies have shown that aloe vera can be used to treat dermatitis, including atopic dermatitis or radiation dermatitis (Richardson et al., 2005; Finberg et al., 2015).

Aloe vera (L.) Burm.f. (Aloe vera), a traditional Chinese medicine cataloged in the Pharmacopoeia of the People's Republic of China, had been widely used traditionally for the treatment of constipation, wound healing, anorexia, and dyspepsia (Shi et al., 2021). Aloe vera contains aloin, emodin, polysaccharides, vitamins (A, C, E), amino acids, and other biologically active constituents, and is proven to have anti-inflammatory, anti-oxidant, immune modulation, and anti-tumorigenic effects (Ali and Wahbi, 2017). Merchant et al. (2007) reported that the APP skin cream common toxicity criteria (CTC) score, an acute radiation morbidity scoring criteria, was no larger than the aloe vera CTC score in all patients during radiation therapy. Furthermore, in 9 patients (20%), the aloe vera CTC score was larger than the APP skin cream CTC score, which suggested aloe vera was a safe and useful medicine for treating radiation therapy (Merchant et al., 2007). In contrast to this result, Ahmadloo et al. (2017) demonstrated that aloe vera had no association with the prevalence or severity of dermatitis.

Although the association between aloe vera and radiation dermatitis had been extensively studied, the effects of aloe vera in the prevention or treatment of radiation dermatitis were conflicting. Therefore the systematic review and cumulative analysis aim to provide a better understanding of the effectiveness and safety of aloe vera in the prevention or treatment of radiation dermatitis and to provide objective meaningful information to guide clinicians in clinical practice.

Materials and methods

This systematic review and cumulative analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Supplementary Table S1). The detailed methods and information about this review could be found in the PROSPERO (ID: CRD42022335188, http://www.crd.york.ac.uk/PROSPERO).

Data sources and searches

MEDLINE (PubMed), EMBASE (OVID), Cochrane Library databases, PsychINFO, Web of Science, China National Knowledge Infrastructure (CNKI), and Chinese Wan Fang Database were systematically searched for the relevant studies up to March 2022. The searching strategy was restricted to human subjects, while there were no language restrictions for the published articles. The searching keywords in PubMed database for English language was: {["Aloe" (Mesh)] OR (Aloe vera)} AND {["Dermatitis" (Mesh)] OR (Dermatitides)}.

Assessment of radiation-induced dermatitis

The occurrence and severity of RID were diagnosed were graded using the Radiation Therapy Oncology Group (RTOG) standard, at the end of radiation therapy. According to the RTOG, the severity of RID would be 0 to 4 categories: grade 0, grade 1, grade 2, grade 3, and grade 4. High grade indicated greater severity of RID. Other assessments were also considered to be eligible, e.g., RID could be judged by a health care provider, as reported in the included studies.

Inclusion criteria

The inclusion criteria for this study were listed as followed. 1) The study design should be conducted according to the patient, intervention, comparison, outcome, and study design (PICOS); The question guiding for this cumulative analysis was: Does aloe vera decrease the risk of RID? The compositions for the PICOS evidence were: cancer patients under radiation therapy (P); the usage of aloe vera (I); compared to those without aloe vera (C); the diagnosis of RID (O); any study designs (S). Furthermore, any trials presented with the relative risk (RR) and its 95% confidence intervals (CI) were also considered to be eligible.

Exclusion criteria

In this study, we only included studies that reported human subjects, thus the *in vitro* and *in vivo* studies were excluded. Studies that failed to provide the data from the control participants were also excluded. Moreover, those publications belonging to review, comment, letter, and case reports could be also eliminated.

Data extraction

The relevant information was independently extracted by two authors through a standardized data collection form. These data included the first authors' names, country or region of the study, study design, the publication year, gender, types of cancer radiotherapy, dose of radiation (Gy), study period, the demographic and mean age of the participants with both groups, type of aloe vera, and assessment of RID.

Risk of bias in the included studies

The risk of bias among the included studies was judged by Cochrane's risk of the bias assessment tool. Based on the guideline of the Cochrane collaboration, the quality of the eligible studies was evaluated by the study design, methodology, and analysis. According to the different items, the included study could be assessed by a three-point scale: yes (low risk of bias), no (high risk of bias), and unclear (without specific statement).

Statistical analyses

The cumulative RR with the corresponding 95% CI was applied to evaluate the strength of the association between aloe vera treatment and the risk of RID. Results derived from the combined RR with a two-tail p value < 0.05 were presumed as statistically significant. The I^2 statistic analysis was performed to identify the heterogeneity of a combined analysis. $I^2 > 50\%$ was considered to be substantial heterogeneity, while p-value of the Q test < 0.10 was assessed to be statistically significant. Since the presence of the different study designs as well as the study sample, a random effect model was applied when combining

