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Nigella sativa L. for prevention of acute radiation dermatitis in breast cancer: A randomized, double-blind, placebo-controlled, clinical trial

Mohammadreza Rafati[a], Arash Ghasemi[b], Majid Saeedi[c], Emran Habibi[d], Ebrahim Salehifar[e], Mahmood Mosazadeh[f], Monireh Maham[a,*]

[a] Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[b] Department of Radiotherapy, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[c] Department of Pharmaceutics, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[d] Department of Pharmacognosy and Biotechnology, Pharmaceutical Sciences Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[e] Department of Clinical Pharmacy, Gastrointestinal Cancer Research Center, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Sari, Iran
[f] Health Sciences Research center, Addiction Institute, Mazandaran University of Medical Sciences, Sari, Iran

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ABSTRACT

Objective: The present study aimed to evaluate the effectiveness of *Nigella sativa* L. (*N. sativa*) extract on preventing the incidence of acute radiation dermatitis (ARD) in breast cancer patients.
Methods: Sixty-two breast cancer patients undergoing radiotherapy (RT) were randomly assigned to receive*N. sativa* 5% gel or placebo. Patients were instructed to apply the medications twice daily during RT period. The severity of ARD, the incidence of moist desquamation, worst experienced pain, and skin-related quality of life (SRQOL) scores were assessed weekly during RT.
Results: Patients who were treated with the *N. sativa* gel developed ARD significantly less frequently compared to those who used the placebo ($p < 0.05$ for all weeks except week 2, $p = 0.36$). The incidence time of grade 2 and 3 of Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) toxicity was prolonged significantly with *N. sativa* gel as compared to placebo (35 vs. 29 days, $p = 0.00$ and 42 vs. 40 days, $p = 0.01$, respectively). Furthermore, the occurrence of moist desquamation was delayed in the *N. sativa* gel group compared with the placebo group (37 vs. 33 days, $p = 0.01$). The mean score of the worst pain that patients experienced in the placebo group was significantly higher than that of the *N. sativa* gel group at week 3 (2.5 ± 0.5 vs. 1.2 ± 0.3, $p < 0.05$). Nonetheless, the application of *N. sativa* gel had no significant effect on the SRQOL of patients at any week.
Conclusion: *N. sativa* extract significantly decreases the severity of ARD and delays the onset of moist desquamation in breast cancer patients.

1. Introduction

Adjuvant radiotherapy (RT) is a fundamental treatment for breast cancer patients. It has been demonstrated to diminish local recurrence risk and have a beneficial effect on patient survival.[1] Acute radiation dermatitis (ARD) is the most frequently reported adverse effect of breast RT.[2] ARD is a general term describing a wide spectrum of cutaneous reactions which may vary considerably in severity, course, and prognosis.[3] Mild dermatitis, the first clinically apparent skin change, presents with follicular or dull erythema and dry desquamation accompanied by edema, pruritus, pain, and hyperpigmentation. Moderate dermatitis is characterized by persistent tender or bright erythema with moderate edema and may lead to moist desquamation in skin folds. Severe dermatitis manifests as confluent moist desquamation and pitting edema that may progress to ulceration with deep necrosis and secondary infections.[4,5]

Abbreviations: N. sativa, *Nigella sativa* L; ARD, acute radiation dermatitis; RT, radiotherapy; TQ, thymoquinone; TCs, topical corticosteroids; HPLC, high-performance liquid chromatography; MASCC, Multinational Association of Supportive Care in Cancer; RTOG/EORTC, Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer; DLQI, Dermatology Life Quality Index; SPSS, statistical package for the social sciences

* Corresponding author at: Department of Clinical Pharmacy, Faculty of Pharmacy, Mazandaran University of Medical Sciences, Km 18 Khazarabad Road, Sari, Mazandaran, Iran.
E-mail address: m.maham@mazums.ac.ir (M. Maham).

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ARD typically begins within 1–4 weeks following the initiation of breast RT and persists across the course of treatment.[6] The higher incidence of ARD in breast cancer patients is caused by the proximity of the RT target to the skin and failure to preserve it from a high dose of irradiation.[7] The occurrence of ARD can impair a patient's daily physical functioning and has a profound impact on the skin-related quality of life. It may also be the determinant of RT interruption or cessation, which could negatively influence cancer treatment.[2] Therefore, the prevention of ARD is a crucial priority in breast RT.[8]

Despite the existence of various topical agents used for the prevention of ARD in clinical practice, guidelines do not support their use.[2,9] Currently, topical corticosteroids (TCs) are the only prophylactic agents that have been suggested with ample evidence.[10] Concerns about adverse reactions from prolonged use of TCs affirm the need for further investigations into more effective, less toxic agents.[11]

Nigella sativa L. (*N. sativa*), commonly known as black cumin, is a medicinal plant that has a rich background in Persian complementary and alternative medicine.[12] *N. sativa* has been traditionally used as a remedy for fatigue improvement, chronic headache, fever, infection, inflammation, rheumatism, cough, bronchitis, asthma, cardiovascular, gastrointestinal, and metabolic disorders.[12] *N. sativa* oil has also been recommended as an ointment for external irritations, wounds, and different inflammatory dermatologic disorders.[13] Animal and clinical studies have demonstrated the anti-inflammatory, immunomodulatory, antioxidant, analgesic, and antimicrobial properties of *N. sativa*.[14,15] According to the published literature, the active component of *N. sativa* essential oil, thymoquinone (TQ), showed these biological properties.[16]

To the best of the authors' knowledge, no study to date has evaluated the effectiveness of *N. sativa* extract or TQ on ARD. Therefore, this study investigated the effectiveness of *N. sativa* extract in the prevention of ARD in breast cancer patients.

