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Original Article

Zinc Sulphate for Prevention of Breast Cancer Radiation Therapy-Induced Dermatitis: A Three-arm Triple-blinded Randomized Clinical Trial

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Abstract

Background: Radiation therapy (RT)-induced dermatitis is a common side effect in breast cancer patients that impacts quality of life and treatment compliance. Although zinc sulphate has shown potential for reducing skin lesions in preclinical studies, clinical evidence is still limited.

Methods: In this three-arm triple-blinded randomized trial, 180 breast cancer patients scheduled for whole breast RT were allocated to receive zinc sulphate 150mg/day (n=60), zinc sulphate 100 mg/day (n=60), or placebo (n=60) during RT. The primary outcome was dermatitis severity per Radiation Therapy Oncology Group (RTOG) criteria at pre-specified time points through weeks 1 to 5 during RT and months 1 and 2 after RT cessation.

Results: Dermatitis severity was significantly lower in both zinc sulphate arms versus placebo from weeks 3-5 of RT ($p<0.01$). Moreover, the 150 mg/day arm showed lower dermatitis severity versus 100 mg/day in week 5 of RT ($p<0.001$), with mean RTOG scores of 0.33±0.47 for 150 mg/day, 0.75±0.62 for 100 mg/day, and 1.30±0.74 for the placebo group. Analysis of dermatitis trends revealed a dose-dependent pattern, with 150 mg/day showing an earlier plateau in severity escalation. No significant drug adverse effects were observed.

Conclusions: Zinc sulphate supplementation during breast cancer RT mitigates the incidence and severity of acute radiation dermatitis in a potentially dose-dependent manner, which demonstrates the potential to improve patient quality of life by reducing RT-related skin toxicity. Further research on optimal dosing and long-term effects is warranted.
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1. INTRODUCTION

Breast cancer is a significant public health concern, being the most common cancer among women and the fifth cause of cancer-attributed mortality worldwide (1, 2). Radiation therapy (RT) continues to play a pivotal role in the management of breast cancer, either as part of the primary treatment regimen or postoperatively, to reduce the risk of local recurrence (3, 4). While RT has contributed to improved survival rates and enhanced local control, it is not without its own set of challenges and adverse effects (5).

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RT-induced dermatitis, also referred to as radiation dermatitis, is one of the most prevalent side effects experienced by breast cancer patients. RT-induced dermatitis typically manifests as erythema, pruritus, desquamation, and pain in the irradiated skin areas, significantly impacting the patient's quality of life and treatment compliance (6, 7). Despite advances in RT techniques and dose fractionation, the incidence of radiation dermatitis remains high, affecting up to 95% of breast cancer patients receiving RT (8).

Numerous approaches have been explored to alleviate the burden of RT-induced dermatitis, ranging from topical agents and dressings to oral supplements (9). One such candidate is zinc sulphate, a readily available and cost-effective micronutrient with well-documented anti-inflammatory and wound-healing properties (10). Zinc plays a crucial role in skin integrity, deoxyribonucleic acid (DNA) repair, and immune function (11, 12). Studies have reported that zinc supplementation is beneficial in the treatment of several inflammatory dermatological diseases (13). Moreover, preclinical studies (14, 15), and preliminary clinical investigations (16, 17) have suggested its potential in reducing the incidence of radiation-induced lesions. Mechanistically, zinc serves as a cofactor for over 1000 enzymatic reactions, which regulates DNA and RNA polymerases critical for cellular repair and acts as an antioxidant protecting against radiation-induced free radical damage, maintaining epithelial barrier function by promoting cellular growth and inhibiting apoptosis (18, 19). Furthermore, zinc deficiency has been directly linked to impaired wound healing and various skin disorders, supporting its therapeutic potential in radiation-induced skin toxicity (20, 21).

Zinc supplementation has an established safety profile with minimal adverse effects when used at therapeutic doses, and its low cost and widespread availability make it an attractive intervention for routine clinical implementation, particularly in resource-limited settings where expensive supportive care options may not be feasible (22).

To date, clinical studies have focused on the effects of zinc sulphate supplementation on RT-induced mucositis, particularly in head and neck cancer (16, 17), and there is a paucity of randomized clinical trials that provide evidence on the efficacy of zinc sulfate for preventing and treating RT-induced acute dermatitis, particularly in the context of breast cancer. To our knowledge, no previous randomized controlled trial has evaluated distinct dosages of zinc sulphate supplementation for preventing acute radiation dermatitis in the breast cancer population, which represents a critical knowledge gap given that breast cancer patients comprise one of the largest populations receiving RT.

