Review Article

Topical treatment for prevention and management of acute radiation dermatitis in breast cancer patients: an integrative review

Terapia tópica para prevenção e tratamento da radiodermatite aguda das mamas: revisão integrativa da literatura

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■ **ABSTRACT**

Introduction: Radiotherapy plays an important adjuvant role in the surgical treatment of breast cancer by reducing locoregional recurrence and improving overall survival. However, up to 95% of patients experience some degree of radiodermatitis. This study aims to review the literature regarding topical agent therapies in preventing and treating acute radiation dermatitis in breast cancer patients. **Methods:** Integrative review of LILACS, Medline and Cochrane Library databases. We searched for original articles published between 2010 and 2020, including the descriptors breast neoplasms, radiodermatitis, skincare, and skin cream. **Results:** The initial search returned 158 articles. After screening for eligibility, 48 articles were included. Forty different topical agent therapies were identified and grouped into seven categories to facilitate data analysis: herbal medicines, hormones/vitamins/growth factors, topical corticosteroids, barrier products (film or cream), hyaluronic acid, silver-based dressings and others. **Conclusions:** This review identifies that topical corticosteroids of high (betamethasone-17-valerate) and medium potency (mometasone furoate 0.1%), as well as barrier films such as Mepitel®, Mepilex Lite®, and Hydrofilm®, are effective in managing acute breast radiodermatitis. The other topical agent therapies did not show benefits in preventing and/or treating acute radiodermatitis or have limited evidence.

Keywords: Breast neoplasms; Radiodermatitis; Skin care; Skin cream; Review.

■ **RESUMO**

Introdução: A radioterapia desempenha um importante papel adjuvante ao tratamento cirúrgico do câncer de mama, pois diminui as taxas de recorrência local e aumenta a sobrevida global. Entretanto, até 95% das pacientes expostas à radiação ionizante desenvolverão algum grau de radiodermatite. O presente estudo revisa a literatura referente às terapias tópicas disponíveis para prevenção e tratamento da radiodermatite aguda das mamas, sintetizando as evidências disponíveis e auxiliando a tomada de decisão clínica. **Métodos:** Revisão integrativa da literatura publicada nos últimos 10 anos, utilizando as bases de dados LILACS, Medline e Biblioteca Cochrane. Foram utilizados os descritores neoplasias da mama, radiodermatite, higiene da pele e creme para a pele. **Resultados:** Dos 158 artigos encontrados, 48 foram incluídos nesta revisão. Foram identificadas 40 diferentes terapias tópicas que foram agrupadas em sete categorias para facilitar a análise e interpretação dos dados: fitoterápicos, hormônios/vitaminas/fatores de crescimento, corticoesteroides, barreira (filme ou creme), ácido hialurônico, curativos à base de prata e outros. **Conclusões:** Existe evidência científica proveniente de ensaios clínicos randomizados de boa qualidade embasando a indicação dos corticosteroides tópicos de alta (valerato de 17-betametasona) e média potência (furoato de mometasona 0,1%), assim como de filmes barreira como Mepitel®, Mepilex Lite® e Hydrofilm®,

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Article received: July 1, 2021.
Article accepted: December 13, 2021.

Conflicts of interest: none.

DOI: 10.5935/2177-1235.2022RBCP.606-en

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no manejo da radiodermatite aguda das mamas. As demais terapias não mostraram benefícios na prevenção e/ou tratamento da radiodermatite ou têm evidência científica limitada, contraindicando ou restringindo sua utilização na prática clínica.

Descritores: Neoplasias da mama; Radiodermatite; Higiene da pele; Creme para a pele; Revisão.

INTRODUCTION

According to data from the American Cancer Society, breast cancer accounts for 30% of all cancer cases in women, and an estimated 281,550 new cases were estimated in 2021. The incidence of this neoplasm increased by 0.5% between 2008 and 2017, probably due to decreased fertility, increased overweight and obesity in the female population[1].

Breast cancer treatment is multimodal and depends on factors such as staging at diagnosis, tumor biological characteristics, and patient-related factors. The available treatment modalities are radical or conservative surgery, radiotherapy, chemotherapy, hormone therapy and biological therapy, which are often associated individually for each case[2].

Radiotherapy plays an important role as an adjuvant to the surgical treatment of breast cancer, decreasing local recurrence rates and increasing overall survival. It is estimated that up to 95% of irradiated patients will develop some degree of radiodermatitis (RDTE). In addition to interfering with the quality of life, skin toxicity induced by radiotherapy, depending on the severity, can delay or interrupt adjuvant treatment[3,4].

RDTE is an acute or chronic inflammatory condition caused by skin exposure to ionizing radiation resulting in changes in the epidermis, dermis and local vascularization. It is a dose and time-dependent condition with a progressive spectrum of skin changes such as erythema, hyperpigmentation, dry desquamation, wet desquamation, necrosis and local ulceration[3]. Such changes are part of the most commonly used RDTE assessment and classification scales: Radiation Therapy Oncology Group (RTOG) and National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE)[5].

The main risk factors for the development of RDTE are related to the characteristics of the patient and the radiotherapy technique used, such as radiotherapy dose greater than 50Gy; conventional-dose splitting regimen; use of bolus or boost techniques; among others. It is known that a body mass index greater than 25kg/m^2, smoking and the presence of large breasts are factors that predispose to moderate and severe forms of RDTE[6,7]. On the other hand, the main protective factors concern the radiotherapy technique used, and intensity-modulated radiotherapy (IMRT) and prone position have been proven to reduce radio-induced skin toxicity[5].