FIGURE 1
Flow chart of study selection. 201 studies were firstly identified and fourteen eligible studies were finally included after screening.
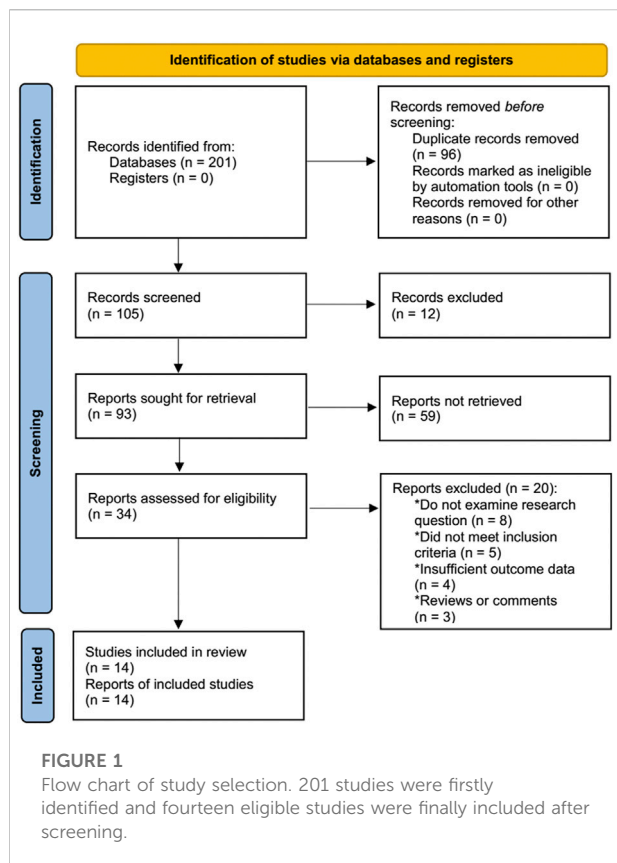
the RR. To detect the origin of the substantial heterogeneity, a sensitivity analysis was performed. Both Begg's rank correlation test and Egger's regression asymmetry test were used to assess the publication bias. In this cumulative analysis, the statistical analyses were performed with both the STATA (version 13.0, Stata Corp LP, College Station, Texas, United States) and the RevMan review management software (version 5.4).

Results

Literature search

During the initial searching, 201 studies were detected. Among them, 91 publications were derived from PubMed and 37 publications were from the CNKI, while the remainder of 73 studies were detected from the EMBASE, Cochrane Library databases, PsychINFO, Web of Science, and Wan Fang Database. Based on a review of the titles and abstracts, 167 publications were eliminated due to duplicate and ineligible issues, leaving 34 potential studies for further full-text evaluation. Of which, 20 studies were eliminated for reasons, e.g., eight studies did not comply with the research question, five studies for failing to meet the inclusion criteria, four studies for insufficient outcome

data, and three studies being to as a review or comment article. Finally, a total of fourteen studies (Williams et al., 1996; Deng and Feng, 2006; Liu et al., 2006; Yao et al., 2006; Liu, 2007; Hong et al., 2009; Wu and Dong, 2009; Haddad et al., 2013; Hoopfer et al., 2015; Wu et al., 2015; Ahmadloo et al., 2017; Zhong et al., 2017; Wang et al., 2018; Zhao et al., 2018) were considered to be eligible for further systematic review and quantitative analysis. The selection process of the fourteen publications was shown in Figure 1.

Study characteristic

The descriptive characteristics of the fourteen eligible studies were summarized in Table 1. These included studies were all randomized control designed, and published between 1996 and 2018. Among the fourteen studies, one study was conducted in the United States, one in Saudi Arabia, two in Iran, and the reminder nine studies originated from China. A total of 1,572 participants (mean age: 46.5–56 years) were enrolled. The number of the aloe vera group and the control group was comparable (792 vs. 780). All these included studies provided the data on the total incidence of RID in both the study and the control group, while eight studies also provided the number of RID in each grade of dermatitis (Grade 0–4, Table 2). The types of cancer radiotherapy included nasopharyngeal carcinoma, breast cancer, and many other malignancies. In this study, both male and female participants were included. The study period ranged from 2 to 10 weeks. The single dose of radiation ranged from 40–74 Gy, and the total radiation quantity ranged from 2,000–7,000 Gy. The sample size in each included study ranged from 48 to 300 participants. The type of aloe vera included fresh, gel, cream, and lotion aloe. The assessment of dermatitis was mainly following the Radiation Therapy Oncology Group standard (RTOG), but the RID evaluation in one study was judged by a health care provider.

Risk of bias assessment

Among the fourteen included studies, only Ahmadloo et al. (2017)'s study was judged as low risk of bias, and the remaining thirteen studies were evaluated to present with a high risk of bias (Figure 2).

Synthesis of results

As shown in Figure 3, the cumulative RR from twelve included studies indicated that patients with radiotherapy pretreated with aloe vera were associated with a significantly lower risk of RID compared

TABLE 1 Characteristics of the fourteen included studies.

