

The Efficacy of Licorice Root (*Glycyrrhiza Glabra*) and Yarrow (*Achillea Millefolium*) in Preventing Radiation Dermatitis in Patients with Breast Cancer, A Randomized, Double-Blinded, Placebo-Controlled Clinical Trial

Mona Malekzadeh¹, Saleh Sandoughdaran^{1,2}, Fatemeh Homayi Shandiz³, Soheyla Honary⁴

¹Department of Radiation Oncology, Shohada-e-Tajrish Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ³Department of Radiotherapy-Oncology, Omid and Ghaem Hospitals, Mashhad University of Medical Sciences, Mashhad, Iran. ⁴Department of Pharmaceutics, Mazandaran University of Medical Sciences, Sari, Iran.

Abstract

Background: Radiation dermatitis is one of the most common side effects of radiotherapy for breast cancer, affecting approximately 85 percent of patients. The aim of this study is to assess the effect of Licorice root (*Glycyrrhiza glabra*) and Yarrow (*Achillea millefolium*) on preventing radiotherapy-induced dermatitis in breast cancer patients. **Methods:** Seventy-five patients with breast cancer who had undergone mastectomy and were planned to receive radiotherapy (RT) were enrolled in this randomized, double-blind, placebo-controlled study. The extract of *Achillea millefolium* and *Glycyrrhiza glabra* root were incorporated into a vanishing cream base. Patients were randomly divided into three groups and received *Glycyrrhiza glabra* cream, placebo or *Achillea millefolium* cream for five weeks during RT. The rate and grade of radiation dermatitis were recorded at baseline, at the end of third week and at the end of treatment using a modified Radiation Therapy Oncology Group (RTOG) grading tool. **Results:** At the end of the third week, the group receiving *Achillea millefolium* cream showed milder skin complications than other groups. At the end of treatment, rate of skin complications in groups receiving herbal drugs was lower than placebo group but it was not statistically significant. **Conclusions:** In conclusion, the results of this study did not present a significant difference between *Glycyrrhiza glabra*, *Achillea millefolium* and placebo on preventing radiation dermatitis.

Keywords: Breast cancer- glycyrrhiza glabra- achillea millefolium- radiation dermatitis

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Introduction

Breast cancer is the most common cancer in women and is still the most common cause of cancer-related death in women worldwide [1]. It has been shown that adjuvant Radiotherapy (RT) for breast cancer presents a benefit in terms of reducing local recurrence and deaths resulting from breast cancer [2]. Side effects of radiotherapy are inevitable; however, effort must be made to minimize them as much as possible without sacrificing the efficacy of the treatment. Reports suggest that approximately 87% of patients are expected to suffer from skin reaction [3].

The level of damage is related to the amount of radiation exposure. Long-term and extreme level of exposure might even result in death [4, 5]. Most clinicians advocate the use of various topical agents, however, no standard clinical strategy has been established for preventing radiation dermatitis [6-8].

In recent years, there has been growing interest in using natural products to treat modern medical conditions. *Glycyrrhiza glabra* (Licorice) and *Achillea millefolium* (Yarrow) both are herbal plants which are known for their anti-inflammatory and anti-oxidant effects [9, 10]. Licorice have been traditionally used as a demulcent, expectorant,

Corresponding Author:

Dr. Saleh Sandoughdaran

Department of Radiation Oncology, Shohada-e-Tajrish Hospital, Faculty of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Email: Sandoughdaran@sbmu.ac.ir

antioxidant, and a remedy for inflammation, as well as flavoring and sweetening agents. It is also reported to have radio protective activity in several studies.[11-14] Yarrow is used popularly as an appetizer, wound healer, diuretic and is reported to be as effective as nonsteroidal alternative therapy for atopic dermatitis [15, 16]. However, to the best of our knowledge the effect of these herbal drugs against radiotherapy induced skin dermatitis has not been investigated.

the aim of this randomized, double-blind, placebo-controlled study was to evaluate the ability of these two herbal drugs in reducing radiation dermatitis severity in patients receiving radiotherapy for breast cancer.