Considering the high prevalence of RT-induced skin toxicity and its negative impact on the quality of life among breast cancer patients, this randomized clinical trial aimed at investigating the role of zinc sulphate as a prophylactic and therapeutic agent in mitigating RT-induced acute dermatitis in breast cancer patients.

2. METHODS

2.1. Study setting

This study aimed to assess the efficacy of zinc sulphate in the prevention and treatment of acute dermatitis following breast cancer RT. The study was conducted between May 2021 and June 2022 at the Radiation Oncology Department of Afzalipour Hospital, the referral radiation oncology center in Kerman, southeast Iran.

2.2. Ethical approval

The study protocol was reviewed and approved by the institutional ethics committee of Kerman University of Medical Sciences (Ethics code: IR.KMU.REC.1399.203). The protocol for this study was prospectively registered in the Iranian Registry of Clinical Trials (Registration number: IRCT20200621047857N1). Written informed consent was obtained from all participants upon enrollment, including detailed information about the study's purpose, potential risks, benefits, and the voluntary nature of participation.

2.3. Participants

Study participants were recruited from newly diagnosed histopathologically-confirmed breast cancer cases who were scheduled to initiate RT after breast cancer surgery. The inclusion criteria were patients with (a) age above 18, (b) non-inflammatory breast cancer, (c) previous lumpectomy or mastectomy (with or without chemotherapy) who were candidates for whole breast RT, and (d) Karnofsky Performance Scale (KPS) score above 70. The exclusion criteria were patients with (a) previous history of breast or thoracic irradiation, (b) inflammatory breast lesions, (c) history of breast reconstruction surgery, (d) bilateral breast cancer, (e) diabetes, (f) receiving corticosteroids during study period, (g) smoking, (h) antioxidant (vitamin C, E) supplements consumption during study period, (i) history of connective tissue disorders, and (j) history of malabsorption syndromes.

In this study, all patients were scheduled to undergo 25 whole breast RT sessions (50 Gy irradiation dose). The

minimum sample size for this study was calculated to be 42 in each group using *a priori* approach based on the findings of a previous study (17), and considering an α error of 5% and a power of 80% utilizing GPower version 3.1 software. To enhance the power of the study and account for a 10% potential dropout, we recruited 60 participants in each group.

2.4. Study design and interventions

This study employed a three-arm, triple-blinded, randomized clinical trial design. Participants were randomly allocated into one of the three treatment groups in a 1:1:1 ratio. A computer-generated randomization was created by an independent researcher who was not involved in the patient's care. This list was used to allocate patients into one of the three following arms:

Arm A: Receiving zinc sulphate capsules three times a day (150 mg/day) for the whole RT period.

Arm B: Receiving zinc sulphate capsules two times a day (100 mg/day) and placebo once a day for the whole RT period.

Arm C: Receiving placebo three times a day for the whole RT period.

In this study, 220 mg zinc sulphate capsules (each containing 50 mg elemental zinc) provided by *Alhavi Pharmaceutical Company, Tehran, Iran* were used. Placebo capsules were identical in appearance to the zinc sulphate but without an effective substance (starch powder) provided by *Behsaz Arshian Daroo Company, Shiraz, Iran*. The zinc sulphate dosage was selected based on previous studies, which demonstrated the efficacy of zinc sulphate in preventing radiation-induced oropharyngeal mucositis in head and neck cancer patients (23-25). We also utilized a 100 mg/day dose, which represents a moderate therapeutic dose that falls within the established safe range for zinc supplementation while allowing us to evaluate potential dose-response relationships. These doses have been safely used in previous clinical trials without significant adverse effects (23-25). A triple-blinded design was utilized where participants were unaware of their assigned treatment group, and the investigating physicians and healthcare providers were also unaware of the patients' treatment assignment. Moreover, the statistician analyzing the data was also blinded to the treatment groups until the analysis was finalized. The blinding was maintained using identical packaging and labeling for zinc sulphate and placebo formulations. To ensure that patients in Arm B remain blinded to their assigned treatment, the capsules were provided in two distinct packages, emphasizing that every day, two capsules shall be taken from package 1 and one from the other package. For patients in arm A, both packages contained zinc sulphate capsules, while in patients in arm B, package 1 contained zinc sulphate and the other contained a placebo. Accordingly, for patients in arm C, both packages contained placebo. Drug treatments were initiated on the first day of RT and were continued until the last session of RT. Patients were educated on the importance of treatment compliance and received instructions on how to take the capsules. Compliance was monitored through follow-up visits by pill counting. Patients received regular reinforcement about the importance of adherence during follow-up visits.

