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# Prophylaxis of Radiation-Induced Dermatitis in Patients With Breast Cancer Using Herbal Creams: A Prospective Randomized Controlled Trial

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## Abstract

Radiation-induced toxicity is a major limiting factor for prescribing radiation dose in cancer radiotherapy. Skin reaction to radiation is one of the primary concerns, which could affect quality of life of the patients both physically and mentally. Reviews of the literature show limited number of effective reagents for its prophylaxis. In this study, we attempted to determine whether prophylactic treatment of the 3 different herbal creams containing *Centella asiatica*, *Cucumis sativus*, and *Thunbergia laurifolia* extracts as well as a commercial moisturizing cream could reduce acute skin reaction in breast cancer patients undergoing radiotherapy. A total of 153 breast cancer patients undergoing radiotherapy were randomly assigned into 5 different groups with one group receiving no treatment. The patients were instructed to apply their designated creams once daily from their first radiotherapy session until 1-month post-irradiation. Their skins were graded by a radiation oncologist on a weekly basis until 1-month post-irradiation to identify any skin reactions. The results showed that the administration of the herbal creams or the moisturizing cream could neither reduce the severity nor delay the onset of dermatitis compared with the no treatment group. However, despite the limited benefits from the prophylaxis, the *Cucumis sativus* cream was shown to help with the skin recovery post-irradiation. These results suggested that breast cancer patients undergoing radiotherapy should be advised to apply moisturizing cream to the area of irradiated skin.

## Keywords

radiodermatitis, prophylaxis, radiation toxicity, natural product, herbal extract

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## Introduction

During radiotherapy process, radiation exposure to skin is inevitable. A certain amount of radiation dose is absorbed to the skin and could cause acute skin damage and reaction. The degree of toxicity depends on various factors, including radiation dose and fractionation, location and area of exposed skin, and radiosensitivity of patient. Approximately 85% of patients undergoing radiation therapy will experience noticeable skin reactions.[1] Radiation-induced skin toxicity includes several symptoms and could be categorized into different grading scales, based on the Radiation Therapy Oncology Group, from mild erythema and dry desquamation to confluent moist and ulceration. Skin toxicity could not only physically afflict the patient but also affect the patient's appearance and self-confidence, which may subsequently lead to lowered quality of life. Reactive treatment strategy, once skin reaction has occurred, may not

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be the best option.[2] Therefore, prophylactic treatment is preferred for both delaying the onset and reducing the severity of the skin reactions. This could potentially improve patient adherence to cancer treatments as well as maintain overall quality of life.

Currently, there are no standard guidelines for practice in order to prevent or lower the frequency of radiation-induced skin reaction. However, a number of reports have attempted to identify reagents, treatments, or interventions that could prevent such skin toxicities. Reviews of the literature show no significant evidence to support any particular agent for prevention and management of radiation-induced skin toxicities mostly due to variation in practice.[1,3] Neither are any recommended products based on evidence-based practice, nor is the efficacy of radiodermatitis prevention or treatment of these products reliable.[4,5] It was previously suggested that moist skin care using urea cream was effective in reducing severity of acute skin reactions.[6] Additionally, recent reports have suggested topical uses of steroids, calendula, *Hypericum perforatum*, and neem oil for the management of acute radiodermatitis.[7,8] In this study, we selected 3 different moisturizing herbal extract creams to further identify whether these herbs, based on their known properties in traditional medicine and availability of access in the market, could be beneficial for reducing radiation-induced skin toxicity. A commonly used moisturizing cream has been included as the control to assess the herbs' prophylactic property.

*Centella asiatica* (Asiatic pennywort) is known for its wide range for treatments of diseases and is recommended as a medicine for wound healing and skin conditions such as leprosy.[9] The main constituents of *C asiatica* are pentacyclic triterpenes, which promote fibroblast proliferation, as well as collagen synthesis. Thus, the plant has been involved in cosmetic products for skin care.[10] *Cucumis sativus* (cucumber) has a very high water content and soothing property against skin irritation and swelling. The fruit has also been used to relieve sunburn.[11] Likewise, *Thunbergia laurifolia* Lindl (laurel clockvine) has been shown to accelerate healing rate in burn wounds and its constituent, rosmarinic acid, also has antinociceptive and anti-inflammatory effects.[12,13] Due to the therapeutic potentials for skin symptoms of these 3 plants, we decided to test their efficacy in prophylactic treatment for preventing and reducing severity of radiation-induced skin reaction.