2. Material and methods

2.1. Nigella sativa extraction and phytochemical analysis

N. sativa seeds were purchased from a medicinal plant store in Sari, Iran and authenticated by the Herbarium of Pharmacognosy and Biotechnology Department of Mazandaran University of Medical Sciences (MAZUMS, Sari, Iran) with voucher number AE1-21-151. The seeds were cleaned, rinsed with distilled water, and dried until constant weight was achieved. The dried seeds were then pulverized and passed through a 2-mm (10-mesh) sieve. The resulting homogenous powder was macerated in a methanol (Merck, Germany) and water (80:20 v:v) mixture for 48 h (1:15 w/v); afterwards, the hydroalcoholic extract of *N. sativa* was filtered through filter paper (Whatman®, UK), and solvents were removed using a rotary evaporator (Heidolph, Germany).

The *N. sativa* extract was standardized based on TQ, using a validated HPLC method with minor modifications.[17] In brief, TQ quantification was conducted using Knauer HPLC apparatus coupled with a UV/vis detector (Knauer, Germany). A mobile phase of acetonitrile (Merck, Germany) and water (50:50 v:v) was pumped through a reversed-phase C18 analytical column (Eurospher II, Knauer, Germany) at a flow rate of 1.0 mL/minute. UV detection was carried out at 254 nm. The TQ content in *N. sativa* extract was expressed as percentage of gram of TQ per gram of *N. sativa* extract (%w:w).

2.2. Nigella sativa gel preparation

Different gelling agents at various concentrations were used for the preparation of *N. sativa* gel. The best formulation consisted of 5% *N. sativa* dried extract (w/w), 5% glycerol (Scharlau, Spain), 1% polyacrylic acid (Carbopol®940, BF Goodrich, USA), 0.09% triethanolamine (Scharlau, Spain), 0.18% methylparaben, and 0.02% propylparaben (Merck, Germany) made up to 100% with distilled water. The *N. sativa* gel was processed through several steps. First, the *N. sativa* extract was added to glycerol and stirred vigorously. Then, Carbopol® was dispersed in preserved water and kept aside to swell and subsequently homogenized using a double-bladed mixer (IKA, Germany) at 400 rpm for one hour. Finally, the extract mixture was added to polymer dispersion under constant mixing at 600 rpm for 15 min. After that, triethanolamine was added until a gel was formed. The placebo gel, containing all of the aforementioned ingredients except the *N. sativa* extract, was prepared in the same manner. The final formulation of both gels were evaluated for physical stability and controlled for microbial limitations according to the United States Pharmacopeia.[18] Both gels were supplied by the Pharmaceutics Department of MAZUMS (Sari, Iran) and dispensed in identical tube containers (each tube containing 50 g of gel) labeled with the randomization code, study protocol directions, and storage conditions. The TQ content in *N. sativa* gel was expressed as percentage of gram of TQ per gram of *N. sativa* gel (%w:w).

2.3. Participants

Eligible patients were adult females (age ≥18 years) with a histologically confirmed diagnosis of localized invasive breast carcinoma, who were scheduled to receive adjuvant RT (minimum total prescribed dose, 50 Gy) after breast surgery (breast conserving surgery or mastectomy). Patients with a prior history of RT to the treatment field, concurrent chemotherapy with RT (trastuzumab and hormonal therapy were allowed), inflammatory or metastatic breast carcinoma, generalized skin disorders, connective tissue disorders, or those who had a known allergy or hypersensitivity to *N. sativa* or any ingredients of the gel were excluded from the study.

2.4. Study design

This randomized, double-blinded, placebo-controlled clinical trial was conducted in the Radiotherapy Department of Imam Khomeini Hospital affiliated with MAZUMS (Sari, Iran) from June to September 2018. The study protocol was approved by the Ethics Committee of MAZUMS (IR.MAZUMS.REC.1397.1731) and registered in the Iranian Registry of Clinical Trials (IRCT20090813002342N7). All participants provided written informed consent before enrolling in the study.

Eligible participants were randomly allocated to receive the *N. sativa* gel or the placebo using a computer-generated random number list prepared by an investigator without any clinical involvement. The patient, the researcher, and the radiation-oncologist were not aware of the patients' allocated gel. The patients were advised to apply a thin layer of their allocated gel on the area of skin being irradiated twice a day at least two hours before and after RT. After applying the gel, patients were asked to wait for at least 10 min before dressing and not to wash the affected area for at least 2 h. All applications of the gels started on Day 1 of RT and continued until the end of RT.

During RT, patients were reminded to adhere to the skin-care recommendations of the clinical practice guidelines for the prevention of acute radiation reactions from the MASCC Skin Toxicity Study Group (e.g., gently washing the affected skin with water, with or without a mild soap; avoiding any scrubbing of the skin while washing and drying; and wearing soft, loose-fitting, cotton clothing).[9] Patients were also apprised not to use any other topical agents during the study period. To increase adherence during the study, all patients were regularly receiving face-to-face interviews and treatment reminder short messages on their cell phones. In the matter of confluent moist desquamation, the application of either the *N. sativa* gel or the placebo was stopped and appropriate wound care products were prescribed.

