A systematic review of Aloe vera in Chemotherapy & Radiotherapy induced inflammation in cancer patients: unraveling the antiproliferative and proapoptotic effects on cancer

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ABSTRACT

Background: Aloe vera has gained attention for its antioxidant, immunomodulatory, and anti-inflammatory properties, particularly in managing chemotherapy-induced inflammation in cancer patients. **Aim:** The purpose of this systematic review is to assess the potential benefits of aloevera in all cancer chemotherapy and radiotherapy induced inflammation. **Materials and method:** Data extraction was done in literature databases. PICO and PRISMA analysis were done. A total of nine articles were included for the study based on the inclusion and exclusion criteria. Quality assessment was done using Office of Health Assessment and Translation Assessment tool **(**OHAT). **Results:** The results of the systematic review indicate that the antioxidant properties of the plant may contribute to its preventive mechanism against radiation induced inflammation. All the included studies does not have definitely high risk of bias. **Conclusion:** Aloe vera may be a useful adjunct therapy to reduce radiation-induced side effects in cancer patients, but more research is needed to confirm its efficacy and optimal usage. However, further clinical trials are necessary to confirm its therapeutic role and safety in improving the outcomes of radiotherapy in cancer patients.

Keywords: aloe vera, cancer, inflammation, radiotherapy, chemotherapy.

INTRODUCTION

Aloe vera, sometimes also known as *Aloe barbadensis*, is a cactus-like perennial plant with fleshy leaves that belongs to the family Asphodelaceae. The Aloe vera plant has been utilized

in traditional folk leveraging its natural properties.[1] Aloe vera was introduced to China and southern European countries in the 17th century.[1,2] It also has an important place in the field of traditional medicine in some modern cultures, such as China, Japan, and India. [3] In the United States, Aloe vera first gained popularity in the 1930s, as an effect of studies indicating efficacy in treating-ray burns.[4,5] Aloe vera has commonly been used in thermidor skin problems. Aloe vera products for topical use are derived from a clear, viscous liquid that appears when the leaves of the plant are cut, and this liquid instrumently an ingredient in cosmetics and alternative medicine products.[6] These products are claimed tube effective in the treatment of many dermal and mucosal problems such as wounds, burns, frostbite, xerosis, psoriasis, eczema, genital herpes, aphthous stomatitis, and seborrheic dermatitis.[7,8] Aloe vera products for oral consumption include capsules made of Aloe leaves, dried latex, and Aloe vera juice. These products are utilized especially in the repercussion of constipation because of a laxative effect.[3,8]

In laboratory studies, Aloe vera has demonstrated to have some anti-oxidant, anti-inflammatory, immunomodulatory, and anti-cancer properties.[7-11] The immunomodulatory properties of Aloe vera, which contains many active components, are attributed to Alemanni, while its anti-proliferative properties are attributed to the component's anthracene and anthraquinone.[10] Cancer as a major public health problem is responsible for 13% (7.6 million deaths) of all deaths in the world.[11] Radiation can enhance the efficacy of chemotherapy regimens and perhaps serve as the primary treatment option. Radiation treatment is necessary for roughly two-thirds of cancer patients. Radiation damages DNA, leading to the generation of free radicals and anti-inflammatory reactions at the site of action. Radiation therapy can cause undesirable consequences, such as acute responses within hours. Aloe vera may improve wound healing on the epidermis and dermis, perhaps reducing radiation-related harmful effects. Aloe vera can improve wound oxygenation and reduce dead tissue at radiation locations, potentially mitigating the detrimental effects of radiation therapy.[12] Hence this systematic review aims to assess the potential of Aloe vera in chemotherapy & radiotherapy induced inflammation.

MATERIALS AND METHODS

The literature review was carried out in a systematic manner which includes the following steps: the research question, formulating a strategy for conducting a literature search, searching the literature and retrieving articles, data extraction, interpretation, and evaluation of evidence gathered from the literature.