Study	Study design	Gender	Study period	Types of cancer radiotherapy	Dose of Gy	Study group case/total (grade 1–4 dermatitis)	Placebo group case/total (grade 1–4 dermatitis)	Mean age (years)	Type of aloe vera	Assessment of dermatitis
Williams (18) 1996 United States	RCT-double-blinded	Female	NA	Breast cancer	45–60	88/97	94/97	NA	Gel	Judged by health care provider
Deng (19) 2006 China	RCT	Both sexes	NA	Nasopharyngeal carcinoma	60–72	4/35	10/32	S: 48.5 C: 47	Fresh aloe vera	Radiation therapy oncology group standard
Liu (20) 2006 China	RCT	Both sexes	NA	Various types of cancers	NA	25/40	36/40	NA	Fresh aloe vera	Radiation therapy oncology group standard
Yao (21) 2006 China	RCT	Both sexes	NA	Various types of cancers	Total dose: 3,000–7,000	20/34	31/35	S: 56 C: 53	Fresh aloe vera	Radiation therapy oncology group standard
Liu (22) 2007 China	RCT	Both sexes	NA	Various types of cancers	Total dose: 2000–7,000	2/30	20/30	30–78	Gel	Radiation therapy oncology group standard
Hong (23) 2009 China	RCT	Both sexes	NA	Nasopharyngeal carcinoma	7,000	50/50	50/50	S: 48 C: 49	Fresh aloe vera	Radiation therapy oncology group standard
Wu (24) 2009 China	RCT	Both sexes	2 weeks	Nasopharyngeal carcinoma and breast cancer	Nasopharyngeal carcinoma: 70; Breast cancer: 50	24/24	24/24	NA	Gel	Radiation therapy oncology group standard
Haddad (25) 2013 Iran	RCT	Both sexes	5 weeks	Various types of cancers	40–70	46/53	50/53	52 (21–78)	Lotion	Radiation therapy oncology group standard
Hoopfer (26) 2015 Saudi Arabia	RCT	Females	4 weeks	Breast cancer	45–50	7/81	5/77	NA	Aloe vera cream	Radiation therapy oncology group standard
Wu (27) 2015 China	RCT	Both sexes	7–10 days	Various types of cancers	NA	15/60	35/60	NA	Fresh aloe vera	Radiation therapy oncology group standard
Ahmadloo (28) 2017 Iran	RCT	Females	5 weeks	Breast cancer	50	45/50	47/50	S: 48.5 C: 47	Gel	Radiation therapy oncology group standard
Zhong (29) 2017 China	RCT	Both sexes	2–3 weeks	Nasopharyngeal carcinoma	50–74	52/153	97/147	S: 49.4 C: 46.5	Fresh aloe vera	Radiation therapy oncology group standard
Wang (30) 2018 China	RCT	Females	5–6 weeks	Breast cancer	50–60	33/36	34/36	52	Fresh aloe vera	Radiation therapy oncology group standard
Zhao (31) 2018 China	RCT	Both sexes	6–7 weeks	Nasopharyngeal carcinoma	50–60	29/49	39/49	S: 51 C: 49.5	Gel	Radiation therapy oncology group standard

Note: Study group = patients under radiotherapy pretreated with aloe vera ($n = 792$), Control group = placebo group, patients under radiotherapy receiving conventional treatments ($n = 780$), the incidence rate of Grade 1–4 dermatitis in the study group and the control group was 56% (440/792) vs. 73% (572/780), NA, not available.

TABLE 2 The incidence of grade 2–4, grade 2, grade 3, and grade 4 radiation-induced dermatitis in both the aloe vera group and the control group.