## Materials and Methods

### *Patient Selection and Allocation*

Patients undergoing radiotherapy for breast cancer at the Department of Radiation Oncology, Chulabhorn Hospital, during 2016 to 2018, for either curative or palliative purpose with the total physical doses between 40 and 50 Gy, with an optional boosted dose of 10 or 16 Gy, were included in the study. A total of 153 patients were randomized into 5 different groups designating different skin products for prevention of skin reactions and dermatitis. The first group was the standard care, which received only instructions of care but no cream for any treatment (no treatment). The second group received a commercialized nonfragrant moisturizing cream (control). The third group received the *C asiatica* extract cream (7% weight/weight [w/w]). The fourth group received the *C sativus* (cucumber) extract cream (20% w/w), and the last group received *T laurifolia* extract cream (5% w/w). The patients in the latter 4 groups were instructed to apply their designated creams once daily, preferentially after bath at night. The patients were given their designated creams to be used from their first irradiation until 1 month after their last radiotherapy session. The patients were blinded regarding which cream they had received. This study was a parallel study with equal randomization ratio between groups.

The inclusion criteria for the patients were female, aged between 20 and 80 years, diagnosed with breast cancer, and required radiotherapy for their treatments. The exclusion criteria include being pregnant, previously underwent radiotherapy for breast cancer, or being illiterate.

The sample size was calculated based on the sample size of the study by Momm et al,[6] which showed that 3% urea cream could reduce grade III radiation-induced dermatitis from 56% to 22% ($P = .0007$), having 25 patients in the control group and 63 in the experimental group. Using STATA/SE 12 (StataCorp LP, College Station, TX) to calculate the sample size for 2-sample comparison of proportions yielded a sample of size of 30 in each group, a total of 150 for 5 different groups.

The patients were randomized in the 5 different groups using block randomization method with a block of 4 subjects. A randomization sequence, with designated color codes for corresponding treatment groups, was generated from a statistician who did not involve in the study. Following the sequence, the radiation oncology nurses at the study site were responsible for designating the patients into each block. The patients were asked to participate in the study, inquired for their informed consents, and given the color codes of the study groups they were assigned to. Additionally, the products used in the study were prepared from the manufacturer with the exact color codes. The nurses were uninformed regarding which color corresponded to which product.

This study was approved by the Committee on Human Rights Related to Research Involving Human Subjects, Chulabhorn Research Institute (Reference Number 005/2559). This study was registered with ClinicalTrials.gov Identifier Number NCT02922244 under the study title of "Effects of Herbal Products on Reduction of Radiation-induced Dermatitis in Breast Cancer Patients." All the participants had provided informed consents prior to participating in the study.

### Herbal Creams

The herbal creams used in the study were manufactured by Chaopraya Abhaibhubejhr Hospital, GMP (Good Manufacturing Practice) Certificate Number 1-2-08-17-16-00006. The herbal creams contained no fragrant and had been commercialized for skin care purposes. The proportions of the herbal extracts in the creams were *C asiatica* 7% (w/w), *C sativus* 20% (w/w), and *T laurifolia* Lindl 5% (w/w). The moisturizing cream was a commercialized product of Johnson & Johnson containing no fragrance. All the tested creams were registered with Thai Food and Drug Administration for external use.

### Allergy Test

Prior to being enrolled in the study, the subjects were questioned whether they were allergic to any of the plants or the moisturizing cream. The subjects were asked to apply their designated cream on the back of their ear and reported any signs of allergy within 24 hours. Allergic subjects were not included in the study.

### Skin Grading

Radiation-induced dermatitis grade was assessed on a weekly basis until the end of the radiotherapy course and at 1-month follow-up by a radiation oncologist following the toxicity criteria of the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer.[14] The radiation oncologists who graded the skin were blinded regarding which creams the patients had received.

### Patient Satisfaction

Due to slight differences in texture and thickness of the creams, the subjects were surveyed, toward the end of their treatments, for their satisfaction regarding their designated creams. A scale of 1 to 5 was used for their satisfactory with 5 being mostly satisfied and 1 being least.

### Statistical Analyses

Data were analyzed using 1-way analysis of variance, exact probability, Kruskal-Wallis, and log-rank tests, as indicated in each Table and Figure. All statistical analyses were performed using STATA/SE 12. $P$ value $<.05$ was considered significant.

## Results

A total of 153 patients were enrolled in the study after 200 were assessed for eligibility; 20 of them declined to participate and 27 of them did not meet the inclusion criteria. As shown in the CONSORT (Consolidated Standards of Reporting Trials) diagram (Figure 1), the patients were randomized into 5 different groups following the block randomization method. All patients received their allocated treatments; however, one patient in the moisturizing cream group and 2 patients in the cucumber cream group decided to cease their treatments. The remaining 150 patients, 30 in each group, completed their prophylactic treatments until 1 month after their final radiation therapy session.