Research question

Aloe vera has gained attention for its potential anti-inflammatory properties, particularly in managing chemotherapy-induced inflammation in cancer patients. Chemotherapy often triggers severe inflammation as a side effect, which can lead to mucositis, dermatitis, and other inflammatory responses. Aloe vera, known for its antioxidant, immunomodulatory, and anti-inflammatory effects, may offer protective benefits. The research question is "what is the potential role of Aloe vera in preventing and managing chemotherapy-induced inflammation across various cancer types?"

PICO

- **Population:** participants with cancer and undergoing cancer treatment.
- **Intervention:** Aloe Vera
- **Comparison:** Placebo
- **Outcome:** Reduction in the cancer chemotherapy & radiotherapy induced inflammation

Inclusion Criteria:

- This Investigation reviews randomized control trial conducted from 2001-2024.
- It Incorporates complete articles retrieved from search engine such as PubMed, Elsevier, and Cochrane.
- The study specifically explores the impact of Aloe vera on cancer prevention.
- The study consists of comprehensive articles written exclusively in English.

Exclusion Criteria:

- Limit to studies that use cancer cell lines as the primary focus or focus on non-cancer related pathways.
- Excludes the research published in non-English languages.

Information Sources, Search Strategy, and Study Selection

Information Sources:

- PubMed
- Cochrane Library
- Embase
- Elsevier Scopus
- Science Direct

Search Strategy:

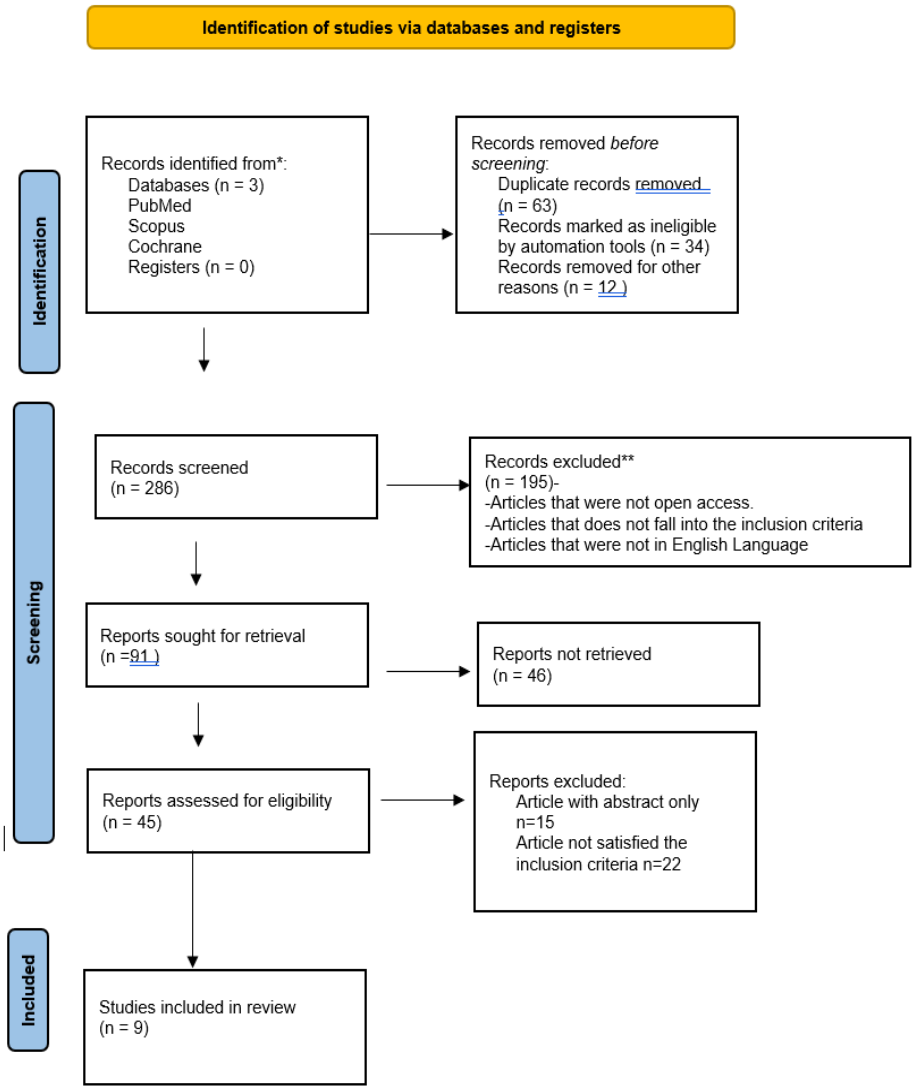
An electronic search was conducted on the above mentioned databases. The keywords used were a combination of keywords and MeSH terms such as "Aloe vera," "inflammation" "efficacy," "radiotherapy induced inflammation" and "dermatitis" MeSH terms were used with Boolean operators (Aloe vera) AND (cancer radiotherapy induced inflammation) AND (efficacy); (Aloe vera) AND (inflammation) AND (efficacy); (Aloe vera) AND (cancer chemotherapy induced inflammation); (Aloe vera) OR (aloe barbadensis) AND (inflammation).