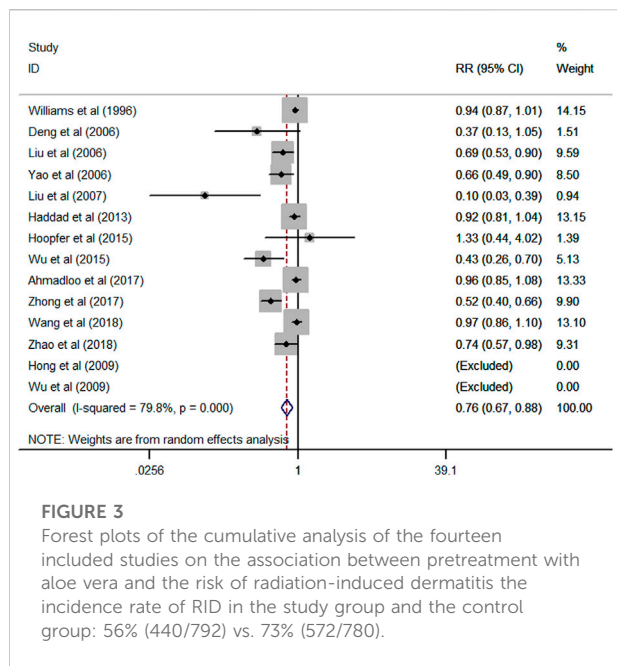| Study	Radiation induced dermatitis					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 2–4
Williams (18) 1996	S: 0/97	S: 0/97	S: 4/97	S: 0/97	S: 0/97	S: 4/97
	C: 0/97	C: 0/97	C: 5/97	C: 5/97	C: 0/97	C: 10/97
Deng (19) 2006	S: 15/35	S: 16/35	S: 7/35	S: 2/35	S: 0/35	S: 9/35
	C: 4/32	C: 11/32	C: 14/32	C: 9/32	C: 2/32	C: 25/32
Hong (23) 2009	S: 0/50	S: 50/50	S: 0/50	S: 0/50	S: 0/50	S: 0/50
	C: 0/50	C: 42/50	C: 5/50	C: 3/50	C: 0/50	C: 8/50
Wu (24) 2009	S: 0/24	S: 21/24	S: 3/24	S: 0/24	S: 0/24	S: 3/24
	C: 0/24	C: 10/24	C: 14/24	C: 0/24	C: 0/24	C: 14/24
Wu (27) 2015	S: 45/60	S: 10/60	S: 5/60	S: 0/60	S: 0/60	S: 5/60
	C: 25/60	C: 10/60	C: 15/60	C: 5/60	C: 5/60	C: 25/60
Ahmadloo (28) 2017	S: 5/50	S: 31/50	S: 12/50	S: 2/50	S: 0/50	S: 14/50
	C: 3/50	C: 36/50	C: 6/50	C: 5/50	C: 0/50	C: 11/50
Wang (30) 2018	S: 3/36	S: 16/36	S: 15/36	S: 2/36	S: 0/36	S: 17/36
	C: 2/36	C: 14/36	C: 17/36	C: 3/36	C: 0/36	C: 20/36
Zhao (31) 2018	S: 20/49	S: 18/49	S: 11/49	S: 0/49	S: 0/49	S: 11/49
	C: 10/49	C: 17/49	C: 21/49	C: 1/49	C: 0/49	C: 22/49
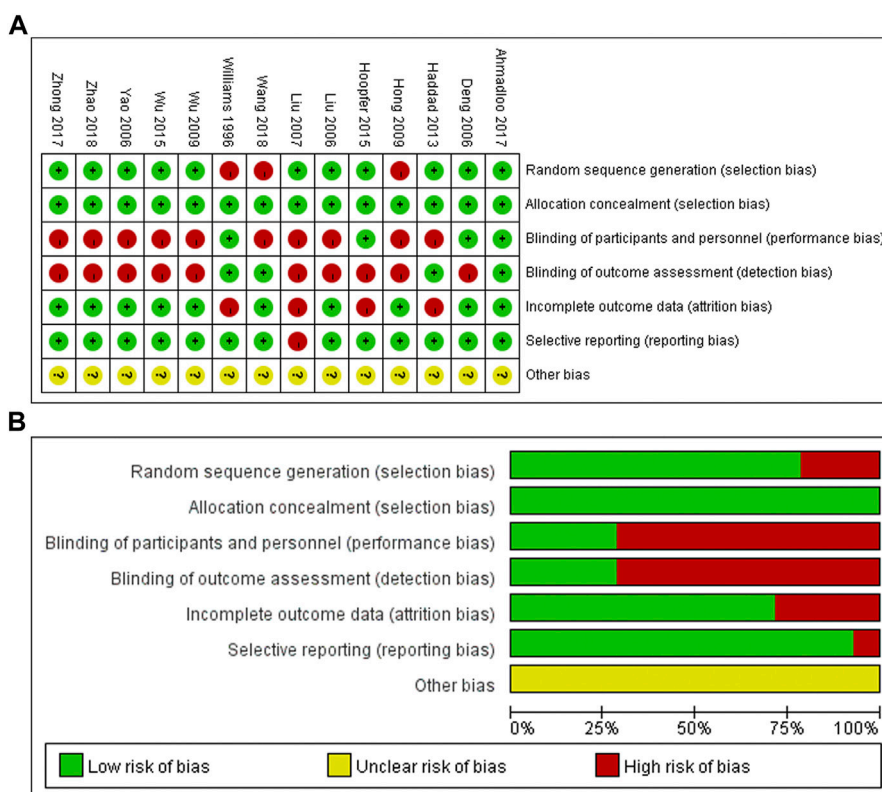
FIGURE 2
Risk of bias among the fourteen included studies (A,B). The results turned out that most of the included studies (13/14, 93%) were with high risk of bias.
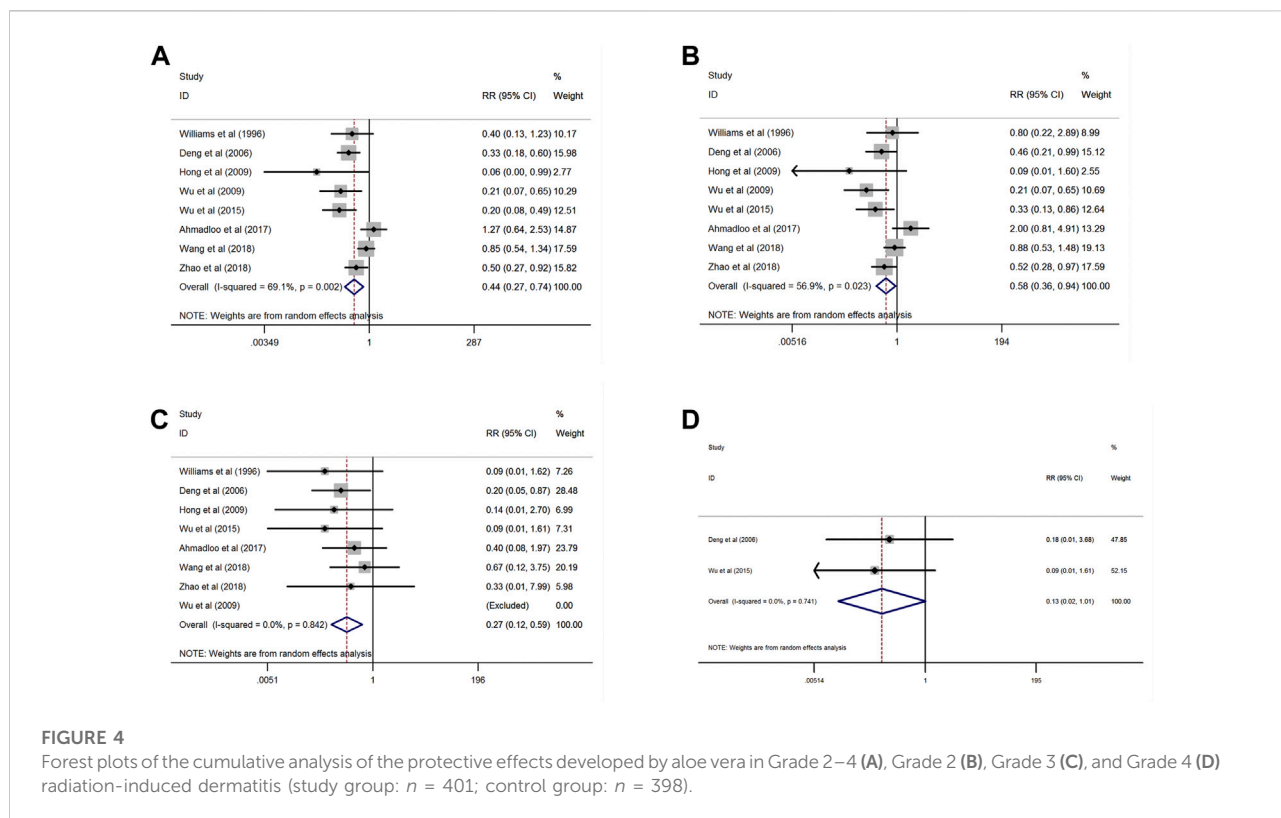
FIGURE 3