2.5. Radiation therapy technique

The RT protocol was planned with a treatment planning system (Core plan software, version 2010, Korea) after computed tomography scans of the patient were taken. The RT protocol of lymph node-

Table 1
Fitzpatrick skin phototype classification.

Skin phototype	Score	Overall skin phototype description
I	0-6	Always burns, never tans (pale white skin)
II	7-13	Always burns easily, tans minimally (white skin)
III	14-20	Burns moderately, tans uniformly (light brown skin)
IV	21-27	Burns minimally, always tans well (moderate brown skin)
V	28-34	Rarely burns, tans profusely (dark brown skin)
VI	≥35	Never burns (deeply pigmented dark brown to black skin)

Adapted from Ref. 19.

negative patients was 42.56 Gy/16FR (hypofractionated RT) five times a week and of lymph node-positive or mastectomy patients was 50 Gy/25FR (conventional RT) five times a week. Photons were used for RT (Linac Simens Primus Dual, Germany). Based on the patient's age and pathological findings, an electron or photon boost was utilized (10 Gy/4 or 5FR) in the last week of RT.

2.6. Assessment

Patients' skin phototypes were determined at baseline using the Fitzpatrick skin phototype scale (Table 1).[19] Patients were evaluated weekly after every fifth RT session for ARD severity, moist desquamation, and worst experienced pain. ARD severity was scored using the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria based on the clinical presentation (Table 2).[5] The size and severity of moist desquamation were assessed by the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) criteria based on the clinical presentation (Table 2).[20] The worst experienced pain was evaluated using a visual analog scale. The skin-related quality of life of the patients was appraised using the Dermatology Life Quality Index (DLQI).[21]The patients were requested to biweekly complete the DLQI form considering their feelings during the prior two weeks. To assess participants' adherence, they were requested to bring their tubes at each weekly visit to determine the remaining amount of gel. They were considered to be adherent to their treatment if they applied one tube (50 g) of *N. sativa* gel or placebo at the end of the second week.

2.7. Sample size, study end points, and statistical analysis

The sample size was determined to be at least 26 in each group considering a type one error (α) = 0.05 and a power of 80%.[22] Thirty-one women were included in each group to cover potential loss to follow-up or withdrawal. The primary endpoint was to determine whether the *N. sativa* gel could reduce the incidence of ARD in comparison with the placebo. The secondary outcomes were to assess if *N. sativa* gel delayed the onset of ARD, reduced RT-induced symptoms such as pain and moist desquamation, or improved the skin-related quality of life compared with the placebo.

The Intention-to-treat (ITT) approach was carried out for analysis of the study. Results with a p-value < 0.05 were considered statistically significant. To evaluate differences between groups, the independent samples t-test or the Mann-Whitney U test was applied for continuous variables, and the Chi-Square test or Fisher exact test was applied for categorical variables. The Kaplan-Meier method with the Log-Rank test was used to estimate the time of occurrence of specified skin toxicity. The generalized estimating equations (GEE) method was purposed to estimate the time-trend effect of the intervention and time-intervention interaction. All statistical analyses were performed by SPSS software version 23.0 (SPSS Inc., Chicago, IL, USA).

Table 2
Acute radiation dermatitis scoring criteria.

	Grade					
	0	1	2	3	4	5
Radiation dermatitis	No change over baseline	Follicular, faint or dull erythema /epilation /dry desquamation/decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis	
Skin ulceration (moist desquamation)	None	Combined area of ulcers < 1 cm; nonblanchable erythema of intact skin with associated warmth or edema	Combined area of ulcers 1 - 2 cm; partial thickness skin loss involving skin or subcutaneous fat	Combined area of ulcers > 2 cm; full-thickness skin loss involving damage to or necrosis of subcutaneous tissue that may extend down to fascia	Any size ulcer with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures with or without full thickness skin loss	Death

Adapted from Ref. 5 Adapted from Ref 20.