Unlike radiotherapy techniques, which have already standardized protocols to reduce the risk of skin toxicity to the patient, the management of RDTE remains heterogeneous. Numerous topical and curative drugs for the prophylaxis and treatment of RDTE have been investigated in the medical literature, but a large number of proposed interventions, the heterogeneity of reported results and the quality of studies make clinical decisions challenging[8]. Thus, it is necessary to carry out extensive research in the medical literature in search of available evidence on this topic.

OBJECTIVE

To carry out an integrative review of the literature on the use of topical therapy for the prevention and treatment of RDTE in female patients with breast cancer undergoing adjuvant radiotherapy.

METHODS

This is a descriptive, exploratory study that rigorously followed the six steps recommended for the development of an integrative literature review[9].

A search was carried out for articles published between 2010 and 2020 in the Latin American and Caribbean Literature in Health Sciences (LILACS), Medical Literature Analysis and Retrieval System Online (Medline) and Cochrane Library databases.

Four controlled descriptors were used: breast neoplasms, radiodermatitis, skin hygiene and skin cream. Original articles from primary or secondary studies were included, with female patients undergoing breast radiotherapy, published in full in Portuguese, English or Spanish, and which could be accessed online. Secondary articles, such as literature reviews and meta-analyses, were not included. However, the primary articles that made up such studies did. Articles that evaluated different anatomical sites of the breasts, publications of study protocols, studies with unavailable full text, studies that evaluated non-topical therapies, such as oral medications or non-invasive technologies, and duplicates were excluded.

After analyzing the articles' abstracts, those that met the inclusion criteria were read in full by a single reviewer and organized using a synthesis tool developed by the main author. The data obtained were organized in an Excel spreadsheet, and the respective references were stored in the bibliography manager software EndNote (Clarivate Analytics).

RESULTS

The bibliographic research structured according to the previously established methodology resulted in selecting this integrative review's 48 original primary articles (Figure 1). As for the type of study, 35 (73%) randomized clinical trials (RCTs) were found; three non-randomized clinical trials (6%), five pilot studies (11%), two case series (4%), one case-control study (2%), one retrospective study (2%) and one prospective cohort (2%).

In the 48 studies in this review, 40 different interventions for the prevention or treatment of breast RDTE were identified, which were grouped into seven categories to facilitate their analysis and interpretation (Table 1).

Herbal medicines

No benefits were found from the use of *Aloe vera* extract[10], curcumin gel[11]; *Calendula officinalis* cream[12-14], *Centella Asiatica* extracts 7%, *Cucumis sativus* 20%, *Thunbergia laurifolia* 5%[15], *Boswellia serrata* cream 2%[16], ointment of beta-sitosterol 0.25% (Mebo®)[17], fatty acid emulsion[18,19], blend of essential oils[20], omega ^{3,6,9} (Quinovit®)21 and Jaungo ointment (shikonin 0.07mg/g + decursin 3.6mg/g)[22] in the management of RDTE of the breasts.

A double-blind, randomized clinical trial with 47 patients showed that 3% sodium pentaborate pentahydrate gel decreased the rate of RDTE grade RTOG > 2 in the subgroup of patients undergoing radical or conservative surgery who did not receive radiotherapy boost (34% vs. 67% $p=0.03$)[23].

Studies that evaluated silymarin 0.25%[24], emulsion of olive oil and calcium hydroxide[25] and natural extracts (SkinSave®)[26] showed a reduction in the proportion of patients with RDTE[24,25], less pain[24] and erythema[26]. Table 2 summarizes the data for this group.