Study Selection:

- Initial screening of titles and abstracts based on inclusion and exclusion criteria.

- Full-text review of selected articles.
- Data extraction from eligible studies using a standardized for

FIGURE 1: PRISMA flow diagram for recently conducted systematic reviews that solely involved database and registration searches [13]


Identification of studies via databases and registers
Identification
Records identified from*:
Databases (n = 3)
PubMed
Scopus
Cochrane
Registers (n = 0)
Records removed *before screening*:
Duplicate records removed (n = 63)
Records marked as ineligible by automation tools (n = 34)
Records removed for other reasons (n = 12)
Screening
Records screened
(n = 286)
Records excluded**
(n = 195)-
-Articles that were not open access.
-Articles that does not fall into the inclusion criteria
-Articles that were not in English Language
Reports sought for retrieval
(n =91)
Reports not retrieved
(n = 46)
Reports assessed for eligibility
(n = 45)
Reports excluded:
Article with abstract only n=15
Article not satisfied the inclusion criteria n=22
Included
Studies included in review
(n = 9)

RESULTS

TABLE 1: Characteristics of intervention in the study

Authors	Type of study	Sample size	Patient Characteristics	Duration	Patient Allocation
Sue Heggie et al 2002[14]	Double Blind Phase III Clinical study	225	Breast cancer patients with radiation therapy	2 weeks	**Experimental arm:** 98% aloe vera gel **Control arm:** aqueous cream
Catherine K.Su et al, 2004[15]	Phase II Double-Blind Randomized study	58	Head and neck cancer patients receiving radiotherapy	7 weeks	**Study group:** Aloe vera n=28 **Placebo group** n=30
Donna Hoopfer et al 2015[16]	Three-Arm Randomized Phase III Trial	248	Breast cancer patients undergoing radiation therapy	6 weeks	**Study group:** Aloe cream n=81 **Placebo group:** Placebo cream n=77 **Control group:** Powder group n=79
Adeleh Sahebnasagh et al 2020[17]	Randomized, double-Blind, Placebo-Controlled	42	Pelvic cancer patients receiving external-beam radiotherapy	5 weeks	**Study group:** Aloe vera ointment 3% n=19 **Placebo group** n=23
Muaaz Alkhouli et al 2020[18]	Randomized Controlled Clinical Trial	26	Children with acute lymphoblastic leukemia undergoing chemotherapy	8 weeks	**Group 1:** 70% Aloe vera solution **Group 2:** 5% sodium bicarbonate
Adeleh Sahebnasagh et al 2022[19]	Randomized, Placebo-Controlled	20	Colorectal cancer patients undergoing radiotherapy	6 weeks	**Study group:** 12 patients received topical Aloe vera 3% ointment at a dose of 1 gm/ twice a day