The demographic data of enrolled subjects showed that the patients with breast cancer had an average age of 55.7 years as they were randomized into each group having a similar age ($P = .707$). Slightly more patients had tumors on their right breast, with 3 of them required radiation therapy on both breasts. Patients with breast cancer staged IIA were the majority who enrolled in this study. The patients with underlying diseases were distributed relatively evenly across the groups ($P = .751$), as presented in Table 1. Concerning the radiation treatment, based on Table 2, more patients were irradiated using intensity-modulated radiation therapy field-in-field technique followed by 3-dimensional planning technique. Most patients received a total dose of 50 Gy in 25 fractions (2 Gy per fraction). Bolus placement was achieved in half of the patients with 38% of them required boosting doses of radiation. This might not have affected the patients, as a previous report indicated that bolus placement had no significant effect on skin reaction.[15] Although the boosting techniques were different among the groups, most patients received an extra 10 Gy of electron in 5 fractions for their radiation boosts. The statistical analyses showed no significant differences among the groups except that the boosting irradiation was mainly achieved by electron irradiation mostly for the no treatment group ($P = .043$).

Concerning the different radiation doses and fractionations provided to the patients, between 40 and 50 Gy, which could causes diverse degree of dermatitis, as shown in Table 2, the numbers of patients receiving hypofractionated and standard irradiation were similar across all the groups, with 26 to 28 patients receiving 50 Gy (2 Gy, 25 fractions) for all groups ($P = .563$). Radiation doses between 40and 50 Gy (hypofractionated vs standard regimen) were demonstrated in previous studies not to yield significant difference in cosmesis to the skin.[16,17] Therefore, we believe that the dose variation did not significantly affect our dermatitis outcomes among the groups.

In addition to radiation therapy, most patients also received other treatments, including adjuvant and neoadjuvant chemotherapy. More patients received adjuvant chemotherapy; however, chemotherapy was not significantly different among the treatment groups ($P = .569$). As we followed the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for breast cancer,