Forest plots of the cumulative analysis of the fourteen included studies on the association between pretreatment with aloe vera and the risk of radiation-induced dermatitis the incidence rate of RID in the study group and the control group: 56% (440/792) vs. 73% (572/780).

the control group, resulting in these two studies could not be included in the statistical analyses with the STATA (displayed with "Excluded" in Figure 3).

In the subgroup analysis, as presented in Figure 4A, the pooled incidence of Grade 2–4 RID was also dramatically lower in the group of aloe vera as compared to the placebo group (RR = 0.44, 95% CI: 0.27–0.74, p = 0.002; heterogeneity: I^2 = 69.1%, p = 0.002). When separated by each Grade of RID, the cumulative RR derived from eight included studies consistently suggested that pretreatment with aloe vera might significantly reduce the incidence of Grade 2 RID compared to the controls (RR = 0.58, 95% CI: 0.36–0.94, p = 0.026; heterogeneity: I^2 = 56.9%, p = 0.023, Figure 4B). In line with this finding, aloe vera usage also associated with a lower incidence of Grade 3 RID than the control group (RR = 0.27, 95%CI: 0.12–0.59, p = 0.001; heterogeneity: I^2 = 0.0%, p = 0.842, Figure 4C).

However, as displayed in Figure 3D, when restricted to Grade 4 RID, the quantitative synthesis of the results from two included studies revealed that the incidence of RID was comparable

FIGURE 4

Forest plots of the cumulative analysis of the protective effects developed by aloe vera in Grade 2−4 **(A)**, Grade 2 **(B)**, Grade 3 **(C)**, and Grade 4 **(D)** radiation-induced dermatitis (study group: n = 401; control group: n = 398).

to the control group (those without aloe vera usage) (overall RID incidence: RR = 0.76, 95% CI: 0.67–0.88, p < 0.001; heterogeneity: I^2 = 79.8%, p < 0.001). Of note, Hong et al. and Wu et al. (2015)'s study showed the incidence of RID was 100% in both the study and

between aloe vera and the control group (RR = 0.13, 95%CI: 0.02–1.01, p = 0.051; heterogeneity: I^2 = 0.0%, p = 0.741, Figure 4D). This result indicated aloe vera exerted no protective effect against Grade 4 RID.

TABLE 3 Sensitivity analyses after each study was excluded by turns.