					Placebo: 8 patients given placebo
Tharatorn Tungkasamit et al 2022[20]	Randomized, multicenter double-Blind Placebo-Controlled	120	Head and neck cancer patients undergoing radiation therapy	8 weeks and follow up	**Study group:** Aloe vera arm n=60 **Control group:** Placebo arm n=60
Celia Jimenez Garcia et al 2024[21]	Controlled Clinical Trial (Alantel Trials)	88	Breast cancer patients undergoing radiation therapy	4 weeks	**Experimental group:** Alantel cream n=44 **Control group:** Placebo cream n=44
Lucksika Wanichtanom et al 2024[22]	Randomized, Single-Blinded Phase II trial	61	Cancer patients receiving capecitabine	4 weeks	**Study group:** Aloe Vera plus 10% Urea Cream n=30 **Control group:** 10% Urea Cream n=31

- Patient characteristics broadly describe the population involved in each trial.
- Patient allocation refers to the study design (e.g., randomized controlled trial, double-blind) regarding how participants were assigned to treatment groups.

TABLE 2: Characteristic of the primary outcome and results of studies included in the current study

Authors Name	Effect Measure	Result
Sue Heggie et al 2002[14]	Reduction in the skin adverse effects of radiation therapy	Aloe vera gel does not significantly reduce radiation-induced skin side effects than aqueous cream p value <0.001*
Catherine K.Su et al, 2004[15]	Reduction in radiation induced oral mucositis	Aloe vera had low mucositis grade than the placebo group but was not statistically significant p value 0.39
Donna Hoopfer et al 2015[16]	Reduction in acute skin toxicity	Aloe vera cream did not demonstrate significant reduction in acute skin toxicity compared to powder or placebo cream in breast cancer patients undergoing radiation therapy. p value 0.283
Adeleh Sahebnasagh et al 2020[17]	Reduction in adverse effects followed by malignant pelvic disease	Aloe vera ointment was effective in the prevention of symptoms of acute radiation induced proctitis in patients undergoing radiotherapy for pelvic cancers p value=0.009
Muaaz Alkhouli et al 2020[18]	Prevention of chemotherapy-induced oral mucositis	Topical application of aloe vera solution effectively prevented chemotherapy-induced oral mucositis in children with acute lymphoblastic leukemia. P value <0.001
Adeleh Sahebnasagh et al 2022[19]	Prevention of acute radiation-induced proctitis in colorectal cancer	Significant reduction in severity and incidence of acute radiation proctitis with Aloe vera. Descending trend of CRP levels in the study group. (p value = 0.042)
Tharatorn Tungkasamit et al 2022[20]	Reduction in severity of radiation-induced dermatitis (RID)	Significant differences were seen between the study and control groups at 5^{th}, 6^{th}, 7^{th} and 8^{th} weeks. p value =0.001 Aloe vera gel reduced moderate to severe grades of skin erythematous but there was no prophylactic efficacy in radiation induced dermatitis.
Celia Jimenez Garcia et al 2024[21]	Reduction in radiation induced dermatitis in patients with breast cancer	To verify the Aloe vera cream advantages at high concentrations over the other moisturizing cream.

Lucksika Wanichtanom et al 2024[22]	Prevention of Hand Foot Syndrome	Aloe vera gel with urea cream combination showed efficacy in preventing Hand Foot Syndrome compared to urea cream alone. P value=0.045

TABLE 3: QUALITY ASSESSMENT OF ALL THE INCLUDED STUDIES

Author name	Randomization	Allocation Concealment	Comparison group	Confounding	Experimental conditions	Blinding	Complete outcome data	Exposure Characterization	Outcome Assessment	Outcome Reporting	No other threats
Sue Heggie et al 2002[14]											
Catherine K.Su et al, 2004[15]											
Donna Hoopfer et al 2015[16]											
Adeleh Sahebnasagh et al 2020[17]											
Muaaz Alkhouli et al 2020[18]											
Adeleh Sahebnasagh et al 2022[19]											