2.5. Study outcomes and data collection

Data regarding tumor grading and type of surgery were extracted from clinical records. The study outcome was the severity of dermatitis according to the Radiation Therapy Oncology Group (RTOG) criteria for acute skin toxicity, as follows:

Grade 0: No skin changes

Grade 1: Follicular, faint or dull erythema, epilation, dry desquamation, or decreased sweating

Grade 2: Tender or bright erythema, patchy moist desquamation, moderate edema

Grade 3: Confluent moist desquamation other than skin folds, pitting edema

Grade 4: Ulceration, hemorrhage, necrosis

Patients were visited by a single investigator physician who was blinded to treatment allocation, in the first session of RT and weekly (after every five RT sessions) for five weeks, and thereafter, one month and two months after the final session of RT. The presence and severity of dermatitis were evaluated according to the RTOG criteria.

2.6. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) software (version 26.0. SPSS, Inc., Chicago, IL, USA) and R 4.5.1 statistical software. The "ggwithinstats " command was used for generating diagrams. Between-group comparisons were made using Kruskal-wallis test. To examine the trend of changes in RTOG severity of skin lesions, a Friedman's test was utilized separately for each group, followed by Bonferroni's adjustment for pairwise comparisons. Also, to examine the difference in the mean RTOG of two simultaneous factors on the trend, a two-tailed repeated measures test was used. A p-value less than 0.05 was considered statistically significant.

3. RESULTS

A total of 180 female breast cancer patients (age range: 35 to 74) were enrolled in the study. Table 1 represents the clinical characteristics of study participants. In terms of tumor staging, the majority of patients were graded as T_2N_0 (20.6%), T_2N_1 (18.9%), T_1N_0 (13.9%), and T_1N_1 (12.2%). Considering the type of surgery, 40% had undergone modified radical mastectomy (MRM) and 60% had undergone breast-conserving therapy (BCT) or breast-conserving surgery (BCS) prior to RT (**Table 1**).

Figure 1 represents the patient recruitment process. Patients were assessed against the predefined study criteria. A total of 180 patients were allocated into three distinct arms, each consisting of 60 individuals. All patients were closely monitored for treatment adherence and completed their RT course. There were no mortalities in the study period (**Figure 1**).

Table 1. Clinical characteristics of study participants

Variables		No. (%)
Tumor stage	T1 N0	25 (13.9)
	T1 N1	22 (12.2)
	T1 N2	6 (3.3)
	T2 N0	37 (20.6)
	T2 N1	34 (18.9)
	T2 N2	19 (10.6)
	T2 N3	4 (2.2)
	T3 N0	18 (10.0)
	T3 N1	7 (3.9)
	T3 N2	4 (2.2)
	T4 N1	2 (1.1)
	TX N1	2 (1.1)
Type of surgery	MRM	72 (40.0)
	BCT/BCS	106 (60.0)

MRM: Modified radical mastectomy; BCT: Breast-conserving therapy; BCS: Breast-conserving surgery

RTOG skin toxicity was compared in follow-up time points between the three groups. The distribution of dermatitis grades in study groups and study timepoints are demonstrated in Table 2 (Table 2). In the first week during RT, no skin lesions were noted among study participants. In the second week during RT, there was no significant difference in the severity of skin lesions among the three groups (p=0.561). However, in the third (p=0.004) and fourth (p<0.001) weeks of RT, dermatitis severity was significantly higher in the placebo group compared to both intervention groups. Similarly, in the fifth week during RT, dermatitis severity was significantly higher in the placebo group compared to both intervention groups; moreover, dermatitis severity was significantly lower in the 150 mg/day treatment group compared to the 100 mg/day treatment group (p<0.001). Findings did not reveal any statistically significant difference in the severity of dermatitis among the three groups, one month (p=0.058) and two months after RT cessation (p=0.134) (Table 3).