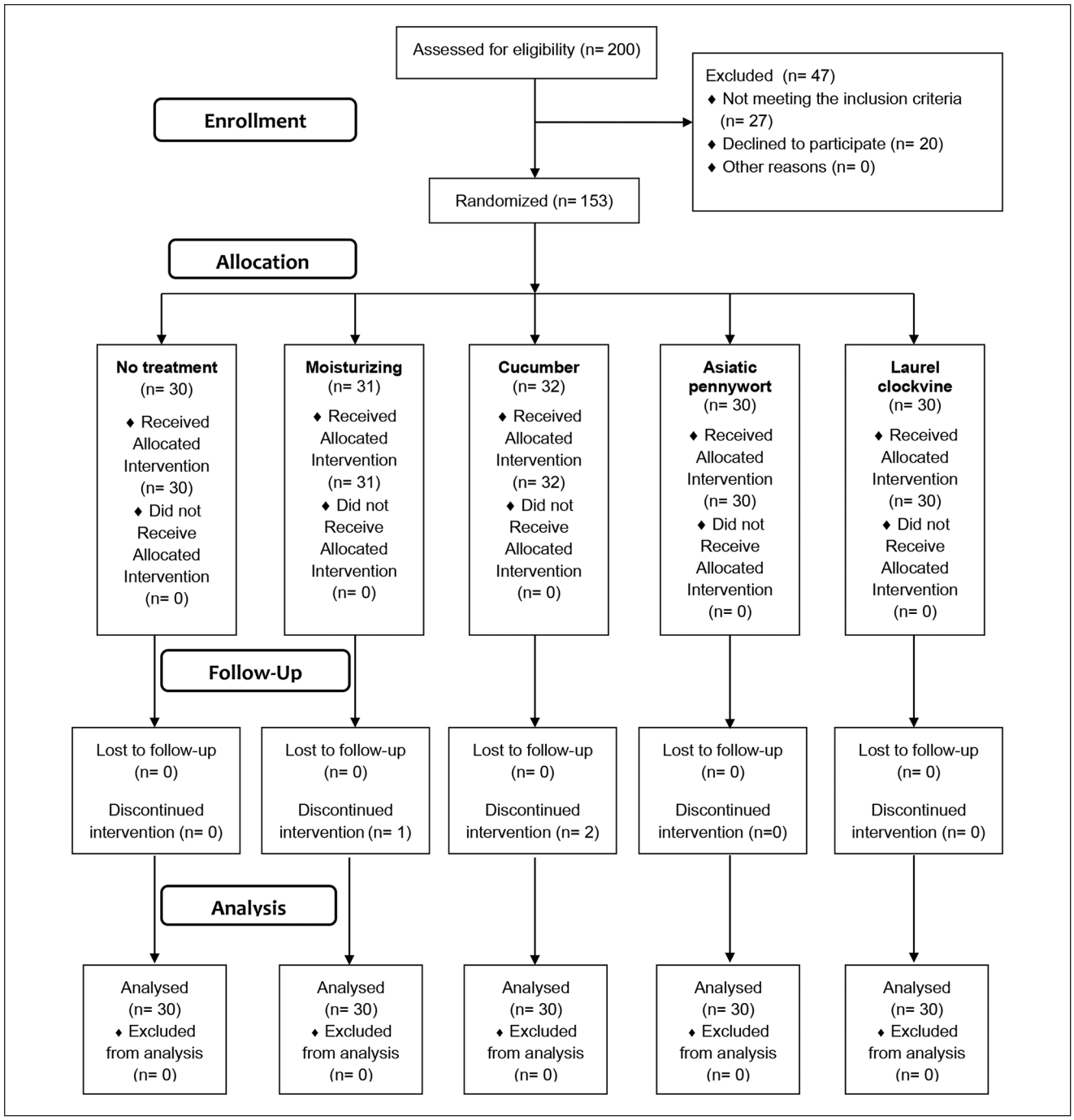


**Figure 1.** CONSORT (Consolidated Standards of Reporting Trials) diagram of the study showing the number of patients assessed for eligibility, randomized, and follow-up including the data analyzed.

none of the patients received concurrent chemoradiation therapy; thus, we assumed that adjuvant or neoadjuvant chemotherapy might not play a significant role on dermatitis during radiotherapy.

More patients received mastectomy, prior to being treated with radiation, than lumpectomy for their tumor mass; yet, the treatment was not significantly different among the treatment groups ($P = .569$). The patients also received different hormone, as listed in Table 3, as well as other medication including Herceptin for therapy; however, the statistical analysis also showed no significant outcomes. Neither concomitant tamoxifen or letrozole with radiation

**Table 1.** Demographic Data of the Patients.[a]

| Variable | Total, n (%) | No Treatment, n (%) | Control, n (%) | *Centella asiatica*, n (%) | *Cucumis sativus*, n (%) | *Thunbergia laurifolia*, n (%) | *P* |
|---|---|---|---|---|---|---|---|
| **Age**[b] | 55.7 ± 10.7 | 53.4 ± 13.2 | 56.8 ± 9.4 | 56.7 ± 11.4 | 55.1 ± 9.0 | 56.5 ± 10.4 | .707 |
| **Breast tumor (side)** | | | | | | | .775 |
| **Both** | 3 (2.0) | 0 | 1 (3.33) | 1 (3.33) | 1 (3.33) | 0 | |
| **Left** | 70 (46.67) | 13 (43.33) | 14 (46.67) | 13 (43.33) | 12 (40.0) | 18 (60.0) | |
| **Right** | 77 (51.33) | 17 (56.67) | 15 (50.0) | 16 (53.33) | 17 (56.67) | 12 (40.0) | |
| **Underlying disease** | | | | | | | .751 |
| **No** | 78 (52.0) | 15 (50.0) | 13 (43.33) | 17 (56.67) | 15 (50.0) | 18 (60.0) | |
| **Yes** | 72 (48.0) | 15 (50.0) | 17 (56.67) | 13 (43.33) | 15 (50.0) | 12 (40.0) | |
| **Stage** | | | | | | | .752 |
| **0** | 10 (6.67) | 2 (6.67) | 2 (6.67) | 2 (6.67) | 3 (10.0) | 1 (3.33) | |
| **I** | 2 (1.33) | 0 | 2 (6.67) | 0 | 0 | 0 | |
| **IA** | 25 (16.67) | 5 (16.67) | 4 (13.33) | 7 (23.33) | 4 (13.33) | 5 (16.67) | |
| **IIA** | 30 (20.0) | 7 (23.33) | 6 (20.0) | 2 (6.67) | 8 (26.67) | 7 (23.33) | |
| **IIB** | 26 (17.33) | 5 (16.67) | 7 (23.33) | 1 (3.33) | 5 (16.67) | 8 (26.67) | |
| **IIIA** | 25 (16.67) | 5 (16.67) | 4 (13.33) | 7 (23.33) | 4 (13.33) | 5 (16.67) | |
| **IIIB** | 14 (9.33) | 2 (6.67) | 3 (10.0) | 5 (16.67) | 2 (6.67) | 2 (6.67) | |
| **IIIC** | 16 (10.67) | 3 (10.0) | 2 (6.67) | 5 (16.67) | 4 (13.33) | 2 (6.67) | |
| **IV** | 2 (1.33) | 1 (3.33) | 0 | 1 (3.33) | 0 | 0 | |

[a]Exact probability test, one-way analysis of variance.
[b]Ages of the patients are shown as mean ± standard deviation.