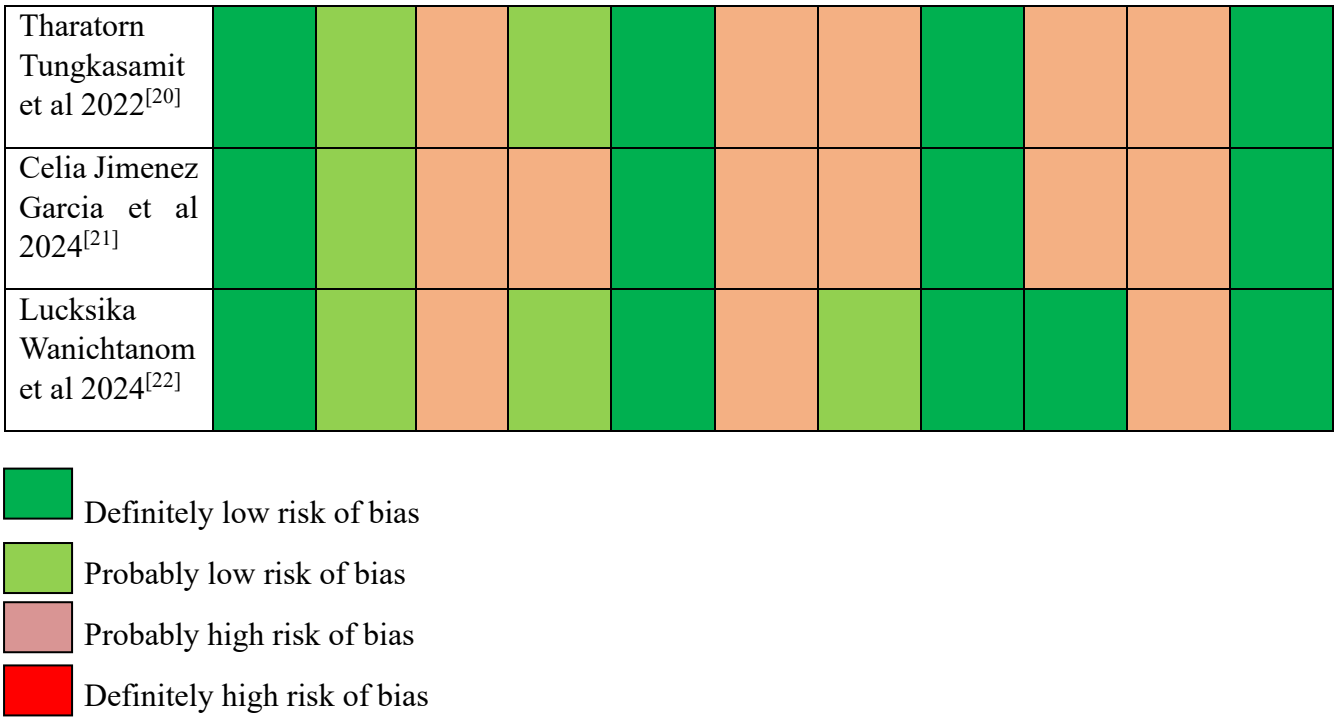


Table 3 shows the Risk of bias in all the included studies based on the Office of Health Assessment and Translation (OHAT) Assessment tool [25][26]