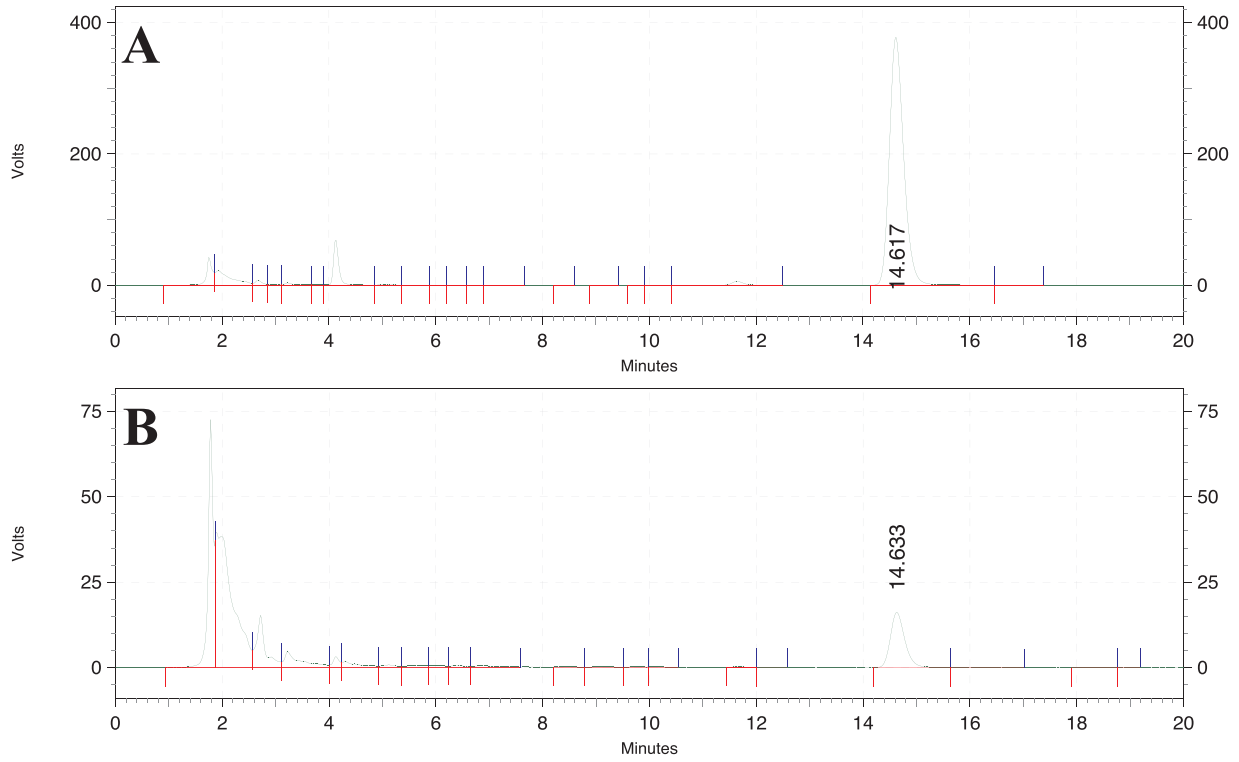

Fig. 1. HPLC/UV chromatogram at λ 254 (A) Thymoquinone standard (50mcg/ml), (B) Nigella sativa extract.

3. Results

3.1. Determination of thymoquinone

The HPLC analysis of the *N. sativa* extract (extraction yield: 14.21%) demonstrated a retention time of 14.6 min for TQ (Fig. 1). The TQ content of the *N. sativa* extract and of the *N. sativa* gel was 0.23% and 0.01% w:w, respectively.

3.2. Patients' characteristics

A total of 62 patients were recruited and randomized into two interventions in the current study. Of these 62 patients, five patients withdrew from the study, and 57 patients completed it. A CONSORT flow diagram of the study is presented in Fig. 2.[23] There were no significant differences between the study groups based on patients' baseline and treatment characteristics (Table 3).

The mean age of patients was approximately 51 years. The majority of patients were overweight, with a mean BMI of 29.5 kg/m^2. Most of the study population received chemotherapy (87.1%). Almost one fourth (22.6%) of the patients had concurrent hormonal therapy. The common RT protocol was conventional RT (82.3%) with boost (88.7%). All patients were adherent to *N. sativa* gel or placebo during the study. The *N. sativa* gel was well tolerated, and no adverse effects were reported by any patient in either group.

3.3. Skin toxicity

3.3.1. Incidence of skin toxicity

The analysis of the skin toxicity grade by RTOG/EORTC toxicity scores demonstrated a significant difference between the *N. sativa* gel group and the placebo group in all weeks except week 2 (all other weeks had $p < 0.05$, but week 2 had $p = 0.36$). Patients treated with the *N. sativa* gel had a significantly lower percentage of incidence of skin toxicity (RTOG/EORTC toxicity grade ≥ 2) at weeks 3, 4, and 5 ($p = 0.03$, 0.00, and 0.05, respectively; Fig. 3) and incidence of skin toxicity (RTOG/EORTC toxicity grade = 3) at week 6 ($p = 0.01$; Fig. 4).

When investigating the RTOG/EORTC toxicity scores based on weeks of RT, a significant difference was observed in the *N. sativa* gel group in comparison with the placebo group ($p = 0.00$). There was also a statistically significant time effect ($p = 0.00$), but the difference between the two groups in time*group interaction effect was not statistically significant ($p = 0.46$).

Additionally, there was a significant difference between the two groups in the size and severity of moist desquamation at weeks 5 and 6 ($p = 0.01$ and 0.01, respectively). This result indicated that the *N. sativa* gel decreased the size and severity of the moist desquamation as compared with the placebo. However, GEE analysis demonstrated that there were no statistically significant differences in group effect ($p = 0.62$) or time*group interaction effect ($p = 0.22$).

3.3.2. Time to incidence of skin toxicity

The Kaplan–Meier estimates indicated that the mean time for the incidence of skin toxicity (RTOG/EORTC toxicity grade 2) of the *N. sativa* gel group was approximately 35 days and for the placebo group was 29 days. However, the mean time for the incidence of skin toxicity (RTOG/EORTC toxicity grade 3) of the *N. sativa* gel group was approximately 42 days and for the placebo group was 40 days.

The Log-Rank test showed there was a statistically significant difference between the two groups for the incidence of RTOG/EORTC toxicity grades 2 and 3 ($p = 0.00$ and 0.00, respectively; Table 4). This indicated that the incidence of RTOG/EORTC toxicity grades 2 and 3 was delayed in the *N. sativa* gel group as compared with the placebo group.