**Table 2.** Numbers of Patients Who Underwent Different Radiation Treatment Delivery Schemes.[a]

| Variable | Total, n (%) | No Treatment, n (%) | Control, n (%) | *Centella asiatica*, n (%) | *Cucumis sativus*, n (%) | *Thunbergia laurifolia*, n (%) | *P* |
|---|---|---|---|---|---|---|---|
| ***Radiation delivery technique*** | | | | | | | .907 |
| **3D** | 51 (34.0) | 12 (40.0) | 10 (33.3) | 11 (36.7) | 10 (33.3) | 8 (26.7) | |
| **IMRT** | 2 (1.3) | 1 (3.3) | 1 (3.3) | 0 | 0 | 0 | |
| **IMRT (FIF)** | 87 (58.0) | 16 (53.3) | 16 (53.3) | 17 (56.7) | 17 (56.7) | 21 (70.0) | |
| **3D + IMRT** | 10 (6.7) | 1 (3.3) | 3 (10.0) | 2 (6.7) | 3 (10.0) | 1 (3.3) | |
| **Main** | | | | | | | .563 |
| **40 Gy/15 Fr** | 1 (0.7) | 1 (3.3) | 0 | 0 | 0 | 0 | |
| **42.4 Gy/16 Fr** | 1 (0.7) | 0 | 0 | 1 (3.3) | 0 | 0 | |
| **42.5 Gy/16 Fr** | 1 (0.7) | 1 (3.3) | 0 | 0 | 0 | 0 | |
| **42.5 Gy/25 Fr** | 4 (2.7) | 0 | 1 (3.3) | 1 (3.3) | 1 (3.3) | 1 (3.3) | |
| **42.56 Gy/16 Fr** | 6 (4.0) | 2 (6.7) | 0 | 1 (3.3) | 3 (10.0) | 0 | |
| **45.22 Gy/17 Fr** | 1 (0.7) | 0 | 0 | 0 | 0 | 1 (3.3) | |
| **48 Gy/24 Fr** | 1 (0.7) | 0 | 1 (3.3) | 0 | 0 | 0 | |
| **50 Gy/25 Fr** | 135 (90.0) | 26 (86.7) | 28 (93.3) | 27 (90.0) | 26 (86.7) | 28 (93.3) | |
| **Bolus** | | | | | | | .196 |
| **No** | 75 (50.0) | 20 (67.7) | 13 (43.3) | 17 (56.7) | 12 (40.0) | 13 (43.3) | |
| **Yes** | 75 (50.0) | 10 (33.3) | 17 (56.7) | 13 (43.3) | 18 (60.0) | 17 (56.7) | |
| **Boost** | | | | | | | .238 |
| **No** | 93 (62.0) | 13 (43.3) | 20 (66.7) | 20 (66.7) | 19 (63.3) | 21 (70.0) | |
| **Yes** | 57 (38.0) | 17 (56.7) | 10 (33.3) | 10 (33.3) | 11 (36.7) | 9 (30.0) | |
| **Boosting technique** | | | | | | | .043 |
| **3D** | 2 (3.5) | 0 | 0 | 2 (20.0) | 0 | 0 | |
| **Electron** | 54 (94.7) | 17 (100) | 9 (90.0) | 8 (80.0) | 11 (100) | 9 (100) | |
| **IMRT** | 1 (1.8) | 0 | 1(10.0) | 0 | 0 | 0 | |
| **Boost** | | | | | | | 1.000 |
| **10 Gy/5 Fr** | 56 (98.25) | 16 (94.1) | 10 (100) | 10 (100) | 11 (100) | 9 (100) | |
| **16 Gy/8 Fr** | 1 (1.75) | 1 (5.9) | 0 | 0 | 0 | 0 | |

Abbreviations: 3D, 3-dimensional; IMRT, intensity-modulated radiation therapy; FIF, field-in-field; Gy, Gray; Fr, fraction.
[a]Exact probability test, Kruskal-Wallis test.