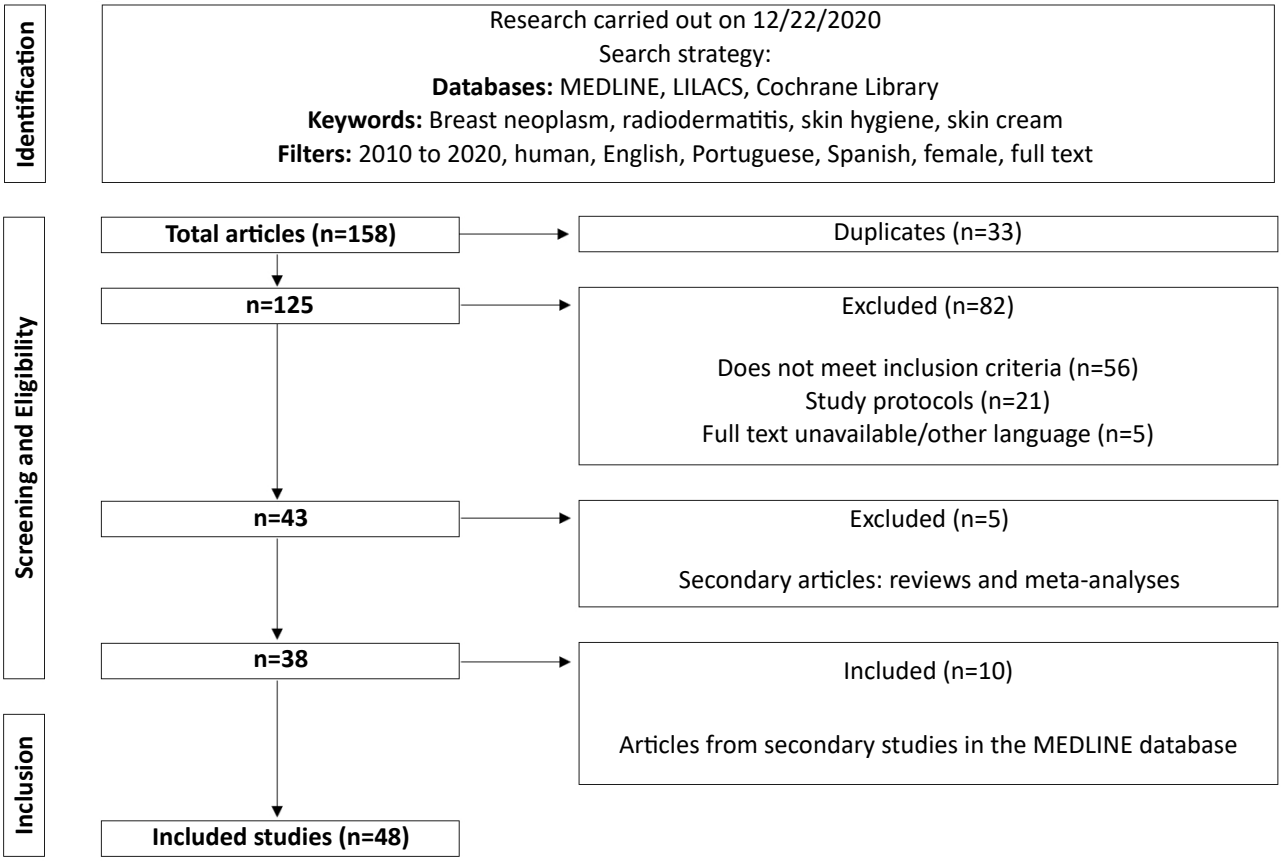

Figure 1. Flowchart of the steps for identification and selection of articles in this review.

Table 1. Topical therapies from this integrative review and their respective references.

Herbal Medicines	References
Aloe barbadensis extract 30mg/100ml	10
Curcumin Gel (PsoriaGold®)	11
Calendula officinalis cream	12-14
Asian centella 7%, *Cucumis sativus* 20%, *Thunbergia laurifolia* 5%	15
Boswellia serrata cream 2%	16
Beta-sitosterol Ointment 0.25% (Mebo®)	17
Fatty Acids and Linoleic Acid (WO1932)/ Ultra Emu Oil®	18.19
Blend of essential oils	20
Omegas 3,6,9 (Quinovit®)	21
Jaungo Ointment (shikonin 0.07mg/g + decursin 3.6mg/g)	22
Sodium pentaborate pentahydrate 3% gel	23
Silymarin 0.25% (Leviaderm®)	24
Olive oil and calcium hydroxide emulsion	25
Emulsion of natural extracts (SkinSave®)	26
Hormones, vitamins and growth factors	
Melatonin cream (Praevoskin®)	27
Recombinant epidermal growth factor (EGF) cream	28
Vitamin D (Daivonex®)	29
Vitamin E	21
Topical corticosteroids	
Mometasone Furoate 0.1%	14.30-32
1% hydrocortisone	33
17-Betamethasone Valerate (Betnovat®)	34.35
Barrier	
Silicone film (Mepitel®/Mepilex Lite®)	36-40
Hydrofilm®	41
Cavilon® (barrier cream)	42.43
Silicone gel (XtrataXRT®)	44
Hyaluronic acid	
Hyaluronic acid gel, serum or cream	14,21,45-46,47
Silver	
48 silver impregnated film	48
1% silver sulfadiazine	49
Others	
HPR Plus® (free fatty acids, ceramides and hyaluronic acid)	11
Commercial formulations (Neoviderm®/Ixoderm®)	21
Aquafor® (panthenol and glycerin ointment)	50
Trolamine (Biafine RE®)	50
RadiaCare®	50
Hydrophilic gel with polyurethane polymers (Hydrosorb®)	51
Mucopolysaccharide Polysulfate 5mg/g (Hirudoid®)	52
Sucralfate	53.54
Flamigel® (hydroactive colloid gel)	55.56
3% urea lotion	57

Hormones, vitamins and growth factors

Melatonin-based cream (Praevoskin®) reduced the incidence of grade 1 and 2 RDTE in the intervention group (59% vs. 90%, $p=0.03$), with the benefit being greater in the subgroups of patients >50 years ($p= 0.021$) and smokers ($p=0.007$)[27].

Recombinant epidermal growth factor (EGF) cream and vitamin D ointment could not prevent the onset or progression of RDTE[28,29]. In the study that evaluated vitamin E, a 55% prevalence of grades 1-2 RDTE was observed in the group of 20 patients who used this therapy (11/20)[2].

Corticosteroids

Topical corticosteroids were studied in seven RCTs, six of which were double-blind, and one was a pilot study, totaling 794 patients. Four of the seven studies evaluated 0.1% mometasone furoate; two, 17-betamethasone valerate; and one, 1% hydrocortisone cream.

Mometasone furoate 0.1% reduced the severity of RDTE[30], the incidence of wet scaling and skin toxicity[31]. These benefits were not observed in the pilot study[14] and one of the double-blind RCTs[32]. In the latter, an improvement in the symptoms reported by the patient (secondary outcomes) was observed, such as less local irritation, less persistence and recurrence of symptoms and less discomfort with skin changes[32].

1% hydrocortisone cream was not able to prevent the occurrence of wet desquamation[33]. The use of 17-betamethasone valerate (Betnovat®) twice a day, from the first day of radiotherapy until 14 days after its completion, demonstrated a protective effect against the onset and progression of RDTE, with the benefit being even greater in the subgroup of mastectomy patients[34,35].

Barrier (film or cream)

This intervention has the second largest RCT series, totaling 774 patients in studies evaluating silicone film (Mepitel®/MepilexLite®), Cavilon® cream, silicone gel (XtrataXRT®) and polyurethane film (Hydrofilm®).

Studies with silicone films showed beneficial results. Its application on the breast surface to be irradiated resulted in a lower incidence of erythema[36] and cutaneous toxicity[37,38], a reduction in the rate of wet desquamation[39], and better control of symptoms such as pain, tenderness, itching and local burning[40]. Patients who used Hydrofilm® (polyurethane film) had a lower RDTE score, indicating protection against progression to more severe forms of RDTE, less erythema, itching and pain in irradiated breasts after conservative surgical treatment[41].