Furthermore, the mean time of occurrence of moist desquamation for the *N. sativa* gel group was approximately 37 days and for the placebo group was 33 days. The Log-Rank test demonstrated that there was a statistically significant difference in the incidence of moist desquamation between the two groups ($p = 0.01$; Table 4). This indicated that there was a delay in the onset of moist desquamation in the *N. sativa* gel group as compared with the placebo group.

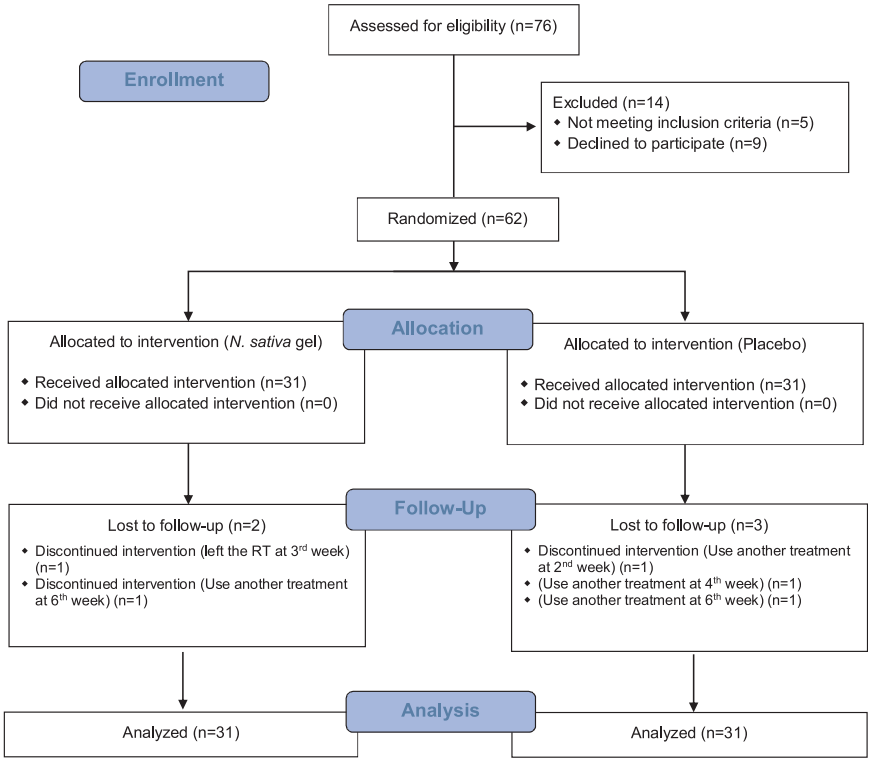

Fig. 2. CONSORT flow diagram.

3.4. Worst experienced pain

Comparisons of worst pain experienced over the past week revealed that the mean score of pain that patients treated with the placebo experienced was significantly higher than that of the *N. sativa* gel group at week 3 (2.5 ± 0.5 vs. 1.2 ± 0.3, $p < 0.05$; Fig. 5) but not at other weeks. The GEE analysis showed that the trend of changes in average pain experienced between groups was significant ($p = 0.00$). There was also a statistically significant time effect ($p = 0.03$). However, the time*group interaction effect was not significant ($p = 0.77$).

3.5. Skin-related quality of life

In terms of skin-related quality of life, there were no differences between the two groups at any week, with all $p > 0.05$ (Fig. 6).

4. Discussion

The present study is the first randomized, controlled clinical trial evaluating the effectiveness of *N. sativa* extract in the prevention of ADR in breast cancer patients receiving adjuvant RT. The results of this study have overall demonstrated that the *N. sativa* gel is superior to the placebo in the prevention of the incidence of ARD and related symptoms. Moreover, patients treated with *N. sativa* gel developed ARD and related symptoms significantly later in comparison with those patients treated with the placebo.

The reaction of the skin to RT is complex and has been related to numerous risk factors, patient-related, treatment-related, or both.[24] The initial fractionated dose of RT develops immediate skin cell damage through the production of free radicals, reactive nitrogen species (NOS), and reactive oxygen species (ROS) that attack cellular structures and produce irreversible double-stranded breaks in DNA. These primary cellular alterations activate different signaling pathways, including an inflammatory response, eventually leading to skin cell death or senescence.[25]

There is evidence that prophylactic use of anti-inflammatory agents can reduce the severity of ARD.[6] Several systematic reviews showed that TCs can be effective for the prevention of ARD. The prophylactic application of TCs can reduce the incidence of moist desquamation and lessen the mean ARD scores. The administration of TCs can also improve patient-reported quality of life and lower subjective symptoms (like pain, burning, and itching)[10,26]. Their anti-inflammatory properties, such as inhibiting leukocyte migration and reducing cytokines production (e. g. IFN-γ, TNF, interleukin1 (IL-1), IL-2, IL6, and histamine), are making TCs ideal for the prophylactic treatment of ARD.[6]

Nonetheless, the regular application of TCs on a large area of the treatment field skin for the prevention of ARD during RT could be associated with numerous side effects. The percutaneous absorption of TCs can produce side effects similar to those usually occurring with their systemic administration.[27]Topical side effects of TCs must also be considered, including atrophy and related changes (such as striae, easy bruising, ulceration, purpura, stellate pseudoscars, and telangiectasia), follicular, pigmentary, and vascular changes, infections, infestations, and miscellaneous others.[28] There are no precise clinical studies regarding the short-term and long-term effects of TCs in combination with RT on skin properties. Additionally, further research is required to determine which type of TC in respect to potency will be more effective in preventing ARD. Accordingly, current clinical practice guidelines do not support or refute the use of TCs for the prevention of ARD.[9]