Materials and Methods

Part I: Preparation of vanishing creams.

The vanishing creams and plant extracts were provided by the Department of Pharmacy of Mazandaran University of Medical Sciences. The amount of the ingredients used to formulate the vanishing creams is presented in Table 1. Mixture A was heated to 70°C. To make mixture B, borax and water were heated. Next, ammonium hydroxide and preservative were added just before emulsification at 72°C. After adding A and B, the mixture (A-B) was kept under slow agitation, until temperature dropped to 55°C. The accurate weight of each dry extracts, which were used in mixture C, was levigated with glycerin and mixed with propylene glycol. Finally, mixture C was added to mixture A-B and stirred well.

Part II: Double-blind randomized clinical trial.

This double-blind randomized clinical trial was conducted at Mashhad University of Medical Sciences, Iran, on patients with diagnosis of breast cancer, scheduled to receive adjuvant radiotherapy. Female patients between 18 and 80 years of age at the time of enrollment who had undergone mastectomy were eligible. All patients had received chemotherapy before radiotherapy. Exclusion criteria included the presence of rashes or unhealed wounds in the radiation field, planned receipt of concurrent chemotherapy with radiation and systemic lupus erythematosus or scleroderma. After obtaining the approval of the Ethics Committee of Mashhad University, the informed consent was obtained from all participants.

Patients were treated to 50 Gray in 25 fractions, over five weeks. Upon confirmation of patient eligibility, demographic data including age, body mass index (BMI), number of chemotherapy courses and the type of drug used in it, duration between last session of chemotherapy and start of radiotherapy, and amount of sweating were collected from patients. Randomization was done by simple computer randomization. All patients were divided into three equal groups, 25 patients in each group. The patients in Group 1, 2 and 3 received *Glycyrrhiza glabra*, placebo and *Achillea millefolium*, respectively, beginning with the start of radiotherapy and continuing every day during the radiotherapy period. Patients were instructed not to apply other topical skin care products during

radiotherapy period.

This study was double-blind and neither the patients nor the physician who reported the skin complication were aware of the type of treatment. The treating physicians were all radiation oncologists who specialize in breast treatment. The treating physicians assessed radiation dermatitis at baseline, at the end of third week (30 Gy) and at the end of treatment (50 Gy) using a modified Radiation Therapy Oncology Group (RTOG) radiation skin-toxicity grading tool as follows:

Grade 0: without changes

Grade 1: Erythema in dermal capillaries or mild erythema, dry desquamation

Grade 2: Sensitive in contact or moist desquamation, skin edematous

Grade 3: All of the above complications and moist desquamation in all area (not exactly in skin folds), sever edematous

Grade 4: Dermal ulceration and necrosis, bleeding

All data were analyzed by SPSS software (version 13). Statistical significance for difference in quantitative variables between the three groups was tested by ANOVA and the comparison of the qualitative variables was conducted by chi-square test. A p-value less than 0.05 was considered statistically significant.

Results

Between November 2005 and April 2009, 75 patients were enrolled and randomized. 25 patients withdrew consent or did not complete the study. Therefore, the number of patients who continued to participate in the trial was 19, 14 and 17 patients in group 1, 2 and 3, respectively (Figure 1). As it is manifested in Table 2, no significant difference was noticed between groups in terms of average age, BMI, number of chemotherapy, diabetes and hypertension, degree of sweating and its severity, and hormone therapy ($p > 0.05$).

As depicted in Table 3, number of total skin complications were similar in group 1 and 2. However, number of total skin complications was lower in patients applying *Achillea millefolium* cream. Although the difference was not statistically significant ($p = 0.53$).