Cavilon® barrier cream prevented the appearance of wet desquamation at the end of radiotherapy exclusively in the subgroup of mastectomized patients, and this benefit was not observed in the 8 to 10 weeks post-radiotherapy follow-up[42]. In addition, its use does not reduce pain and pruritus or delay progression to RDTE grade 2[43]. Silicone gel (XtrataXRT®) was evaluated in a pilot study with 49 patients, and no benefits were observed in the prevention of RDTE[44].

Table 2. Herbal medicines.

Herbal	Reference	Result
Aloe barbadensis extract (30mg/100ml)	10	Negative
Curcumin Gel (PsoriaGold®)	11	Negative
Calendula officinalis cream	12-14	Negative
Asian centella 7%, Cucumis sativus 20%, Thunbergia laurifolia 5%	15	Negative
Boswellia serrata cream 2%	16	Negative
Beta-sitosterol Ointment 0.25% (Mebo®)	17	Negative
Fatty Acids and Linoleic Acid (WO1932)/ Ultra Emu Oil®	18.19	Negative
Blend of essential oils	20	Negative
Omegas 3,6,9 (Quinovit®)	21	Negative
Jaungo Ointment (shikonin 0.07mg/g + decursin 3.6mg/g)	22	Negative
Sodium pentaborate pentahydrate 3% gel	23	Positive
Silymarin 0.25% (Leviaderm®)	24	Positive
Olive oil and calcium hydroxide emulsion	25	Positive
Emulsion of natural extracts (SkinSave®)	26	Positive

Hyaluronic acid

Hyaluronic acid in different presentations as gel, serum or cream was evaluated in five studies, totaling 422 patients. In none of the studies, there was any benefit from the application of this intervention[14,21,45-47]. Topical hyaluronic acid did not prevent the onset or progression of RDTE, in addition to potentially worsening skin toxicity in patients who used it[46].

Silver-impregnated film

Silver-impregnated film was evaluated in RCT with 196 patients undergoing breast-conserving surgery and adjuvant radiotherapy. The results obtained were negative for both preventions of wet desquamation in the inframammary fold and relief of pain and burning[48]. On the other hand, the application of 1% silver sulfadiazine three times a day during the radiotherapy period and up to 7 days after its completion resulted in lower scores on the RTOG score, indicating a protective effect against the onset of moderate and severe forms of RDTE in mastectomized patients[49].

Others

This group comprises 11 studies: five RCTs, two non-randomized clinical trials, one case series, two cohort studies and one case-control study. Double-blind RCTs that evaluated Aquafor® (panthenol and glycerin), Biafine RE® (trolamine), RadiaCare®[50] and HPR Plus® (free fatty acids + ceramides + hyaluronic acid)11 did not observe benefits from the topical use of these substances. The unblinded RCT with 278 patients with RDTE grades 1-2 randomized to topical treatment with Hydrosorb® (hydrogel) was also negative[51].

The application of Hirudoid® from 14 days after the beginning of radiotherapy until 3 months after its completion promoted less desquamation and greater skin hydration in the period of 2 and 4 weeks after the beginning of adjuvant therapy, with no difference at 3 months, as evidenced by the analysis of the corneometry of the breasts of patients submitted to breast-conserving surgery, in an unblinded and non-placebo-controlled RCT[52].

Studies with less evidence indicate some benefits in sucralfate gel 25% (Skincol®)[53,54], hydroactive colloid gel (Flamigel®)[55,56], urea lotion 3%[57] and various commercial formulations[21].

DISCUSSION

In this integrative review, 48 primary studies were identified evaluating topical therapies for the prevention or treatment of RDTE, which were grouped into seven categories.

76% (13/17) of the articles that evaluated herbal medicines found no benefits from this intervention, ten RCT[10-19]. Furthermore, studies with positive results have important methodological limitations, as they are not blinded, controlled or randomized, which determines a high risk of bias[24-26]. Similarly, the evidence favoring 3% sodium pentaborate pentahydrate gel is still limited[23].

It is concluded that there is sufficient scientific evidence to contraindicate the use of most topical herbal formulations in the management of RDTE of the breasts. Such findings agree with those reported in a study published in 2012 that critically evaluated published systematic reviews on the management of RDTE and concluded that topical agents based on *Aloe vera* and *Calendula*, among others, are ineffective[58].

Positive results with the use of melatonin-based cream (Praevoskin®) and 1% silver sulfadiazine need confirmation in studies with larger series, as scored by the authors[27]; or in studies with better methodological design regarding the use of placebo in the control group and efficiency of blinding[49].

Topical corticosteroids have been extensively investigated in RCTs over the last 10 years, building solid evidence from double-blind, placebo-controlled studies favoring 0.1% mometasone furoate and 17-betamethasone valerate[30,31,34,35]. These findings corroborate the results of a systematic review comprising six RCTs published in 2013: a meta-analysis of five RCTs showed that the risk of wet desquamation is 2.5 times lower with topical corticosteroids. A lower mean RDTE score was also evidenced; however, the heterogeneity between the studies did not allow a meta-analysis to be carried out for this outcome[59].

In the review mentioned above, the authors emphasized that future studies should investigate which topical corticosteroid would be most effective in managing RDTE. In the present review, we observed that high (17-betamethasone valerate)[34,35] and medium (0.1% mometasone furoate)[30,31] steroids were beneficial, whereas no benefits were observed from topical hydrocortisone 1 %, a low-potency corticosteroid[33].

The benefit of using silicone barrier films (Mepitel®/MepilexLite®) or polyurethane (Hydrofilm®) is based on the results of RCTs with a restricted series ($n<100$)[36-41]. Furthermore, the risk of observational bias cannot be ruled out due to the absence of blinding in most studies. On the other hand, Cavilon® barrier cream showed a limited and transient benefit in preventing wet peeling[42]. In contrast, silicone gel reduced the incidence of erythema and hyperchromia (secondary outcomes) without changing the severity

of RDTE, which was the primary outcome of the study by Ahn et al.[44].