DISCUSSION

Aloe vera has been found to have potential anti-cancer properties, although more research is needed to confirm its efficacy in cancer prevention. Studies suggest that Aloe vera may have anti-proliferative and anti-tumor effects, inhibiting the growth of cancer cells and inducing apoptosis. The anti-cancer properties of Aloe vera may be attributed to its bioactive compounds, including anthraquinones, polysaccharides, vitamins, minerals, and amino acids. These compounds have antioxidant and anti-inflammatory effects, which may help protect cells from damage and stimulate the immune system to respond to cancer cells. Some studies have demonstrated Aloe vera's potential in preventing or treating various types of cancer, including skin, breast, colorectal, and head and neck cancer. For instance, Aloe vera's antioxidant and anti-inflammatory properties may help prevent skin cancer, while its ability to inhibit cell proliferation may reduce the risk of breast, colorectal, head and neck cancer by inhibiting cell proliferation. A balanced diet, regular exercise, and regular health check-ups remain essential for overall health and cancer prevention. The articles discuss the potential benefits of Aloe vera in preventing and treating various side effects of cancer treatment. However, it is essential to note that more research is needed to confirm Aloe vera's anti-cancer effects in humans, and it should not be used as a replacement for conventional cancer treatment.

Catherine k Su et al 2004,[15] compared the efficacy of oral aloevera and placebo for the prevention of oral mucositis induced by radiotherapy in patients with head and neck cancer. A total of 58 head and neck cancer patients were recruited for the study. There were no statistically significant differences found between the oral Aloe vera and placebo p value 0.39. Aloe vera (82%) showed low grade of mucositis than placebo (93%) with mild difference percentage.

Aloe vera was not beneficial addition to the radiotherapy induced oral mucositis in head and neck cancer patients. The study has a probably high risk of bias for not describing the confounding factors.

Sue Heggie et al 2002[14] aimed to evaluate the efficacy of topical Aloe vera gel in reducing radiation-induced skin toxicity in breast cancer patients undergoing radiotherapy. Skin toxicity, including erythema, desquamation, and pain, is a common side effect of radiation therapy for breast cancer. The trial likely assessed outcomes such as skin toxicity scores, incidence of severe dermatitis, and patient-reported outcomes related to skin symptoms and quality of life. Aloe vera's effectiveness in mitigating acute skin reactions and improving patient comfort during and after radiation therapy would be critical findings. Aloe vera's anti-inflammatory and moisturizing properties make it a potential candidate for managing radiation-induced skin toxicity. Understanding its mechanisms of action in skin protection and its comparative effectiveness against standard care or other interventions is essential for clinical practice. Future research could explore optimal timing and frequency of Aloe vera application during radiotherapy, as well as its potential long-term benefits in preventing chronic skin changes. Comparative studies with different formulations or delivery methods could further optimize supportive care strategies.

Donna Hoopfer et al 2015[16] aimed to compare the efficacy of Aloe vera cream versus placebo cream or powder in reducing radiation-induced skin injury (dermatitis) in breast cancer patients undergoing radiation therapy. Skin toxicity is a common side effect of radiation therapy, impacting patient comfort and treatment completion rates. The study likely assessed acute skin toxicity scores, incidence of severe dermatitis, and patient-reported outcomes related to skin health and quality of life. Aloe vera's effectiveness in mitigating radiation-induced skin toxicity would be crucial for supportive care strategies in breast cancer treatment. The study's design allows for direct comparison of Aloe vera cream with placebo and alternative formulations (powder) in a large patient cohort. Insights into Aloe vera's role in maintaining skin integrity during radiation therapy would inform clinical practice guidelines and optimize skin care protocols. Future research could investigate the long-term effects of Aloe vera on skin recovery post-radiation therapy and explore its potential preventive effects against chronic radiation-induced skin changes. Comparative effectiveness studies with different formulations or delivery methods could provide further insights.

Adeleh Sahebnasagh et al 2020[17] evaluated the aloe vera ointment for preventing acute radiation-induced proctitis (ARP) in pelvic cancer patients undergoing radiotherapy. ARP is a significant concern due to its impact on patient comfort and treatment adherence. Similar to the first study, this trial found that Aloe vera ointment was effective in preventing ARP. Patients who received Aloe vera experienced reduced severity and incidence of ARP symptoms compared to those who received placebo. The consistency in findings across different patient populations (colorectal and pelvic cancer) suggests a robust preventive effect of Aloe vera against ARP. Mechanistic studies could explore whether Aloe vera acts primarily through local mucosal protection or systemic anti-inflammatory pathways.