Several clinical trials have shown that herbal-based topical agents derived from calendula, silymarin, and aloe vera are effective at preventing of ARD owing to their anti-inflammatory and antioxidant properties.[29]

The anti-inflammatory and antioxidant activity of *N. sativa* has been demonstrated in experimental and clinical evidence. Various molecular targets are involved in the anti-inflammatory activity of *N. sativa*, such as the down-regulation of 5-lipoxygenase, cyclooxygenase, and 5-hydroxyleicosa-tetra-enoic acid due to the inhibition of the formation of leukotriene B4 and thromboxane B2 metabolites, the suppression of TNFα, IL-6, and NO production, and the elevation of the IL-10 level.[14,15] The antioxidant activity of *N. sativa* may protect skin cells against RT-induced free radical damage by inhibiting superoxide

Table 3
Patients' baseline and treatment characteristics.

	All(62)	*Nigella sativa* gel (31)	Placebo(31)	*p* value
Clinical Characteristics				
Age				0.40
Mean (SD)	51.4(10.4)	50.2(10.7)	52.5(10.1)	
Tumor type				0.50
Invasive Ductal Carcinoma	50(80.6)	24(77.4)	26(83.9)	
Invasive Lobular Carcinoma	9(14.5)	6(19.4)	3(9.7)	
Medullary Carcinoma	3(4.8)	1(3.2)	2(6.5)	
Tumor size				0.69
Mean (SD)	25.6(14.3)	26.3(14.7)	24.8(14.0)	
Tumor grade				0.05
I	9(14.5)	5(16.1)	4(12.9)	
II	39(62.9)	23(74.2)	16(51.6)	
III	14(22.6)	3(9.7)	11(35.5)	
Surgical procedures				1.00
Breast Conserving Surgery	55(88.7)	28(90.3)	27(87.1)	
Mastectomy	7(11.3)	3(9.7)	4(12.9)	
Previous chemotherapy	54(87.1)	28(90.3)	25(83.9)	0.70
Concurrent hormonal therapy	14(22.6)	4(12.9)	10(32.3)	0.07
Skin type (Fitzpatrick scale)				0.44
II	9(14.5)	6(19.4)	3(9.7)	
III	27(43.5)	14(45.2)	13(41.9)	
IV	26(41.9)	11(35.5)	15(48.4)	
Body Mass Index (kg/m^2)				0.90
Mean (SD)	29.5(4.6)	29.6(5.1)	29.5(4.9)	
Brassiere cup size				0.88
Small	25(45.5)	13(46.4)	12(44.4)	
Large	30(54.5)	15(53.6)	15(55.6)	
Diabetes Mellitus	14(22.6)	4(12.9)	10(32.3)	0.07
Treatment Characteristics				
RT Technique				0.74
CRT	51(82.3)	26(83.9)	25(80.6)	
HRT	11(17.7)	5(16.1)	6(19.4)	
Dose (Gy)				0.60
Mean (SD)	55.8(7.0)	56.2(6.8)	55.3(8.2)	
Fractions				0.60
Mean (SD)	27.7(4.0)	27.9(3.9)	27.4(4.1)	
Boost applied	55(88.7)	28(90.3)	27(88.1)	1.00

Data are presented as number (percentages) unless otherwise noted. (*p*-values were calculated using *t*-test or Chi-square test).
Abbreviations: **CRT** Conventional radiotherapy, **HRT** Hypofractionated radiotherapy.

radical production and lipid peroxidation; it may also intensify the activity of antioxidant enzymes such as catalase, glutathione transferase, superoxide dismutase, and quinone reductase.[14] In addition to the known anti-inflammatory and antioxidant properties of *N. sativa*, data on its' radioprotective effect is limited. Ahlatci et al. demonstrated that the systemic administration of *N. sativa* oil and TQ decreases nitrosative damage in the brain tissue of irradiated rats.[30] Nur Orhon et al. showed that the intragastric administration of *N. sativa* might significantly reduce morphological changes due to the irradiation of jejunal mucosa in the rat.[31] Canakci et al. observed that the topical administration of *N. sativa* to the nasal mucosa is effective in preventing superficial erosion of the nasal mucositis due to RT.[32]

For the first time ever, the present study determined that *N. sativa* gel can significantly delay and decrease the incidence of ARD and its related symptoms in breast cancer patients receiving adjuvant RT compared with those receiving the placebo. In regard to ARD and moist desquamation, the findings of the present study are in agreement with the studies mentioned above. The results of this study support the radioprotective effect of *N. sativa* in breast cancer patients receiving adjuvant RT. Nevertheless, a large multicenter study is required to certify this novel concept for the prevention of ARD in breast cancer patients.