**Table 3.** Numbers of Patients Who Underwent Other Treatments in Addition to Radiation Therapy.[a]

| Variable | Total, n (%) | No Treatment, n (%) | Control, n (%) | *Centella asiatica*, n (%) | *Cucumis sativus*, n (%) | *Thunbergia laurifolia*, n (%) | *P* |
|---|---|---|---|---|---|---|---|
| ***Neoadjuvant/adjuvant*** | | | | | | | .569 |
| **Adjuvant** | 84 (56.0) | 18 (60.0) | 20 (66.67) | 11 (36.67) | 17 (56.67) | 18 (60.0) | |
| **Neoadjuvant** | 31 (20.67) | 5 (16.67) | 6 (20.0) | 8 (26.67) | 7 (23.33) | 5 (16.67) | |
| **Neoadjuvant + adjuvant** | 1 (6.67) | 0 | 0 | 1 (3.33) | 0 | 0 | |
| **Neither** | 34 (22.67) | 7 (23.33) | 4 (13.33) | 10 (33.33) | 6 (20.0) | 7 (23.33) | |
| **Surgery** | | | | | | | .281 |
| **Lumpectomy** | 67 (44.67) | 18 (60.0) | 14 (46.67) | 11 (36.67) | 11 (36.67) | 13 (43.33) | |
| **Mastectomy** | 82 (54.67) | 11 (36.67) | 16 (53.33) | 19 (63.33) | 19 (63.33) | 17 (56.67) | |
| **No surgery** | 1 (0.67) | 1 (3.33) | 0 | 0 | 0 | 0 | |
| **Hormone** | | | | | | | .808 |
| **Arimidex** | 1 (0.67) | 1 (3.33) | 0 | 0 | 0 | 0 | |
| **Letrozole** | 42 (28.0) | 7 (23.33) | 8 (26.66) | 7 (23.33) | 13 (43.33) | 7 (23.33) | |
| **Tamoxifen** | 49 (32.67) | 10 (33.33) | 10 (33.33) | 8 (26.67) | 10 (33.33) | 11 (36.67) | |
| **Tamoxifen+ Arimidex** | 1 (0.67) | 0 | 0 | 1 (3.33) | 0 | 0 | |
| **Tamoxifen + Letrozole** | 3 (2.01) | 1 (3.33) | 0 | 1 (3.33) | 0 | 1 (3.33) | |
| **None** | 54 (36.0) | 11 (36.67) | 12 (40.0) | 13 (43.33) | 7 (23.33) | 11 (36.67) | |
| **Other medication** | | | | | | | .324 |
| **Herceptin** | 22(14.67) | 4 (13.33) | 4 (13.33) | 4 (13.33) | 8 (26.67) | 2 (6.67) | |
| **Traditional medicine** | 1 (0.67) | 1 (3.33) | 0 | 0 | 0 | 0 | |
| **None** | 127 (84.67) | 25 (83.33) | 26 (86.67) | 26 (86.67) | 22 (73.33) | 28 (93.33) | |

[a]Exact probability test.

was shown to affect radiation-induced dermatitis in the previous reports.[18,19]

Based on the data in Table 4, some patients started to show signs of radiodermatitis even after a few fractions of irradiation and their skin reaction became more severe coming into the later weeks of radiation therapy. Only a few patients had grade III acute dermatitis, which were considered severe, either with or without the prophylaxis. The number of patients remained in the later weeks declined, as many patients had completed their radiotherapy courses. Conclusively, during the radiotherapy weeks (week 0 to 6), no cream was superior to the standard care in preventing radiation-induced dermatitis in the patients ($P > .05$) as reflected in Figure 2. However, at 1-month follow-up, the statistical analysis suggested that the cucumber cream was able to reduce the severity of dermatitis down to grade I; while there remained patients with grade II or higher in the other groups ($P = .032$).The data were also analyzed to observe the change in dermatitis from the baseline in each group. The results in Supplemental Figures S1 and S2 (available online) showed that, for both grade I and grade II, there were no significant difference among the groups ($P = .769$ and .535, respectively). In Table 4, at certain weeks and groups, the number may not add up to 30 in all the groups, this was largely due to the patients missed their appointments to visit the radiation oncologist and did not receive timely skin grading. At later weeks, some patients had completed their course, which further decreased the number of patients remained in the groups.

In order to evaluate the practicality of applying the creams for routine uses, we surveyed whether the subjects were satisfied with the creams they were assigned to. The results in Table 5 show that the patients were equally satisfied with all the creams ($P = .613$) having no particular complaint concerning irritation or adverse effects of the creams. The patients were mostly satisfied with the moisturizing cream and least satisfied with the *T laurifolia* cream. None of the patients had any major concerns or complaints toward the use of the creams.

## Discussion

All the creams that have been used in the study are those commercially available in Thailand. Although the results from this study showed that no cream was effective in preventing or delaying radiodermatitis compared with no treatment, the cucumber cream was shown to help in the recovery of the irradiated skin with no patients had higher than grade I skin at 1-month post-irradiation. Cucumber has been a common ingredient for various skin care products in nourishing the skin. It is also shown to provide a soothing effect against skin irritations, reduce swelling as well as relieve the sunburn's pain.[11] This is possibly due to cucumber's protective effects against both reactive oxygen species and reactive carbonyl species by free radical scavenging activity, as cucumber contains flavonoids and tannins.[20,21] Thus, the results suggested that the cucumber cream could be useful in skin recovery after radiation exposure.