Muaaz Alkhouli et al 2020[18] showed that this trial assessed the effectiveness of Aloe vera in preventing chemotherapy-induced oral mucositis (OM) in children with acute lymphoblastic leukemia. OM is a painful condition characterized by inflammation and ulceration of the oral mucosa, affecting eating, drinking, and quality of life. The study likely included measures such

as incidence and severity of OM, duration of symptoms, and impact on nutritional status and quality of life. Aloe vera's efficacy in reducing OM severity and improving symptom management would be critical outcomes. Aloe vera's potential as a mucosal protectant and anti-inflammatory agent makes it a promising candidate for OM prevention. Understanding its mechanisms of action and optimal dosing regimens could enhance supportive care strategies for pediatric oncology patients. Future research could explore Aloe vera's effects in broader pediatric cancer populations and compare its efficacy with other preventive strategies. Mechanistic studies could elucidate pathways through which Aloe vera mitigates chemotherapy-induced mucosal damage. The study likely included measures such as incidence and severity of OM, duration of symptoms, and impact on nutritional status and quality of life. Aloe vera's efficacy in reducing OM severity and improving symptom management would be critical outcomes. Aloe vera's potential as a mucosal protectant and anti-inflammatory agent makes it a promising candidate for OM prevention. Understanding its mechanisms of action and optimal dosing regimens could enhance supportive care strategies for pediatric oncology patients.

Adeleh Sahebnasagh et al 2022[19] investigated the potential of Aloe vera to prevent acute radiation-induced proctitis (ARP) in colorectal cancer patients undergoing radiotherapy. ARP is a common side effect of pelvic radiotherapy, characterized by inflammation and damage to the rectal mucosa. The study found that Aloe vera ointment significantly reduced the severity of ARP symptoms compared to placebo. Additionally, levels of C-reactive protein (CRP), a marker of inflammation, decreased significantly in patients treated with Aloe vera. This suggests a potential anti-inflammatory effect of Aloe vera that may contribute to its preventive mechanism against ARP.The findings are promising as they indicate that Aloe vera could be a cost-effective and relatively safe intervention for managing ARP in colorectal cancer patients. The reduction in CRP levels also suggests a systemic anti-inflammatory effect, which could have broader implications beyond local symptom management. Future research could focus on elucidating the specific mechanisms through which Aloe vera exerts its protective effects against ARP. Long-term follow-up studies could also assess the durability of these effects and explore optimal dosing regimens.

Tharatorn Tungkasamit et al 2022[20] evaluated the efficacy of topical Aloe vera gel in reducing the severity of radiation-induced dermatitis (RID) in head and neck cancer (HNC) patients. RID is a common side effect of radiation therapy, characterized by skin inflammation and damage. Contrary to expectations, the study did not find significant prophylactic efficacy of Aloe vera gel in preventing RID compared to placebo. The results indicated that Aloe vera gel did not reduce the severity or incidence of RID in HNC patients undergoing radiation therapy. The lack of efficacy observed in this trial raises questions about the specific conditions under which Aloe vera may or may not be effective in managing radiation-induced skin toxicity. Factors such as the formulation of Aloe vera, patient-specific characteristics, and the radiation protocol could influence outcomes. On bias assessment probably high risk of bias were seen in comparison group, blinding and the outcome data.

Celia Jimenez Garcia et al 2024[21] published a study protocol on the efficacy of aloe vera for Alantel cream, the management of radiotherapy induced dermatitis in breast cancer patients. The study was planned to conduct in 88 patients with a follow up duration of 22 days. The author discussed that the study will be completed in future to verify the advantages of