We further analyzed the trends of skin lesion severity in each group during the follow-up period. Findings revealed that in the 150 mg/day treatment group, dermatitis severity significantly increased in the third week during RT compared to the first and second weeks (p<0.001). However, no changes were observed until the fifth week during RT. Furthermore, one month after RT cessation, the incidence of dermatitis decreased significantly (p<0.001) (Figure 2-A). In the 100 mg/day treatment (Figure 2-B) and placebo (Figure 2-C) groups, the severity of skin lesions significantly increased in the third week during RT compared to the first and second weeks (p<0.001). Unlike the 150 mg/day treatment group, in the 100 mg/day treatment group and placebo groups, we observed a significant increase in dermatitis severity in the fourth week compared to the third week (p<0.001). However, there was no significant change until the fifth week during RT, and one month after RT cessation, the severity of dermatitis decreased significantly (p<0.001).

4. DISCUSSION

The management of RT-induced dermatitis in breast cancer patients has been a long-standing challenge, given its high incidence, potential for affecting treatment compliance, and its significant impact on patients' quality of life. To the best of our knowledge, our study is among the first clinical studies assessing the efficacy of zinc sulphate supplementation on RT-induced dermatitis. Overall, the results of our study reveal a promising role for zinc sulphate in mitigating the severity and incidence of dermatitis, with potential implications for improving the care and management of breast cancer patients undergoing RT.

Our findings demonstrate a statistically significant lower severity of acute dermatitis in the groups receiving zinc sulphate compared to the placebo group, particularly within weeks 3 to 5 of RT. Moreover, a higher daily dose of zinc sulphate supplement (*i.e.* 150 mg/kg) was associated with less severe dermatitis in week 5 of RT, when compared to 100 mg/kg supplement and placebo. Moreover, analyzing the severity trend of skin lesions during RT, our findings demonstrated that in the 100 mg/day treatment group and the placebo group, the severity of skin lesions followed a similar trajectory, with 150 mg/day treatment showing a

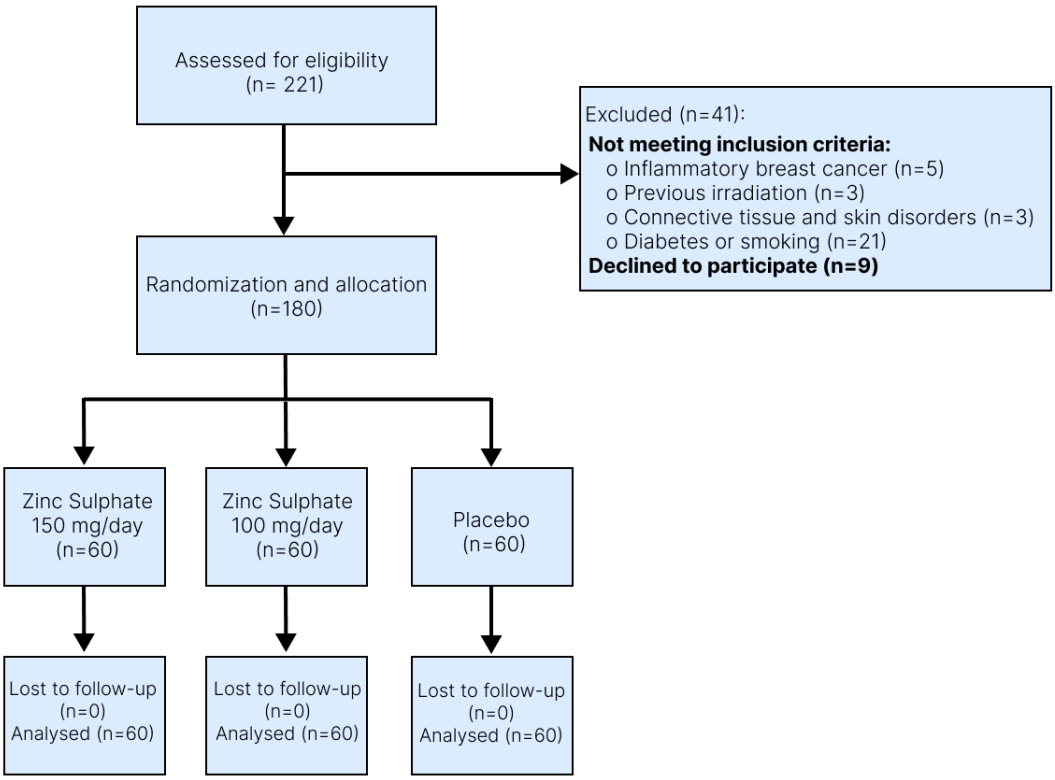

Figure 1. Flowchart of participants' enrollment.