Some limitations of this study were the small number of patients, and lack of ARD measurement after RT completion. Another limitation of the current study was the lack of measurement of chemical constituents of *N. sativa* extract other than TQ that possess antioxidant and anti-inflammatory effects. According to several preclinical and clinical studies, TQ appears to be the main bioactive compound responsible for many of the *N. sativa* seed's antioxidant and anti-inflammatory activities.[14,15] However, the relatively low amount of TQ in the *N. sativa* essential oil is probably insufficient to account for the antioxidant and anti-inflammatory properties of *N. sativa*.[33]

Since the antioxidant and anti-inflammatory effects of some other constituents of *N. sativa* essential oil such as *p*-cymene, *t*-anethole, thymol, and carvone have been demonstrated in various studies, it seems that the antioxidant and anti-inflammatory effects of *N. sativa* extract can also be influenced remarkably by these compounds.[34–38] Therefore, the determination of these active constituents is recommended to achieve the *N. sativa* extract optimal dose to increase its efficacy in ARD prevention.

5. Conclusion

This randomized controlled clinical trial showed that the preventive use of the *N. sativa* gel significantly delayed and decreased the incidence of ARD and moist desquamation in breast cancer patients

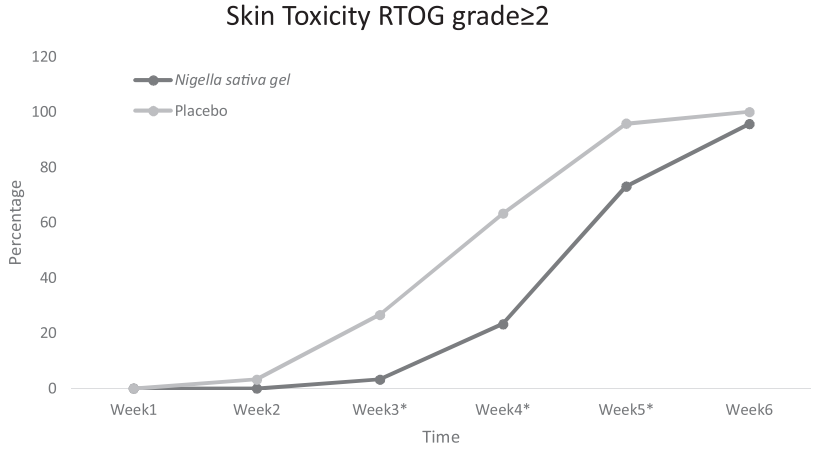

Fig. 3. Percentage of incidence of skin toxicity (RTOG/EORTC toxicity grade ≥ 2) by week and arm.
* Significant difference (p = 0.03, 0.00, and 0.05 at weeks 3, 4, and 5 respectively, Chi-square test).

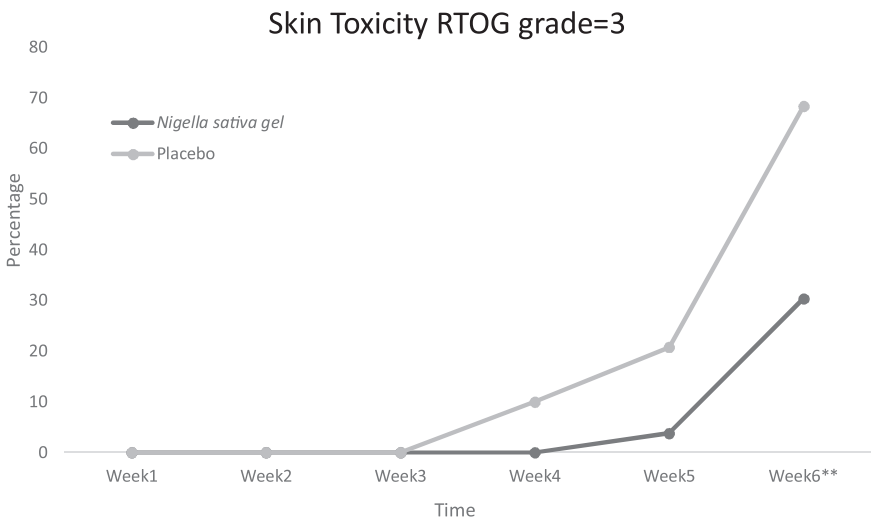

Fig. 4. Percentage of incidence of skin toxicity (RTOG/EORTC toxicity grade = 3) by week and arm.
** Significant difference (p = 0.01 at week 6, Chi-square test).

Table 4
Mean time for the incidence of skin toxicity (RTOG/EORTC toxicity grade 2 and 3) and occurrence of moist desquamation.

	Group	Mean time in days (95%CI)	p value
RTOG/EORTC toxicity = 2	*Nigella sativa* gel	34.7 (32.7-36.7)	0.00
	Placebo	28.7 (26.4-31.0)	
RTOG/EORTC toxicity = 3	*Nigella sativa* gel	41.7 (41.2-42.3)	0.00
	Placebo	40.0 (38.3-41.7)	
Moist desquamation	*Nigella sativa* gel	37.2 (34.9-39.5)	0.01
	Placebo	33.5 (31.4-35.6)	

Results were obtained from Log-Rank test.