**Table 4.** Dermatitis Scores of the Patients.[a]

| Variable | Total, n (%) | No Treatment, n (%) | Control, n (%) | *Centella asiatica*, n (%) | *Cucumis sativus*, n (%) | *Thunbergia laurifolia*, n (%) | *P* |
|---|---|---|---|---|---|---|---|
| ***Week 1*** | | | | | | | .697 |
| **Grade 0** | 105 (77.78) | 19 (70.37) | 21 (84.0) | 25 (83.33) | 21 (77.78) | 19 (73.08) | |
| **Grade 1** | 30 (22.22) | 8 (29.63) | 4 (16.0) | 5 (16.67) | 6 (22.22) | 7 (26.92) | |
| **Week 2** | | | | | | | .975 |
| **Grade 0** | 57 (42.54) | 10 (40.0) | 13 (44.83) | 11 (40.74) | 13 (48.15) | 10 (38.46) | |
| **Grade 1** | 75 (55.97) | 15 (60.0) | 16 (55.17) | 15 (55.56) | 14 (51.85) | 15 (57.69) | |
| **Grade 2** | 2 (1.49) | 0 | 0 | 1 (3.70) | 0 | 1 (3.85) | |
| **Week 3** | | | | | | | .600 |
| **Grade 0** | 16 (11.76) | 2 (7.14) | 4 (14.81) | 4 (14.81) | 5 (17.86) | 1 (3.85) | |
| **Grade 1** | 109 (80.15) | 23 (82.14) | 22 (81.84) | 22 (81.48) | 19 (67.86) | 23 (88.46) | |
| **Grade 2** | 10 (7.35) | 2 (7.14) | 1 (3.70) | 1 (3.70) | 4 (14.29) | 1 (7.69) | |
| **Grade 3** | 1 (0.74) | 1 (3.57) | 0 | 0 | 0 | 0 | |
| **Week 4** | | | | | | | .813 |
| **Grade 0** | 3 (2.26) | 0 | 0 | 2 (6.90) | 0 | 1 (3.85) | |
| **Grade 1** | 94 (70.68) | 20 (76.82) | 18 (75.0) | 19 (65.52) | 20 (71.43) | 17 (65.38) | |
| **Grade 2** | 35 (26.32) | 5 (19.23) | 6 (25.0) | 8 (27.59) | 8 (28.57) | 8 (30.77) | |
| **Grade 3** | 1 (0.75) | 1 (3.85) | 0 | 0 | 0 | 0 | |
| **Week 5** | | | | | | | .531 |
| **Grade 1** | 47 (51.09) | 9 (47.37) | 14 (70.0) | 10 (47.62) | 7 (41.18) | 7 (46.67) | |
| **Grade 2** | 43 (46.74) | 9 (47.37) | 6 (30.0) | 11 (52.38) | 9 (52.94) | 8 (53.33) | |
| **Grade 3** | 2 (2.17) | 1 (5.26) | 0 | 0 | 1 (5.88) | 0 | |
| **Week 6** | | | | | | | .279 |
| **Grade 1** | 10 (38.46) | 4 (57.14) | 0 | 4 (50.0) | 0 | 2 (50.0) | |
| **Grade 2** | 14 (53.85) | 2 (28.57) | 4 (100) | 3 (37.50) | 3 (100) | 2 (50.0) | |
| **Grade 3** | 2 (7.69) | 1 (14.29) | 0 | 1 (12.50) | 0 | 0 | |
| **Follow-up (1 month)** | | | | | | | .032 |
| **Grade 0** | 11 (7.75) | 4 (14.81) | 0 | 3 (10.34) | 0 | 4 (13.33) | |
| **Grade 1** | 124 (87.23) | 22 (81.48) | 26 (92.86) | 25 (86.21) | 28 (100) | 23 (76.67) | |
| **Grade 2** | 6 (4.23) | 0 | 2 (7.14) | 1 (3.45) | 0 | 3 (10.0) | |
| **Grade 3** | 1 (0.70) | 1 (3.70) | 0 | 0 | 0 | 0 | |

[a]Exact probability test.