Formulations based on hyaluronic acid[14,21,45-47], silver-impregnated films[48], Aquafor®[50], Biafine RE®[50], RadiaCare®[50], HPR Plus®[11] and Hydrosorb®[51] were evaluated in RCT and proved to be ineffective in the management of RDTE.

Hirudoid® promoted greater skin hydration, assessed by corneometry, up to 4 weeks after the end of adjuvant RT in patients undergoing conservative surgery. It also improved xerosis and skin scaling without changing the degree of erythema and local pruritus[52]. Thus, the evidence for the indication of Hirudoid® in managing RDTE is still limited.

The positive results reported with the use of 1% silver sulfadiazine[49], 25% sucralfate gel[53,54], hydroactive colloid gel (Flamigel®)[55,56], 3% urea lotion[57] and commercial formulations such as Neoviderm® and Ixoderm® [21], do not come from placebo-controlled RCTs. Thus, such benefits should be carefully evaluated, as the limitations inherent to the methodology of these studies do not allow inferences about the effectiveness of these substances in the management of RDTE.

This integrative review has limitations resulting from the evaluation period restricted to the last 10 years and from exclusively contemplating articles published in journals indexed in the three predetermined languages. However, previously published reviews that considered the literature prior to 2010 concluded that the available evidence regarding topical therapies for RDTE was insufficient, heterogeneous and, therefore, a greater number of better quality studies were needed[58,60,61].

The present study updated the literature related to the topic, clarified questions raised by previous reviews, and critically evaluated the scientific evidence supporting the indication or contraindication of topical therapies available for the management of RDTE of the breasts.

CONCLUSION

For the prevention of breast RDTE, there is sufficient scientific evidence from good quality randomized clinical trials to support the indication of topical corticosteroids, mometasone furoate 0.1% and 17-betamethasone valerate. Barrier films such as Mepitel®, Mepilex Lite® and Hydrofilm® have also been shown to be beneficial.

On the other hand, topical hyaluronic acid formulations, *Aloe barbadensis* extract, *Centella Asiatica* 7%, *Cucumis sativus* 20%, *Thunbergia laurifolia*, *Boswellia serrata* 2%, *Calendula officinalis* cream 5 or 10%, silver-based films, curcumin (PsoriaGold®), HPR plus® cream, 0.25% beta-sitosterol ointment (Mebo®) and Biafine RE® (trolamine) were shown to be ineffective in the management of RDTE of the breasts. Thus, the available evidence contraindicates such substances' use in managing RDTE.

Sodium pentaborate pentahydrate gel 3%, Praevoskin® (melatonin cream), Leviaderm® (silymarin 0.25%), Cavilon®, silver sulfadiazine 1% and Hirudoid® (mucopolysaccharide polysulfate 5mg/g) showed positive results in the management of breast RDTE in clinical trials with limited series and/or of lower methodological quality. Although promising, such substances need additional studies proving their effectiveness.

COLLABORATIONS

MARM Analysis and/or interpretation of data, Final approval of the manuscript, Data collection, Conception and design of the study, Methodology, Writing - Preparation of the original.

MGC Final approval of the manuscript, Conception and design of the study, Writing - Review and Editing, Supervision.

AH Final approval of the manuscript, Conception and design of the study, Writing - Review and Editing.

REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021;71(1):7-33. DOI: 10.3322/caac.21654
2. Brasil. Ministério da Saúde. Instituto Nacional de Câncer (INCA). Tratamento para o câncer de mama. Brasília: Instituto Nacional de Câncer; 2020. Disponível em: https://www.inca.gov.br/controle-do-cancer-de-mama/acoes- de-controle/tratamento
3. Singh M, Alavi A, Wong R, Akita S. Radiodermatitis: A Review of Our Current Understanding. Am J Clin Dermatol. 2016;17(3):277-92. DOI: 10.1007/s40257-016-0186-4
4. Bontempo PMS. Ocorrência de radiodermatite em pacientes com câncer em um hospital de ensino de Brasília [Dissertação de mestrado]. Brasília: Universidade de Brasília; 2017.
5. Kole AJ, Kole L, Moran MS. Acute radiation dermatitis in breast cancer patients: challenges and solutions. Breast Cancer (Dove Med Press). 2017;9:313-23. DOI: 10.2147/BCTT.S109763
6. Sharp L, Johansson H, Hatschek T, Bergenmar M. Smoking as an independent risk factor for severe skin reactions due to adjuvant radiotherapy for breast cancer. Breast. 2013;22(5):634-8. DOI: 10.1016/j.breast.2013.07.047
7. Parker JJ, Rademaker A, Donnelly ED, Choi JN. Risk Factors for the Development of Acute Radiation Dermatitis in Breast Cancer Patients. SKIN J Cutan Med. 2018;2(1):2-11. DOI: 10.25251/skin.2.1.1
8. Ryan JL. Ionizing radiation: the good, the bad, and the ugly. J Invest Dermatol. 2012;132(3 Pt 2):985-93.
9. Grupo Ănima Educação. Manual de Revisão Bibliográfica Sistemática Integrativa: a pesquisa baseada em evidências. Belo Horizonte: Grupo Ănima Educação; 2014.
10. Hoopfer D, Holloway C, Gabos Z, Alidrisi M, Chafe S, Krause B, et al. Three-Arm Randomized Phase III Trial: Quality Aloe and Placebo Cream Versus Powder as Skin Treatment During Breast