Study omitted	RR (95% CI) for remainders	Heterogeneity (%)	
		I^2 (%)	P
Williams et al. (1996)	0.72 (0.61, 0.86)	80.4	<0.001
Deng and Feng (2006)	0.77 (0.68, 0.89)	80.6	<0.001
Liu et al. (2006)	0.77 (0.67, 0.89)	80.3	<0.001
Yao et al. (2006)	0.77 (0.67, 0.89)	80.3	<0.001
Liu (2007)	0.79 (0.69, 0.86)	77.5	<0.001
Haddad et al. (2013)	0.73 (0.62, 0.86)	81.5	<0.001
Hoopfer et al. (2015)	0.76 (0.66, 0.87)	81.4	<0.001
Wu et al. (2015)	0.79 (0.70, 0.91)	78.1	<0.001
Ahmadloo et al. (2017)	0.73 (0.62, 0.86)	80.9	<0.001
Zhong et al. (2017)	0.82 (0.72, 0.92)	71.6	<0.001
Wang et al. (2018)	0.73 (0.62, 0.85)	80.8	<0.001
Zhao et al. (2018)	0.76 (0.66, 0.88)	81.0	<0.001

Abbreviation: RR, relative risk; CI, confidence interval.

The above results indicated that patients pre-treated with aloe vera were associated with a significantly lower incidence of RID, including the overall incidence, Grade 2–4, Grade 2, and Grade 3 RID. Therein, the incidence of Grade 3 RID was the lowest under aloe vera treatment, decreasing the risk of RID by over 70%.

Sensitivity analysis

To evaluate the effect of the single study on the combined quantitative synthesis of RR and the heterogeneity, a sensitivity analysis was properly conducted. As shown in Table 3; Figure 5, after removing anyone of the twelve eligible studies, no substantial difference was detected in the new cumulative RR [ranging from 0.73 (95%CI: 0.62–0.86) to 0.82 (95% CI: 0.72–0.92)]. Regarding the heterogeneity assessment, no remarkable change was observed in the newly generated heterogeneity after omitting any of the included studies (I^2 ranged from 71.6% to 81.5%, all $p < 0.001$). The above results revealed that no single study could dominate the combined RR and the heterogeneity.

Publication bias

The Begg's rank correlation test suggested that there was no significant publication bias underlying this pooled analysis (Begg's, $p > |z| = 0.064$) (Figure 6A). However, the Egger's linear test showed a significant publication bias (Egger's, $p > |t| = 0.005$, 95% CI: −4.17 to −0.96) (Figure 6B).
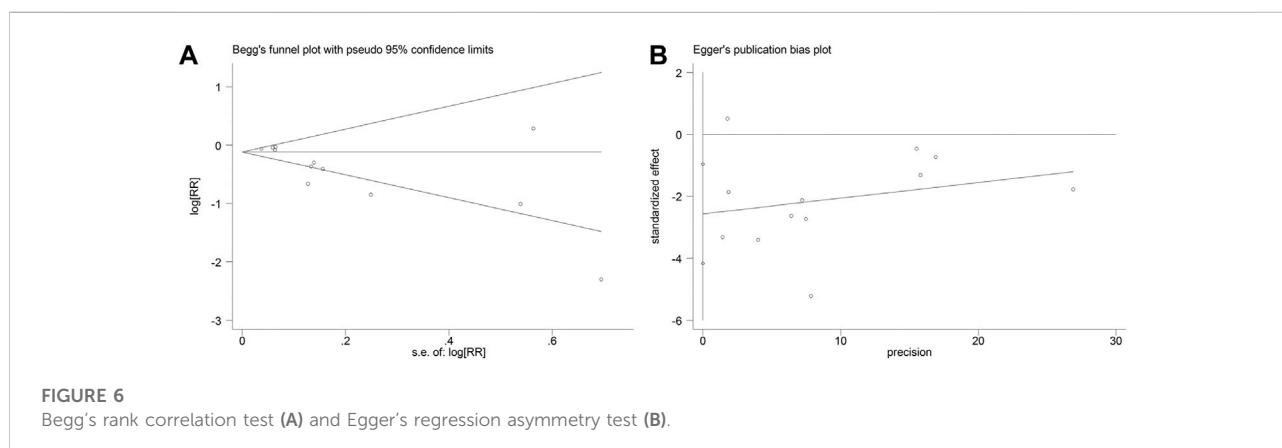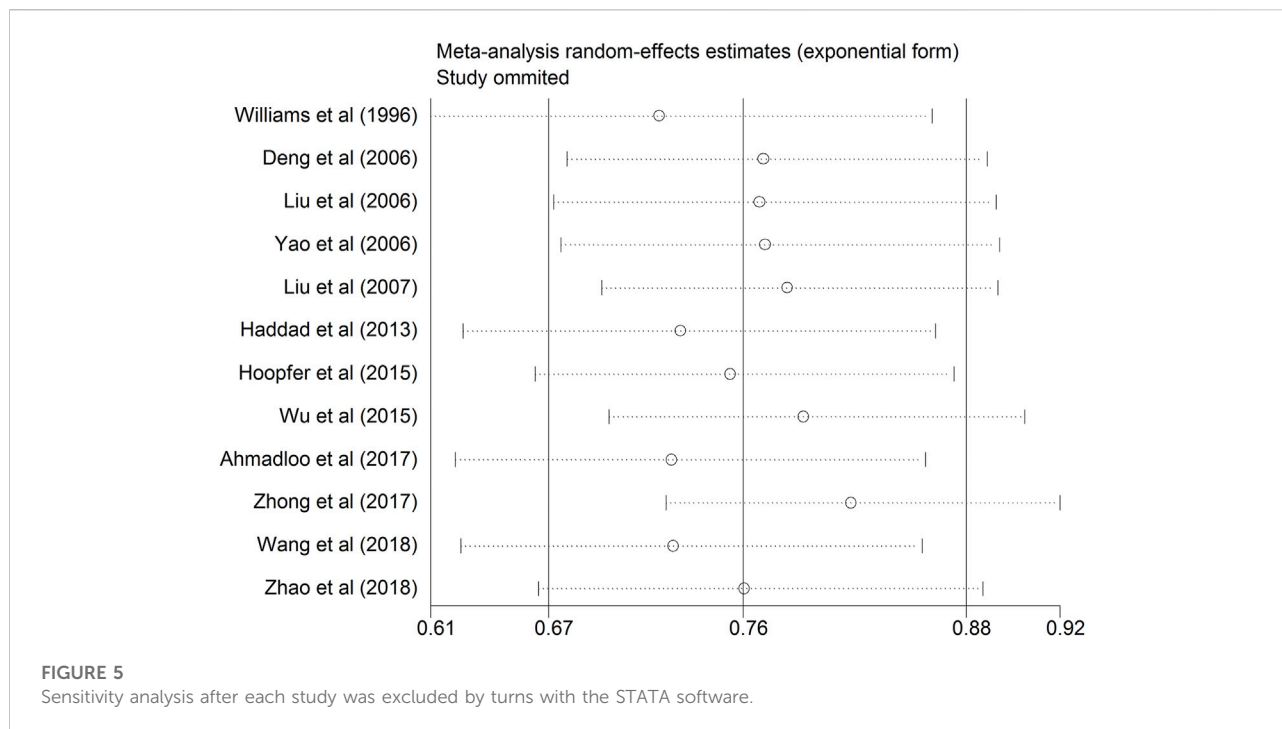
Discussion