significant escalation through the third week of RT. Notably, the two former groups exhibited a distinct pattern with a subsequent rise in dermatitis severity during the fourth week, distinguishing them from the 150 mg/day treatment group. This distinct pattern in severity implies a potential dose-dependent response, emphasizing the importance of considering zinc dosage in the management of radiation-induced dermatitis.

Overall, the decreased severity of acute dermatitis observed in the zinc sulphate group aligns with prior preclinical studies and early-phase clinical investigations that suggested the potential of zinc in mitigating radiation-induced toxicities. The efficacy of zinc sulphate supplementation in alleviating RT-induced dermatitis has only been investigated in a few studies so far. In an experimental study by Ertekin et al., it was found that rats that received oral zinc sulphate (5 mg/kg/day or 10mg/kg/day) before irradiation exhibited less epidermal atrophy and dermal degeneration as well as hair follicle atrophy. Accordingly, a 10 mg/kg/day dose was reported to be superior (14). Findings from another experimental study by Kandaz and colleagues also showed that 50 mg/kg/day oral zinc sulphate was associated with significantly lower radiation dermatitis compared to the control group in rats (15).

Although no clinical study has so far been conducted on the effectiveness of zinc sulphate supplementation on RT-induced dermatitis, there have been some reports on its beneficial effects in radiation-induced mucositis, particularly in head and neck cancers. For instance, a study by Ertekin et al. demonstrated that zinc sulphate supplementation (150 mg/day) was associated with a significantly lower degree of radiation-induced oropharyngeal mucositis compared to placebo in patients with head and neck malignancies (24). In another study by Mosalaei et al, it was reported that oral zinc sulphate was associated with less severe oral mucositis in weeks 4 to 6 during RT in patients with head and neck squamous cell carcinoma (26). However, a more recent systematic review and meta-analysis demonstrated no protective effects of oral zinc sulphate against RT-induced oral mucositis in patients with head and neck cancer (27), highlighting the need for more rigorous clinical trials in this field.

From a pathophysiological standpoint, ionizing radiation possesses the capability to induce direct cellular damage by causing chemical disruptions in the structure of DNA (28).

Table 2. Distribution of RTOG dermatitis grade between study groups.

Time Point	RTOG Grade	Intervention Group Zinc Sulphate (150 mg/day)		Zinc Sulphate (100 mg/day)		Placebo	
		N	%	N	%	N	%
Week 1	0	60	100.0%	60	100.0%	60	100.0%
	1	-	-	-	-	-	-
	2	-	-	-	-	-	-
Week 2	0	54	90.0%	57	95.0%	56	93.3%
	1	6	10.0%	3	5.0%	4	6.7%
	2	-	-	-	-	-	-
Week 3	0	36	60.0%	39	65.0%	22	36.7%
	1	24	40.0%	12	20.0%	28	46.7%
	2	0	0.0%	9	15.0%	10	16.7%
Week 4	0	30	50.0%	24	40.0%	16	26.7%
	1	30	50.0%	27	45.0%	12	20.0%
	2	0	0.0%	9	15.0%	32	53.3%
Week 5	0	40	66.7%	21	35.0%	10	16.7%
	1	20	33.3%	33	55.0%	22	36.7%
	2	0	0.0%	6	10.0%	28	46.7%
1 month after RT	0	56	93.3%	48	80.0%	54	90.0%
	1	4	6.7%	9	15.0%	6	10.0%
	2	0	0.0%	3	5.0%	0	0.0%
2 months after RT	0	58	96.7%	60	100.0%	60	100.0%
	1	2	3.3%	0	0.0%	0	0.0%
	2	-	-	-	-	-	-

Table 3. RTOG Severity of skin lesions during follow-up time points.