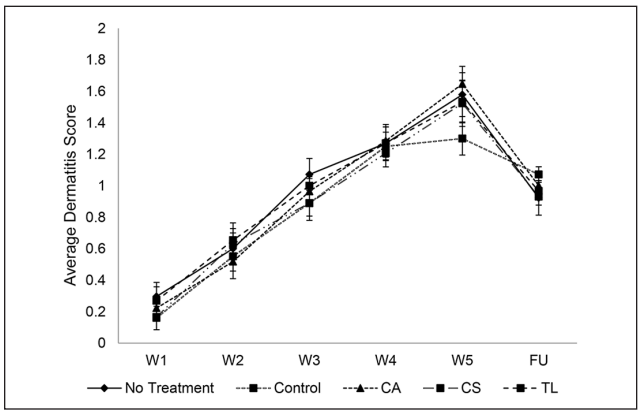


**Figure 2.** The averaged dermatitis scores of the care groups at indicated weeks during the course of breast cancer radiotherapy (Week 1 to Week 5; W1-W5) and at one-month follow-up (FU). The data are presented as means ± standard error of mean. CA, *Centella asiatica*; CS, *Cucumis sativus*; TL, *Thunbergia laurifolia*.

Patient characteristics and treatments were similar among the groups; however, a number of factors have been reported that they could contribute to skin radiosensitivity include diabetes, nicotine abuse, hyperthyroidism, and previous radiation exposure in the same body region.[22] Combination of radiotherapy with systemic chemotherapy may further enhance skin toxicity in the patients including severe xerosis, inflammation, skin thinning, and necrosis of the upper dermis and epidermis.[23] Patients with greater body mass index were also more likely to develop acute skin toxicity.[24] Pathophysiology of the symptom should be considered in developing new prophylactic reagents against the symptom.[5] Despite the fact that none of the creams presented in this study could provide clear protective effects against radiation-induced dermatitis, it is important for the patients to keep irradiated skin moist, as radiation could induce the skin to become xerotic, scaly, and hyperkeratotic, which may disturb patient's comfort.[25] Intensive use of 3% urea lotion has been suggested to protect the irradiated skin as the standard use was much less effective.[26]

**Table 5.** Cream Satisfactory Scores.[a]

| Variable | Total | Control | *Centella asiatica* | *Cucumis sativus* | *Thunbergia laurifolia* | *P* |
|---|---|---|---|---|---|---|
| **Satisfactory (1 = least satisfied; 5 = mostly satisfied)** | 4.61 ± 0.57 | 4.73 ± 0.45 | 4.53 ± 0.63 | 4.70 ± 0.47 | 4.50 ± 0.68 | .613 |

[a]The data are presented as mean ± standard deviation. Kruskal-Wallis test.

A more frequent use of the creams, rather than once a day, could further distinguish the efficacies of the creams in this study than what we observed.

A concern of surface radiation dose on the skin is often raised, particularly if a thick layer of cream or lotion remains on the skin during radiation treatment session, which was the primary reason for not providing any skin care products for the patients. However, it was previously demonstrated that the surface doses only slightly increased when a skin care product is applied on the skin during irradiation.[27] Therefore, breast cancer patients undergoing radiotherapy should be given an instruction to keep irradiated skin moist to reduce the chance to develop acute radiodermatitis.

Although the study was primarily designed to be double-blind, it was not possible to blind the no treatment group. It was also possible that the patients and the radiation oncology nurses who involved in the study could identify which color code was which herbal product due to the scents and other characteristics of the plants. Discussions and exchanges among the patients also affected the blinding. However, the patients were asked to adhere to strictly their designated treatments. The physicians who graded the degree of dermatitis were completely blinded of the patients' treatment designation. Another limitation of this study was the small numbers of subject in each treatment group, which was due to the number of creams we attempted to investigate. A larger number of participants could provide a more robust statistical significance.

This study only concerns acute skin radiodermatitis; however, chronic radiation dermatitis could develop months to years after radiation even though the skin may appear to be normal.[25] Currently, there is no established connection between acute and chronic radiodermatitis. Management of chronic dermatitis is complicated. The current most effective prophylaxis of chronic radiodermatitis is to minimize the dose to healthy skin by using proper radiotherapy technique.[28] Future studies related to radiogenomics and molecular mechanisms causing chronic radiation dermatitis would be beneficial in developing prophylaxis as well as management of the symptom.

## Conclusions

Radiodermatitis is almost an inevitable symptom occurred to those receiving radiotherapy and could greatly disturb quality of life of the patients. Various therapeutic and interventional agents for the management of the symptom have been suggested. The 3 herbal creams of Asiatic pennywort, cucumber and laurel clockvine have been tested as prophylaxis of the symptom. Despite no significant superior outcomes, the cucumber cream showed the potential in helping with the recovery of irradiated skin. A more frequent use, rather than once daily, could further highlight the effects of the creams. Patients should be encouraged to keep their skin clean and moist to lessen the chance of developing severe radiodermatitis.

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The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Supaporn Pithiporn is an employee of Chaopraya Abhaibhubejhr Hospital, and an executive of Chaopraya Abhaiphubejhr Hospital Foundation, which produces the herbal creams used in the study. The other authors declare no conflicts of interest.

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### Supplemental Material

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