Acute dermatitis is a common adverse effect after radiation therapy, affecting over 90% of the patients. The severity of RID varied from erythema to ulcer and necrosis. There are currently numerous methods to prevent, reduce, and treat radiotherapy skin toxicities based on the experiences of the clinicians. Mounting evidence suggests that the traditional medicinal herbs and their extractives have an excellent effect on anti-RID, such as Jaungo, Plantago lanceolate folium, Heijiangdan Ointment, and aloe vera (Skalska-Kaminska et al., 2014; Kong et al., 2016; Yang et al., 2016). Aloe vera, an ancient traditional herbal, exhibits a remarkable anti-inflammatory effect in injury diseases. The first clinical study of aloe vera in the treatment of radiation dermatitis was first reported in 1935 (Williams et al., 1996). Since then, multiple studies have reported the effects of aloe vera in the prevention or treatment of radiation dermatitis. To better assess this role by undertaking a scientific analysis, we conducted a cumulative analysis to evaluate the effect of aloe vera in the prevention or treatment of radiation dermatitis. Fourteen RCTs were finally included for a pooled analysis, enrolling 1,572 participants (mean age: 46.5–56 years). According to the combined RR, patients pretreated with aloe vera substantially reduced the risk of Grade 1–4 RID by as much as 24% (RR = 0.76, 95% CI: 0.67–0.88, $p < 0.001$). In line with this finding, pretreatment with aloe vera was also associated with a significantly lower risk of Grade 2–4 RID when compared to the controls (RR = 0.44, 95% CI: 0.27–0.74, $p = 0.002$). In regard to each grade of RID, aloe vera could reduce the risk of Grade 2 by 42% (RR = 0.58, 95% CI: 0.36–0.94, $p = 0.026$) and Grade 3 by 73% (RR = 0.27, 95% CI: 0.12–0.59, $p = 0.001$). Subsequent sensitivity analyses revealed that no single study could dominate the overall combined RR. Therefore, the present evidence was robust.

As reported, aloe vera is found to contain over 70 potentially active constituents, e.g., vitamins, enzymes, salicylic acids, and amino acids (Surjushe et al., 2008). In 1995, the RTOG institutes showed that aloe vera could be applied as one of the prophylactic treatments for RID (Haddad et al., 2013). Although aloe vera had been already demonstrated to be preventive against radiation dermatitis in the present meta-analysis and some other studies, the specific mechanism for this effect had not been well understood. The pathogenesis of aloe vera is multifactorial, including anti-oxidant activity, anti-inflammatory effects, and the inhibition of vasoconstriction.