Table 1. The Formulation of Vanish Creams

Mixtures	Ingredients	%
A	Stearic Acid	15
	Cetostearyl Alcohol	2
	Mineral Oil	2
B	Borax	1
	Ammonium Hydroxide 28%	1
	Preservative	0.2
	Water	71.2
C	Propylene Glycol	4
	Dry Extract	0.6
	Glycerin	3

Table 2. Baseline Characteristic of Patients

Variable	Licorice	Placebo	Yarrow	P-Value
Number of Patients	19	14	17	
Age (years)	47.53 ± 9.37	46.79 ± 10.56	45 ± 11.59	0.77
BMI (kg/m ²)	27.52 ± 4.41	6.99 ± 5.30	29.93 ± 4.45	0.18
Duration from the End of Chemotherapy	25.79 ± 12.13	28.67 ± 16.03	22 ± 7.29	0.37
Number of Chemotherapy Sessions	7.22 ± 0.94	6.33 ± 1.24	6.78 ± 1.52	0.20
Rate of Diabetes	3 (15.8%)	3 (21.4%)	2 (11.8%)	0.77
Hypertension	1 (5.3%)	1 (7.1%)	0 (0%)	0.56
Rate of Sweating				
High	4 (21.1%)	5 (30.8%)	6 (35.3%)	
Moderate	12 (63.2%)	7 (53.8%)	11 (64.7%)	
Low	3 (15.8%)	2 (15.4%)	0 (0%)	0.28
Hormone Therapy	13 (68.4%)	9 (64.3%)	11 (64.7%)	0.96

*Data are presented as mean ± standard deviation and number (percent).

**P value refers to ANOVA-test and χ^2 -test.

Table 3. Maximum Grade of Radiation Dermatitis at the End of Third Week

Groups	Grade 0	Grade 1	Grade 2	Grade 3	Total
Licorice	10 (62.5%)	5 (31.3%)	1 (6.3%)	0 (0%)	6 (37.6%)
Placebo	7 (53.8%)	5 (38.5%)	1 (7.7%)	0 (0%)	6 (46.2%)
Yarrow	11 (84.6%)	2 (15.4%)	0 (0%)	0 (0%)	2 (15.4%)
P-Value					0.53

*Data are presented as number (percent).

** "Total" refers to the sum of complications from grade 1 to 3.

Table 4. Maximum Grade of Radiation Dermatitis at the End of Treatment

Groups	Grade 0	Grade 1	Grade 2	Grade 3	Total
Licorice	0 (0%)	9 (64.3%)	5 (35.7%)	0 (0%)	14 (100%)
Placebo	1 (7.7%)	5 (38.5%)	6 (46.2%)	1 (7.7%)	12 (92.3%)
Yarrow	2 (14.3%)	7 (50%)	4 (28.6%)	1 (7.1%)	12 (85.7%)
P-Value					0.43

*Data are presented as number (percent).

** "Total" refers to the sum of complications from grade 1 to 3.

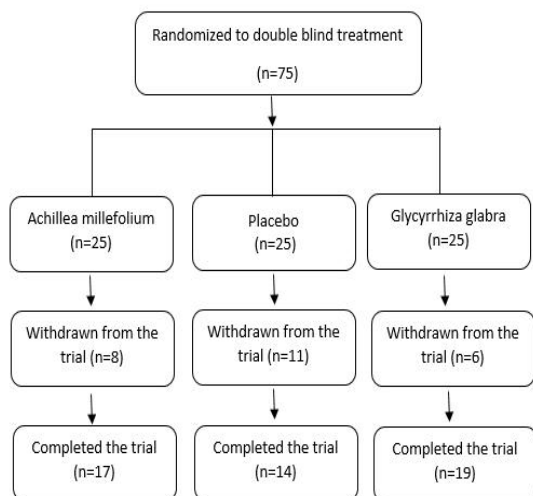


Figure 1. Flowchart Depicting the Study Design.