Timepoint	Zinc Sulphate (150 mg/day)	Zinc Sulphate (100 mg/day)	Placebo	Kruskal-Wallis H	Eta-squared	p-value
Week 1	0	0	0	-	-	-
Week 2	0.10±0.30	0.05±0.22	0.07±0.25	1.154	0.006	0.561
Week 3	0.40±0.49	0.50±0.74	0.80±0.70*	11.248	0.063	0.004
Week 4	0.50±0.50	0.75±0.70	1.27±0.86*	27.227	0.173	<0.001
Week 5	0.33±0.47	0.75±0.62#	1.30±0.74*	49.406	0.290	<0.001
1 month after RT	0.07±0.25	0.25±0.54	0.10±0.30	5.701	0.042	0.058
2 months after RT	0.03±0.18	0	0	4.022	0.022	0.134

Data are expressed as mean ± standard deviation
* Significant difference compared to both treatment groups.
# Significant difference compared to the 150 mg/day treatment group.

Furthermore, following interactions with water or oxygen molecules, radiation has the capacity to generate reactive oxygen metabolites, including superoxide and hydrogen peroxide (29). These metabolites, in turn, instigate cellular demise by inflicting damage to DNA. Radiation exposure also results in the disruption of the epidermis' barrier function (30). As a whole, the acute skin changes observed subsequent to RT can be attributed to a combination of direct tissue injury and localized inflammatory responses. The transient erythema observed within the initial 24 hours following RT initiation is likely a result of capillary dilation and increased vascular permeability, likely induced by the action of inflammatory mediators such as prostaglandins and leukotrienes (31). The more persistent generalized erythema that manifests over the subsequent 2-4 weeks is concomitant with epidermal degeneration and dermal edema, stemming from the infiltration of leukocytes into the underlying tissue. During this period, additional skin changes manifest, including dryness and epilation, which can be attributed to the destruction of sebaceous glands and hair follicles (31).

Zinc's multifaceted roles in skin integrity, immune response, and wound healing mechanisms provide a plausible biological basis for its efficacy observed in our study. Zinc serves as a cofactor for over 1000 enzymatic reactions, and is an essential component for more than 2000 transcription factors (21). Zinc's capacity in the regulation of DNA and RNA polymerases, thymidine kinase, and ribonuclease plays