It was known that ionizing radiation is the direct cause of radiation dermatitis. DNA damage is considered to be the direct consequence of high dose ionizing radiation. Ionizing radiation had been shown to induce DNA damage and cell death (Ghosh and Ghosh, 2021). Meanwhile, ionizing radiation can amplify this effect by promoting the production of reactive oxygen species (ROS) and nitric oxide (NO) (Wilson et al., 2019; Kma and Baruah, 2022). It was reported that irradiated cells produced several enzymes by releasing inflammatory cytokines and growth factors such as NADPH oxidase, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthesize (iNOS), which

FIGURE 5
Sensitivity analysis after each study was excluded by turns with the STATA software.

FIGURE 6
Begg's rank correlation test **(A)** and Egger's regression asymmetry test **(B)**.

stimulated ROS and NO production (Abbaszadeh et al., 2017; Mortezaee et al., 2019; Chen et al., 2020). In addition, superoxide anions induced by the electron transfer chains of mitochondria enhanced intracellular oxidative stress (Brand, 2016). Also, free radicals, the intracellular signals, significantly potentiate the inflammatory response (Ramos-Tovar and Muriel, 2020). Importantly, oxidative stress and inflammation play important roles in radiation dermatitis (Yang et al., 2016; Sheng et al., 2019). Popanda et al. (2003) reported that several DNA damages were observed and DNA repair capacity was severely reduced in patients with radiation dermatitis. Another study showed that 18β-glycyrrhetinic acid significantly ameliorated radiation-induced skin damage by inhibiting NADPH oxidase activity and ROS production, consequently suppressing pro-

inflammatory cytokine production (Su et al., 2018). Previous studies demonstrated that aloe vera had anti-inflammatory and anti-oxidative effects on various diseases such as peptic ulcers, colitis, and skin wounds (Akaberi et al., 2016; Hong et al., 2018). The results are in line with those of other studies. Goyal and Gehlot (2009) reported that aloe vera promoted the activities of both superoxide dismutase (SOD) and catalase, which could be beneficial to promoting free radical scavenging capacity, and consequently reduced the intensity of radiation dermatitis. Furthermore, aloe vera was effective in scavenging ROS and protecting DNA (Goyal and Gehlot, 2009). Haddad et al. (2013) demonstrated that the prophylactic use of aloe vera significantly reduced the intensity of radiation dermatitis. Similarly, Rao et al. (2017) also reported that the application of aloe vera decreased

the incidence of Grade 1, 2, and 3 radiation dermatitis in head and neck cancer. Based on above evidence, aloe vera may mitigate the grade of radiation dermatitis by exerting anti-inflammatory and anti-oxidative effects.

Vascular damage is associated with the pathogenesis of radiation dermatitis (Brown and Rzucidlo, 2011). Additionally, aloe vera had been shown to protect against vascular damage. Soria et al. (2019) reported that immediately after radiation, vascular damage was observed in the brain. In line with the aforementioned studies, a result by Rong et al. (2019) indicated that vascular damage to the skin was rapidly induced in response to radiation. Human fetal skin-derived stem cells (hFSSC) is served as a preferable source for skin tissue regeneration. It has been reported that the hFSSC secretome significantly reduces the intensity of radiation dermatitis by enhancing angiogenesis through up-regulation of vascular endothelial growth factor (VEGF), placental growth factor (PLGF), and transforming growth factor β3 (TGF-β3) (Rong et al., 2019). Aloe vera also had been confirmed to infiltrate into the skin tissue and promote wound healing by improving angiogenesis (Tarameshloo et al., 2012). Consistent with this result, Ali et al. (2021) reported that aloe vera improved angiogenesis by promoting the expression of VEGF in the skin, which ameliorated skin wound healing. Thus, the efficacy of aloe vera on radiation dermatitis may be explained by the proangiogenic effect of aloe vera. Further studies are needed to evaluate the prevention efficacy and potential action mechanism of aloe vera in radiation dermatitis.

As far as we know, this is the first study to quantify the protective effects of aloe vera on RID through a cumulative analysis. Multiple strengths should be acknowledged in the present study. This is a meta-analysis of all the available studies with a larger sample with an evidence-based etiological theory. As a result, the present evidence is creditable for clinical practice. Nevertheless, several inherent limitations could not be ignored when interpreting this data. First, substantial heterogeneities existed in a combined analysis. In general, different study designs, sample sizes, ages of the participants, geographical areas, and confounding factors could all be partly responsible for this remarkable heterogeneity. Second, we only included those studies that were published in English and Chinese, which may induce a selection bias. Third, different ages and various types of cancers were found in these included studies, which may downgrade the evidence of this study. Thus, caution is warranted when interpreting this study. Besides, additional well-designed RCTs with large samples are still warranted to further illuminate the effects of radioprotection developed by aloe vera.

Conclusion

Based on the current evidence, pre-treated with aloe vera was reinforced to significantly reduce the incidence of RID as compared with the conventional treatment. Aloe vera could be served as a standardized product in the prevention or treatment of RID in patients with malignancies, especially for breast cancer and nasopharyngeal carcinoma. On account of the small quantity of relevant RCTs, the conclusions should be interpreted carefully. In the near future, further multicenter RCTs with a large sample size would be required to confirm this finding.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.976698/full#supplementary-material

SUPPLEMENTARY TABLE S1
PRISMA Checklist.

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