Cancer Radiation Therapy. Clin Breast Cancer. 2015;15(3):181-90. e1-4. DOI: 10.1016/j.clbc.2014.12.006
11. Ryan Wolf J, Gewandter JS, Bautista J, Heckler CE, Strasser J, Dyk P, et al. Utility of topical agents for radiation dermatitis and pain: a randomized clinical trial. Support Care Cancer. 2020;28(7):3303-11. DOI: 10.1007/s00520-019-05166-5
12. Siddiquee S, McGee MA, Vincent AD, Giles E, Clothier R, Carruthers S, et al. Efficacy of topical Calendula officinalis on prevalence of radiation-induced dermatitis: A randomised controlled trial. Australas J Dermatol. 2021;62(1):e35-e40. DOI: 10.1111/ajd.13434
13. Sharp L, Finnilä K, Johansson H, Abrahamsson M, Hatschek T, Bergenmar M. No differences between Calendula cream and aqueous cream in the prevention of acute radiation skin reactions--results from a randomised blinded trial. Eur J Oncol Nurs. 2013;17(4):429-35. DOI: 10.1016/j.ejon.2012.11.003
14. Fenton-Kerimian M, Cartwright F, Peat E, Florentino R, Maisonet O, Budin W, et al. Optimal Topical Agent for Radiation Dermatitis During Breast Radiotherapy: A Pilot Study. Clin J Oncol Nurs. 2015;19(4):451-5.
15. Thanthong S, Nanthong R, Kongwattanakul S, Laebua K, Trirussapanich P, Pitiporn S, et al. Prophylaxis of Radiation-Induced Dermatitis in Patients With Breast Cancer Using Herbal Creams: A Prospective Randomized Controlled Trial. Integr Cancer Ther. 2020;19:1534735420920714. DOI: 10.1177/1534735420920714
16. Togni S, Maramaldi G, Bonetta A, Giacomelli L, Di Pierro F. Clinical evaluation of safety and efficacy of Boswellia-based cream for prevention of adjuvant radiotherapy skin damage in mammary carcinoma: a randomized placebo controlled trial. Eur Rev Med Pharmacol Sci. 2015;19(8):1338-44.
17. Geara FB, Eid T, Zouain N, Thebian R, Andraos T, Chehab C, et al. Randomized, Prospective, Open-label Phase III Trial Comparing Mebo Ointment With Biafine Cream for the Management of Acute Dermatitis During Radiotherapy for Breast Cancer. Am J Clin Oncol. 2018;41(12):1257-62. DOI: 10.1097/COC.0000000000000460
18. Jensen JM, Gau T, Schultze J, Lemmnitz G, Fölster-Holst R, May T, et al. Treatment of acute radiodermatitis with an oil-in-water emulsion following radiation therapy for breast cancer: a controlled, randomized trial. Strahlenther Onkol. 2011;187(6):378-84. DOI:10.1007/s00066-011-2224-8
19. Rollmann DC, Novotny PJ, Petersen IA, Garces YI, Bauer HJ, Yan ES, et al. Double-Blind, Placebo-Controlled Pilot Study of Processed Ultra Emu Oil Versus Placebo in the Prevention of Radiation Dermatitis. Int J Radiat Oncol Biol Phys. 2015;92(3):650-8. DOI: 10.1016/j.ijrobp.2015.02.028
20. Halm MA, Baker C, Harshe V. Effect of an essential oil mixture on skin reactions in women undergoing radiotherapy for breast cancer: a pilot study. J Holist Nurs. 2014;32(4):290-303. DOI: 10.1177/0898010114527184
21. Ravo V, Calvanese MG, Di Franco R, Crisci V, Murino P, Manzo R, et al. Prevention of cutaneous damages induced by radiotherapy in breast cancer: an institutional experience. Tumori. 2011;97(6):732-6. DOI: 10.1700/1018.11089
22. Kong M, Hwang DS, Lee JY, Yoon SW. The Efficacy and Safety of Jaungo, a Traditional Medicinal Ointment, in Preventing Radiation Dermatitis in Patients with Breast Cancer: A Prospective, Single-Blinded, Randomized Pilot Study. Evid Based Complement Alternat Med. 2016;2016:9481413. DOI: 10.1155/2016/9481413
23. Aysan E, Idiz UO, Elmas L, Saglam EK, Akgun Z, Yucel SB. Effects of Boron-Based Gel on Radiation-Induced Dermatitis in Breast Cancer: A Double-Blind, Placebo-Controlled Trial. J Invest Surg. 2017;30(3):187-92. DOI: 10.1080/08941939.2016.1232449
24. Becker-Schiebe M, Mengs U, Schaefer M, Bulitta M, Hoffmann W. Topical use of a silymarin-based preparation to prevent radiodermatitis: results of a prospective study in breast cancer patients. Strahlenther Onkol. 2011;187(8):485-91. DOI: 10.1007/s00066-011-2204-z