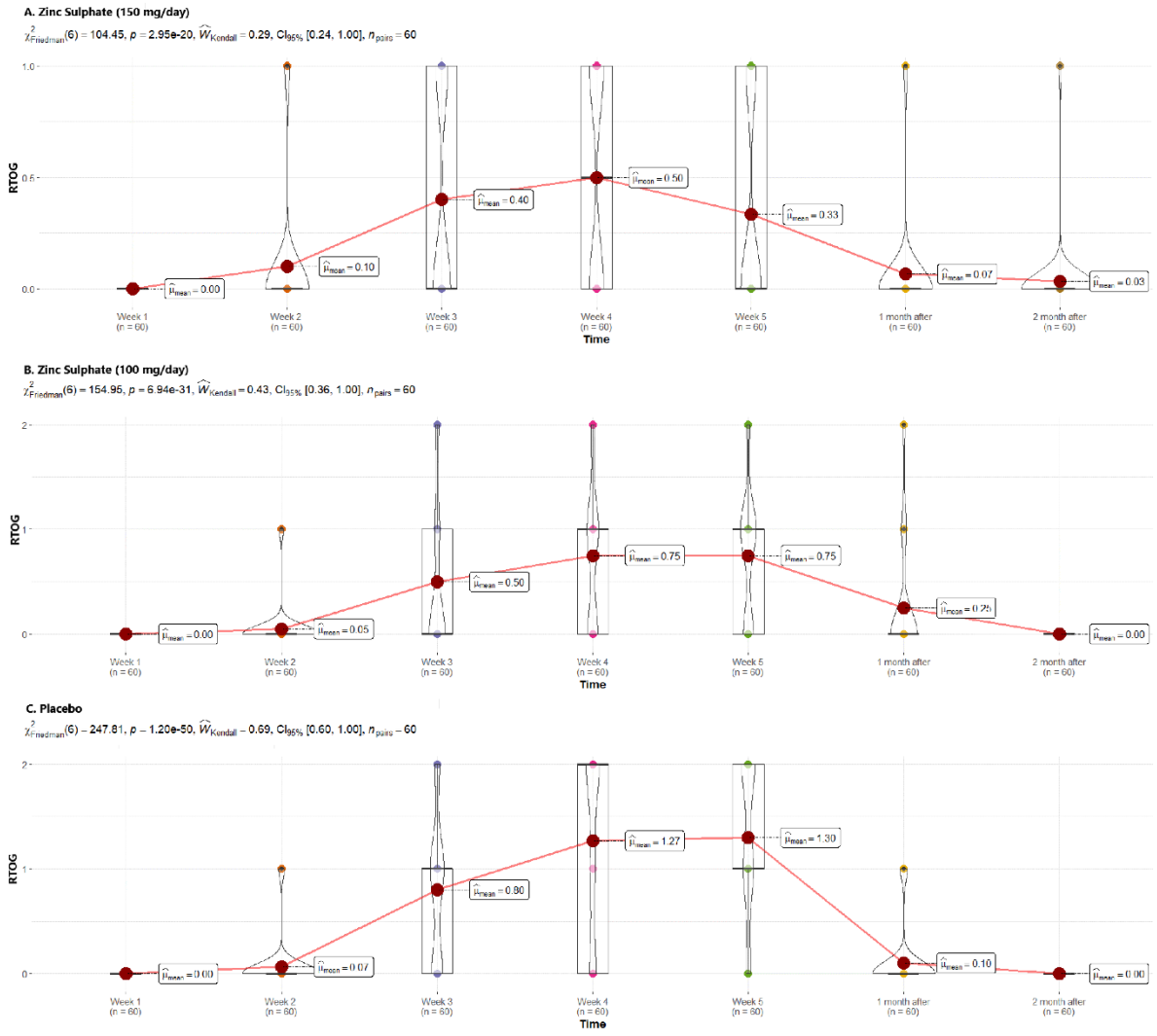

Figure 2. Trends of skin lesion severity according to RTOG during study time points for zinc sulphate (150 mg/day) treatment group (A), zinc sulphate (100 mg/day) treatment group (B), and placebo group (C).

a pivotal role in its physiological function (32, 33). Zinc finger proteins are essential for DNA damage recognition and repair processes, while zinc-dependent enzymes, including DNA polymerases and ligases, facilitate efficient cellular recovery from radiation-induced DNA strand breaks (34, 35). Zinc further contributes to the preservation of epithelial and tissue integrity by fostering keratinocyte and cellular growth and inhibiting apoptosis (36, 37). Additionally, it acts as an antioxidant, protecting against oxidative stress and free radical-induced damage during inflammatory processes (38). Zinc's anti-inflammatory properties operate through inhibition of nuclear factor-κB (NF-κB) signaling pathways, reducing the production of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β that contribute to radiation dermatitis severity (38, 39). A summary of the potential mechanisms is depicted in Figure 3 (Figure 3).

Moreover, an established correlation exists between several skin disorders and either zinc deficiency or the disruption of zinc transporters (21). Taken together, the crucial involvement of zinc in maintaining skin integrity supports its protective attributes against RT-induced dermatitis observed in this study.

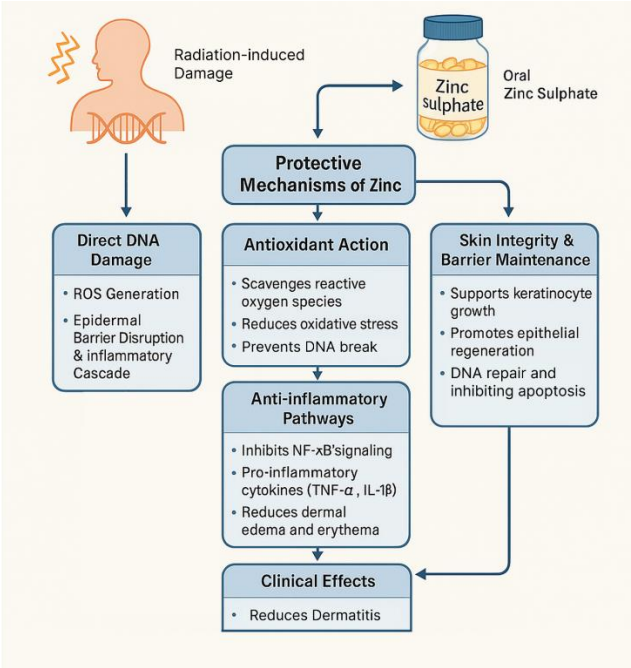

Figure 3. Summary of the potential mechanisms involved in the protective effects of zinc against radiation-induced dermatitis.