At the end of the treatment radiation dermatitis occurred in most of the patients. In placebo group, grade 2 toxicities were higher than other two groups; meanwhile, grade 3 toxicities were similar between group 3 and placebo (Table 4). The rate of severe dermatitis (grade 2 and 3) was higher in placebo group, but it was not statistically significant. No case with grade 4 radiation dermatitis was seen in three groups.

Discussion

Skin toxicity is the most common acute side effect of radiotherapy to the breast that ranges from a mild rash to severe ulceration. Skin reactions to therapeutic radiation depend on the number of radiations, dose, site of radiotherapy treatment, and patients specific factors including use of chemical irritants, nutritional status and presence of skin folds [17-20]. Although routine skin care such as keeping the area dry, not robbing the skin and not

using irritants is important, exclusive use of such handling seems insufficient and prevention of radiation skin damage is a troublesome process for clinicians and patients alike. A wide variety of topical, oral, and intravenous agents have been tested to prevent or to treat radiation-induced skin reactions, but the evidence is insufficient to support the use of a particular agent for this purpose.[7, 8, 21]

Many studies were conducted to find an effective treatment using herbal ingredients to reduce skin reactions, including Aloe-vera, which is widely used to heal burns and wounds [17]. While some studies suggested that Aloe-vera may be useful in preventing radiation induced skin damage, others reported that use of Aloe-vera has no effect or even can worsen dermatitis [22-25].

In the present study, two anti-inflammatory-based herbal drugs were selected based on preclinical activity. The roots of *Glycyrrhiza glabra* popularly known as Licorice have a variety of biological effects, such as anti-inflammatory, anti-ulcer, antihepatotoxic, antimicrobial, anti-oxidant, cytoprotective, and cytotoxic activities[26-31]. Das et al suggested that *Glycyrrhiza glabra* can be used effectively in prevention and treatment of oral mucositis post radiation and chemotherapy in patients of cancer, especially of the head and neck region.[14] In another study, it was shown that Licorice root extract could protect plasmid DNA from radiation-induced strand breaks[32]. Moreover, recently Refahi et al demonstrated that administration of *Glycyrrhiza glabra* extract one hour before thoracic irradiation may be a protective agent against radiation-induced fibrosis in an animal model [11].

Achillea millefolium (Yarrow) is traditionally used in the treatment of gastro-intestinal disorders, healing wounds and providing relief from rashes and itching of various causes. The essential oil of *Achillea millefolium* was reported to possess strong antioxidant and antimicrobial properties.[9, 33, 34] furthermore, cytotoxic or cytostatic effects of extracts of *Achillea millefolium* have been demonstrated against various malignant tumor cell lines and flavonols have been identified as responsible for the antitumor activity[35]. To the best of our knowledge this is the first study that has evaluated the possible protective effect of these herbal drugs against radiotherapy induced skin dermatitis.

The results of this study suggest that usage of *Achillea millefolium*, especially at lower doses of radiation, might decrease radiation induced dermatitis. However, since there were only two cases with grade 1 dermatitis at the end of third week (30 Gy) in this group, more research is required to verify this finding. In the present study, although the severity of skin reactions was lower in two herbal groups, there was not a significant difference between *Glycyrrhiza glabra*, *Achillea millefolium* and placebo on preventing radiation dermatitis at the end of treatment.

The main limitation of current study is its small sample size, which render our findings less conclusive. Hence, further study with a larger sample size is required to evaluate the effects of these drugs on radiation skin

toxicity in breast cancer patients.

In conclusion the results of this study did not present a significant difference between *Glycyrrhiza glabra*, *Achillea millefolium* and placebo on preventing radiation dermatitis. However, the severity of skin reactions was lower in two herbal groups. To better evaluate the effects of these drugs on radiation induced dermatitis in breast cancer patients, a larger sample size is needed.

Conflicts of interest

The authors declare that they have no conflict of interest.

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