25. Chitapanarux I, Tovanabutra N, Chiewchanvit S, Sripan P, Chumachote A, Nobnop W, et al. Emulsion of Olive Oil and Calcium Hydroxide for the Prevention of Radiation Dermatitis in Hypofractionation Post-Mastectomy Radiotherapy: A Randomized Controlled Trial. Breast Care (Basel). 2019;14(6):394-400. DOI: 10.1159/000496062
26. Rizza L, D'Agostino A, Girlando A, Puglia C. Evaluation of the effect of topical agents on radiation-induced skin disease by reflectance spectrophotometry. J Pharm Pharmacol. 2010;62(6):779-85. DOI: 10.1211/jpp/62.06.0015 ISSN 0022-3573
27. Ben-David MA, Elkayam R, Gelernter I, Pfeffer RM. Melatonin for Prevention of Breast Radiation Dermatitis: A Phase II, Prospective, Double-Blind Randomized Trial. Isr Med Assoc J. 2016;18(3-4):188-92.
28. Kong M, Hong SE. Topical use of recombinant human epidermal growth factor (EGF)-based cream to prevent radiation dermatitis in breast cancer patients: a single-blind randomized preliminary study. Asian Pac J Cancer Prev. 2013;14(8):4859-64.
29. Nasser NJ, Fenig S, Ravid A, Nouriel A, Ozery N, Gardyn S, et al. Vitamin D ointment for prevention of radiation dermatitis in breast cancer patients. NPJ Breast Cancer. 2017;3:10. DOI: 10.1038/s41523-017-0006-x
30. Hindley A, Zain Z, Wood L, Whitehead A, Sanneh A, Barber D, et al. Mometasone furoate cream reduces acute radiation dermatitis in patients receiving breast radiation therapy: results of a randomized trial. Int J Radiat Oncol Biol Phys. 2014;90(4):748-55. DOI: 10.1016/j.ijrobp.2014.06.033
31. Ho AY, Olm-Shipman M, Zhang Z, Siu CT, Wilgucki M, Phung A, et al. A Randomized Trial of Mometasone Furoate 0.1% to Reduce High-Grade Acute Radiation Dermatitis in Breast Cancer Patients Receiving Postmastectomy Radiation. Int J Radiat Oncol Biol Phys. 2018;101(2):325-33. DOI: 10.1016/j.ijrobp.2018.02.006
32. Miller RC, Schwartz DJ, Sloan JA, Griffin PC, Deming RL, Anders JC, et al. Mometasone furoate effect on acute skin toxicity in breast cancer patients receiving radiotherapy: a phase III double-blind, randomized trial from the North Central Cancer Treatment Group N06C4. Int J Radiat Oncol Biol Phys. 2011;79(5):1460-6. DOI: 10.1016/j.ijrobp.2010.01.031
33. Meghrajani CF, Co HS, Arcillas JG, Maaño CC, Cupino NA. A randomized, double-blind trial on the use of 1% hydrocortisone cream for the prevention of acute radiation dermatitis. Expert Rev Clin Pharmacol. 2016;9(3):483-91. DOI: 10.1586/17512433.2016.1126506
34. Ulff E, Maroti M, Serup J, Falkmer U. A potent steroid cream is superior to emollients in reducing acute radiation dermatitis in breast cancer patients treated with adjuvant radiotherapy. A randomised study of betamethasone versus two moisturizing creams. Radiother Oncol. 2013;108(2):287-92. DOI: 10.1016/j.radonc.2013.05.033
35. Ulff E, Maroti M, Serup J, Nilsson M, Falkmer U. Prophylactic treatment with a potent corticosteroid cream ameliorates radiodermatitis, independent of radiation schedule: A randomized double blinded study. Radiother Oncol. 2017;122(1):50-3. DOI: 10.1016/j.radonc.2016.11.013
36. Diggelmann KV, Zytkovicz AE, Tuaine JM, Bennett NC, Kelly LE, Herst PM. Mepilex Lite dressings for the management of radiation-induced erythema: a systematic inpatient controlled clinical trial. Br J Radiol. 2010;83(995):971-8. DOI: 10.1259/bjr/62011713
37. Paterson DB, Poonam P, Bennett NC, Peszynski RI, Beekhuizen MJV, Jasperse ML, et al. Randomized intra-patient controlled trial of mepilex lite dressings versus aqueous cream in managing radiation-induced skin reactions postmastectomy. J Cancer Sci Ther. 2012;4(11):347-56. DOI:10.4172/1948-5956.1000166