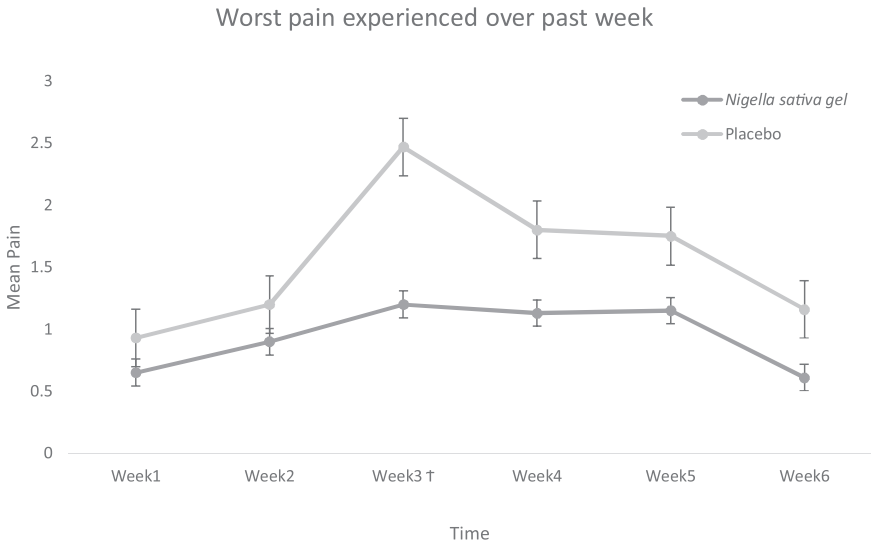

Fig. 5. Mean worst pain experienced over past week by week and arm.
† Significant difference (p < 0.05 at week 3, Mann-Whitney U test).

compared with those receiving the placebo.

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Ethical approval

The study protocol was approved by the Ethics Committee of MAZUMS (IR.MAZUMS.REC.1397.1731) and registered in the Iranian Registry of Clinical Trials (IRCT20090813002342N7).

Declaration of Competing Interest

The authors declare that they have no relevant competing interests.

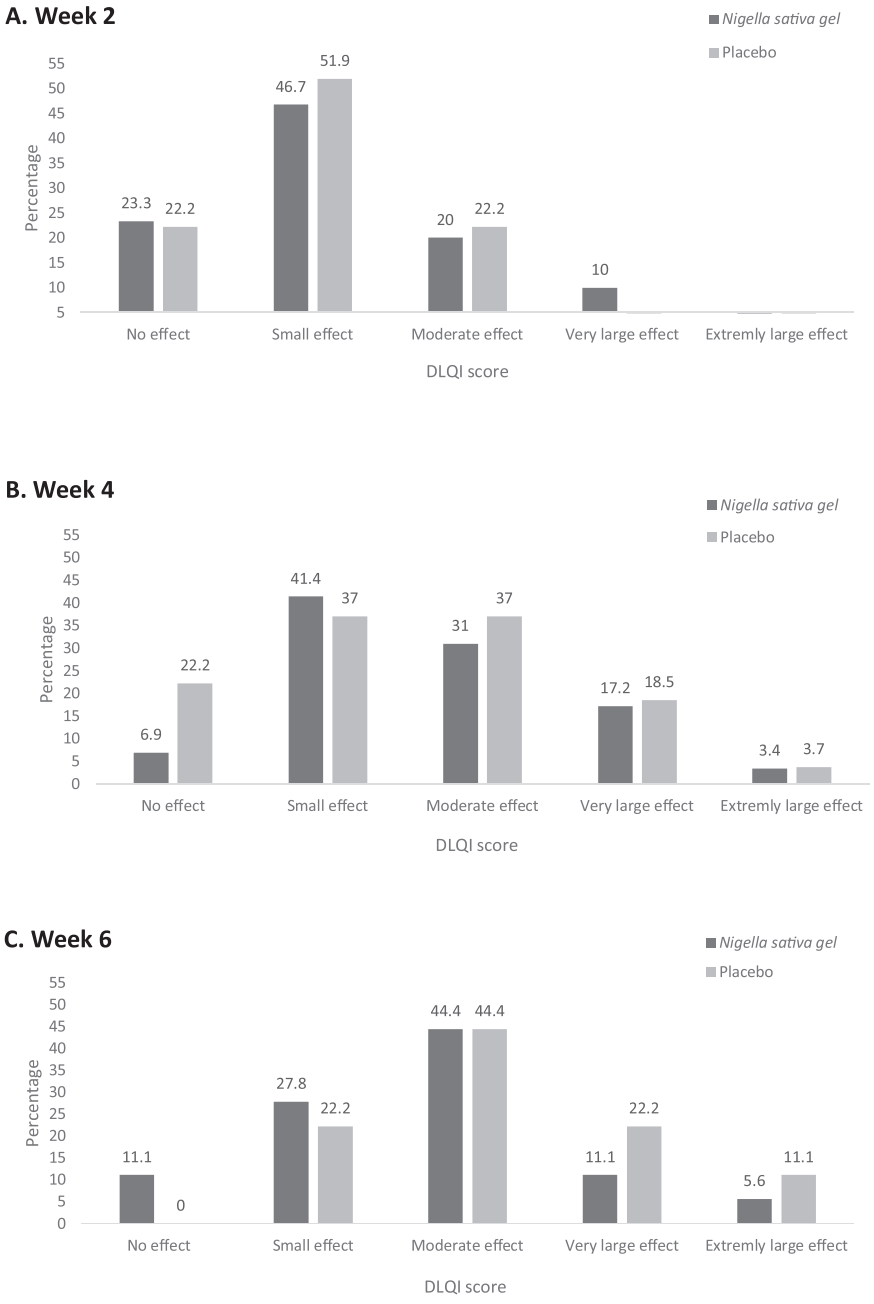

Fig. 6. Skin-related quality of life by treatment group week 2 (A), week 4 (B) and week 6 (C).
There were no differences between the two groups at any week (all $p > 0.05$, Chi-square test).

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