moisturizing cream for the radiotherapy induced dermatitis. Lucksika Wanichtanom et al 2024[22] evaluated the efficacy of a combination therapy of Aloe vera gel and urea cream for preventing hand-foot syndrome (HFS) in cancer patients receiving capecitabine chemotherapy. Capecitabine is an oral anti-cancer medication that acts as a prodrug of fluoropyrimidine and is frequently utilized in the treatment of various cancers. HFS is a common side effect characterized by painful erythema and desquamation on palms and sole the trial randomized patients to receive either Aloe vera gel plus urea cream or urea cream alone. The study's outcome measures likely included incidence and severity of HFS, as well as patient-reported outcomes related to symptom management and quality of life. Combining Aloe vera with urea cream targeted both the inflammatory and moisturizing aspects of HFS management. Aloe vera plus urea cream group had 86.7% of grade 0-1 whereas in urea group only 64.5% had grade 0-1. Grade 2-3 in Aloe vera plus urea group were 13.3% which was less when compared to urea group 35.5%. Aloe vera plus urea cream showed better results when compared to urea cream.

In recent years, Ayurveda has gained prominence as an effective alternative medicine globally, with a focus on natural remedies that promote health and well-being.[24] Among these remedies, Aloe vera has garnered significant attention due to its diverse therapeutic properties, including immunomodulatory, antiviral, and anti-inflammatory effects. Research indicates that Aloe vera contains a variety of essential minerals such as sodium, calcium, potassium, manganese, copper, magnesium, zinc, chromium, and iron, which contribute to its health benefits.[23] Natural products and nutraceuticals like Aloe vera may positively influence skin health and enhance antioxidant status. However, the current body of literature emphasizes the necessity for further research to confirm their efficacy and establish optimal usage guidelines. The effects of Aloe vera on skin damage can vary depending on the specific context and the population studied. For instance, while some studies indicate that Aloe vera may help alleviate symptoms of radiation-induced skin damage in cancer patients undergoing treatment, the results can differ based on individual patient characteristics and treatment protocols. The need for effective treatments is growing along with the global incidence of cancer. Patients with cancer have much longer survival times due to the accessibility of recent advancements in surgery, chemotherapy, and radiation therapy, as well as newer forms of treatment such as immunotherapies and targeted therapies.[23] Cancer is an intricate disease characterized by uncontrolled cell growth and proliferation, leading to tumor formation and metastasis.[24] This systematic review highlights Aloe vera's potential as a supportive therapy in managing side effects associated with cancer treatments such as chemotherapy and radiotherapy. Its antioxidant properties may play a critical role in protecting against oxidative stress induced by radiation therapy. Additionally, Aloe vera's anti-inflammatory properties could help reduce inflammation and promote healing in affected tissues. Despite promising findings regarding Aloe vera's benefits for skin health and its potential role in cancer treatment, it is crucial to approach these claims with caution. In the current systematic review aloe vera did not show promising results in reducing the radiation induced inflammation in breast cancer patients by Sue Heggie et al 2002[14] and Donna Hoopfer et al 2015[16].More rigorous clinical trials are needed to validate the therapeutic efficacy of Aloe vera and to determine the most effective formulations and application methods for different patient populations. Overall, while Aloe vera shows promise as an adjunct therapy in oncology settings, it should not replace conventional treatments but rather complement them in a holistic approach to patient care.

CONCLUSION

Aloe vera has shown potential benefits in reducing radiation-induced side effects in cancer patients across several studies. It has been observed to help prevent acute radiation proctitis in pelvic cancer patients and reduce radiation-induced dermatitis in those with head and neck cancer. Additionally, Aloe vera has demonstrated efficacy in reducing hand-foot syndrome in cancer patients receiving capecitabine and mitigating chemotherapy-induced oral mucositis in children with acute lymphoblastic leukemia. Furthermore, it was not effective in preventing radiotherapy-related inflammation in patients with breast cancer. However, not all studies have consistently reported significant effects of Aloe vera on radiation-induced side effects. Aloe vera may be a useful adjunct therapy to reduce radiation-induced side effects in cancer patients, but more research is needed to confirm its efficacy and optimal usage. However, further clinical trials are necessary to confirm its therapeutic role and safety in improving the outcomes of radiotherapy in cancer patients.

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