38. Morgan K. Radiotherapy-induced skin reactions: prevention and cure. Br J Nurs. 2014;23(16):S24,6-32. DOI: 10.12968/bjon.2014.23.Sup16.S24
39. Herst PM, Bennett NC, Sutherland AE, Peszynski RI, Paterson DB, Jasperse ML. Prophylactic use of Mepitel Film prevents radiation-induced moist desquamation in an intra-patient randomised controlled clinical trial of 78 breast cancer patients. Radiother Oncol. 2014;110(1):137-43. DOI: 10.1016/j.radonc.2014.01.005
40. Møller PK, Olling K, Berg M, Habæk I, Haislund B, Iversen AM, et al. Breast cancer patients report reduced sensitivity and pain using a barrier film during radiotherapy - A Danish intra-patient randomized multicentre study. Tech Innov Patient Support Radiat Oncol. 2018;7:20-5. DOI: 10.1016/j.tipsro.2018.05.004
41. Schmeel LC, Koch D, Stumpf S, Leitzen C, Simon B, Schüller H, et al. Prophylactically applied Hydrofilm polyurethane film dressings reduce radiation dermatitis in adjuvant radiation therapy of breast cancer patients. Acta Oncol. 2018;57(7):908-15. DOI: 10.1080/0284186X.2018.1441542
42. Laffin N, Smyth W, Heyer E, Fasugba O, Abernethy G, Gardner A. Effectiveness and Acceptability of a Moisturizing Cream and a Barrier Cream During Radiation Therapy for Breast Cancer in the Tropics: A Randomized Controlled Trial. Cancer Nurs. 2015;38(3):205-14. DOI: 10.1097/NCC.0000000000000016
43. Shaw SZ, Nien HH, Wu CJ, Lui LT, Su JF, Lang CH. 3M Cavilon No-Sting Barrier Film or topical corticosteroid (mometasone furoate) for protection against radiation dermatitis: A clinical trial. J Formos Med Assoc. 2015;114(5):407-14. DOI: 10.1016/j.jfma.2013.04.003
44. Ahn S, Sung K, Kim HJ, Choi YE, Lee YK, Kim JS, et al. Reducing Radiation Dermatitis Using a Film-forming Silicone Gel During Breast Radiotherapy: A Pilot Randomized-controlled Trial. In Vivo. 2020;34(1):413-22. DOI: 10.21873/invivo.11790
45. Kirova YM, Fromantin I, De Rycke Y, Fourquet A, Morvan E, Padiglione S, et al. Can we decrease the skin reaction in breast cancer patients using hyaluronic acid during radiation therapy? Results of phase III randomised trial. Radiother Oncol. 2011;100(2):205-9. DOI: 10.1016/j.radonc.2011.05.01
46. Pinnix C, Perkins GH, Strom EA, Tereffe W, Woodward W, Oh JL, et al. Topical hyaluronic acid vs. standard of care for the prevention of radiation dermatitis after adjuvant radiotherapy for breast cancer: single-blind randomized phase III clinical trial. Int J Radiat Oncol Biol Phys. 2012;83(4):1089-94. DOI: 10.1016/j.ijrobp.2011.09.021
47. Rahimi A, Mohamad O, Albuquerque K, Kim DWN, Chen D, Thomas K, et al. Novel hyaluronan formulation for preventing acute skin reactions in breast during radiotherapy: a randomized clinical trial. Support Care Cancer. 2020;28(3):1481-9. DOI: 10.1007/s00520-019-04957-0
48. Aquino-Parsons C, Lomas S, Smith K, Hayes J, Lew S, Bates AT, et al. Phase III Study of Silver Leaf Nylon Dressing vs Standard Care for Reduction of Inframammary Moist Desquamation in Patients Undergoing Adjuvant Whole Breast Radiation Therapy. J Med Imaging Radiat Sci. 2010;41(4):215-21. DOI: 10.1016/j.jmir.2010.08.005
49. Hemati S, Asnaashari O, Sarvizadeh M, Motlagh BN, Akbari M, Tajvidi M, et al. Topical silver sulfadiazine for the prevention of acute dermatitis during irradiation for breast cancer. Support Care Cancer. 2012;20(8):1613-8. DOI: 10.1007/s00520-011-1250.
50. Gosselin TK, Schneider SM, Plambeck MA, Rowe K. A prospective randomized, placebo-controlled skin care study in women diagnosed with breast cancer undergoing radiation therapy. Oncol Nurs Forum. 2010;37(5):619-26.
51. Bazire L, Fromantin I, Diallo A, de la Lande B, Pernin V, Dendale R, et al. Hydrosorb® versus control (water based spray) in the management of radio-induced skin toxicity: Results of multicentre controlled randomized trial. Radiother Oncol. 2015;117(2):229-33. DOI: 10.1016/j.radonc.2015.08.028
52. Sekiguchi K, Ogita M, Akahane K, Haga C, Ito R, Arai S, et al. Randomized, prospective assessment of moisturizer efficacy for the treatment of radiation dermatitis following radiotherapy after breast-conserving surgery. Jpn J Clin Oncol. 2015;45(12):1146-53. DOI: 10.1093/jjco/hyv155
53. Kouloulias V, Asimakopoulos C, Tolia M, Filippou G, Platoni K, Dilvoi M, et al. Sucralfate gel as a radioprotector against radiation induced dermatitis in a hypo-fractionated schedule: a non-randomized study. Hippokratia. 2013;17(2):126-9.
54. Falkowski S, Trouillas P, Duroux JL, Bonnetblanc JM, Clavère P. Radiodermatitis prevention with sucralfate in breast cancer: fundamental and clinical studies. Support Care Cancer. 2011;19(1):57-65. DOI: 10.1007/s00520-009-0788-y
55. Censabella S, Claes S, Orlandini M, Braekers R, Thijs H, Bulens P. Retrospective study of radiotherapy-induced skin reactions in breast cancer patients: reduced incidence of moist desquamation with a hydroactive colloid gel versus dexpanthenol. Eur J Oncol Nurs. 2014;18(5):499-504. DOI: 10.1016/j.ejon.2014.04.009
56. Censabella S, Claes S, Orlandini M, Braekers R, Bulens P. Efficacy of a hydroactive colloid gel versus historical controls for the prevention of radiotherapy-induced moist desquamation in breast cancer patients. Eur J Oncol Nurs. 2017;29:1-7. DOI: 10.1016/j.ejon.2017.04.003
57. Pardo Masferrer J, Murcia Mejía M, Vidal Fernández M, Alvarado Astudillo A, Hernández Armenteros ML, Macías Hernández V, et al. Prophylaxis with a cream containing urea reduces the incidence and severity of radio-induced dermatitis. Clin Transl Oncol. 2010;12(1):43-8. DOI: 10.1007/s12094-010-0465-0
58. Chan RJ, Larsen E, Chan P. Re-examining the evidence in radiation dermatitis management literature: an overview and a critical appraisal of systematic reviews. Int J Radiat Oncol Biol Phys. 2012;84(3):e357-62. DOI: 10.1016/j.ijrobp.2012.05.009
59. Meghrajani CF, Co HC, Ang-Tiu CM, Roa FC. Topical corticosteroid therapy for the prevention of acute radiation dermatitis: a systematic review of randomized controlled trials. Expert Rev Clin Pharmacol. 2013;6(6):641-9. DOI: 10.1586/17512433.2013.841079
60. Zhang Y, Zhang S, Shao X. Topical agent therapy for prevention and treatment of radiodermatitis: a meta-analysis. Support Care Cancer. 2013;21(4):1025-31. DOI: 10.1007/s00520-012-1622-5
61. Yee C, Wang K, Asthana R, Drost L, Lam H, Lee J, et al. Radiation-induced Skin Toxicity in Breast Cancer Patients: A Systematic Review of Randomized Trials. Clin Breast Cancer. 2018;18(5):e825-40. DOI: 10.1016/j.clbc.2018.06.015

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