These findings advance the field by providing the first clinical evidence that zinc supplementation can reduce radiation dermatitis in breast cancer patients in a dose-dependent manner. Unlike previous studies that focused on mucositis or used single doses, our three-arm design demonstrates both efficacy and optimal dosing, which suggests a foundation for clinical implementation. Moreover, these results suggest that the biological mechanisms of zinc's protective effects, previously demonstrated in preclinical models, translate effectively to clinical practice in breast cancer RT.

Despite the encouraging results of this study, some limitations should be acknowledged. First, our study primarily focused on the acute phase of radiation dermatitis, with follow-up limited to two months post-radiation therapy. This short follow-up duration limits our understanding of the long-term effects of zinc supplementation on chronic skin changes, late radiation toxicity, or sustained protective benefits. Second, despite our blinded design, potential placebo effects or subtle bias in dermatitis grading cannot be completely eliminated, particularly given the subjective components inherent in clinical assessment scales. Third, our findings may have limited generalizability beyond breast cancer patients or our specific patient population, as we excluded patients with diabetes, smoking history, and other comorbidities that are commonly encountered in clinical practice. We encourage future research to prioritize several key areas in this field. Dose-finding studies are needed to establish optimal zinc supplementation protocols and identify the minimum effective dose while minimizing potential side effects. Additionally, long-term safety and efficacy assessments with extended follow-up periods would provide crucial information about sustained benefits and late toxicity prevention. Moreover, evaluation of zinc supplementation in other cancer types receiving different radiotherapy protocols would establish broader clinical applicability and determine whether our findings extend to other anatomical sites and radiation techniques.

In conclusion, this study provides preliminary clinical evidence supporting the use of zinc sulphate as a preventive and therapeutic measure to decrease the incidence and severity of RT-induced acute dermatitis in breast cancer patients. These findings have the potential to impact clinical practice and improve the overall care and well-being of breast cancer patients undergoing RT. Nevertheless, future research should continue to explore the optimal dosage and duration of zinc supplementation, potential mechanisms of action, and the long-term effects in various cancer populations. Graphical abstract of the study has been provided in **Figure 4**.

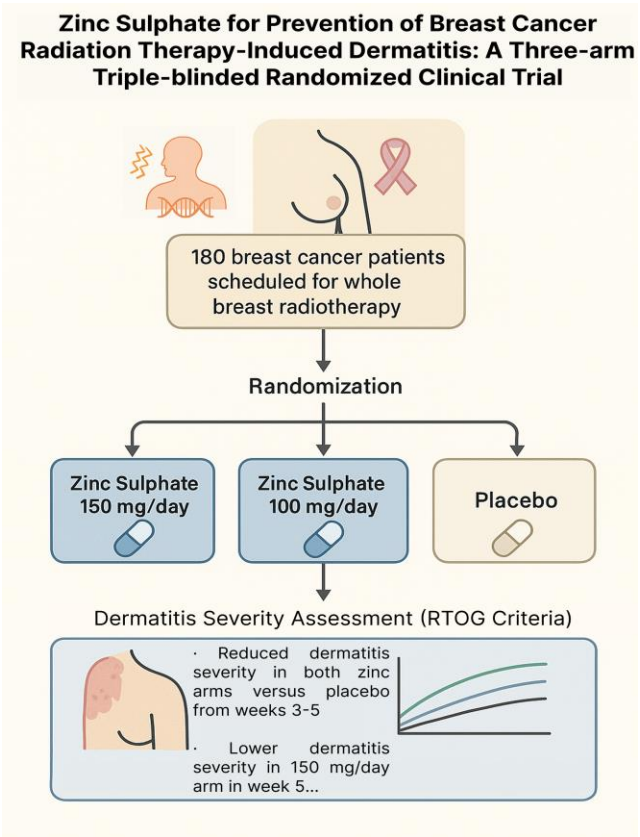

Figure 4. Graphical abstract.

Acknowledgment
None.

Conflict of interest
The authors declare that no conflict of interest exists.

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Ethical statement
All study protocols have been conducted under approval of the Ethics Committee of Kerman University of Medical Sciences (Ethics code: IR.KMU.REC.1399.203). The protocol for this study was prospectively submitted in the Iranian Registry of Clinical Trials (Registration number: IRCT20200621047857N1). Written informed consent was obtained from all participants upon enrollment.

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