

Clinical Update

by Donald J. Brown, N.D.

9. Heftmann E, Ko ST, Bennett RD. Identification of estrone in pomegranate seeds. *Phytochem*. 1966;5:1337-1340.
10. Kim ND, Metha R, Yu W, et al. Chemopreventive and adjuvant therapeutic potential of pomegranate (*Punica granatum*) for human breast cancer. *Breast Cancer Res Treatment*. 2002;71:203-217.
11. Kaplan M, Hayek T, Raz A, et al. Pomegranate juice supplementation to atherosclerotic mice reduces macrophage lipid peroxidation, cellular cholesterol accumulation and development of atherosclerosis. *J Nutr*. 2001;131:2082-2089.
12. Aviram M, Dronfeld L, Rosenblat M, et al. Pomegranate juice consumption reduces oxidative stress, atherogenic modifications to LDL, and platelet aggregation: studies in humans and in atherosclerotic apolipoprotein E-deficient mice. *Am J Clin Nutr*. 2000;71:1062-1076.
13. Aviram M, Dronfeld L. Pomegranate juice consumption inhibits serum angiotensin converting enzyme activity and reduces systolic blood pressure. *Atherosclerosis* 2001;158:195-198.

Calendula Ointment Reduces Radiation-Induced Dermatitis in Breast Cancer Patients

Reviewed: Pommier P, Gomez F, Sunyach MP, et al. Phase III Randomized trial of *Calendula officinalis* compared with trolamine for prevention of acute dermatitis during irradiation for breast cancer. *J Clin Oncol*. 2004;22:1447-1453.

Summary: In a randomized, single-blind clinical trial, 254 women (ages 18-75 years; mean 55.8 years) with breast cancer receiving postoperative radiation therapy were randomized to receive either topical calendula (*Calendula officinalis* L., Asteraceae); ointment in 100 gram tubes or trolamine (Beirdorf, Inc., Wilton, CT). (The calendula extract ointment is sold as Pommade au Calendula par Digestion, made by Boiron Ltd, Levallois-Perret, France.*) Women applied the study medication at least twice a day, but could apply more if their dermatitis and pain warranted additional applications. Participants applied topical treatment at the onset of radiation therapy and until its completion. For inclusion in the trial, women were required to have nonmetastatic adenocarcinoma treated with either lumpectomy or mastectomy with and without adjuvant postoperative chemotherapy or hormonal therapy, and referred to the Department of Radiotherapy (Centre Léon Bérard, Lyon, France) for postoperative radiation therapy. The clinical trial lasted 8 months.

The primary outcome measure was the efficacy of calendula and trolamine for the prevention of grade 2 or higher dermatitis caused by radiotherapy for breast cancer. Skin toxicity grading has previously been defined by the Radiation Therapy Oncology Group (RTOG). Grade 0 corresponds to no physical signs of skin toxicity. Grade 1 skin toxicity displays follicular, faint, or dull erythema (redness of the skin caused by dilation and congestion of the capillaries); epilation (the act or result of removing hair), dry desquamation (the shedding or peeling of the epidermis in

scales), or decrease in sweating. Grade 2 skin toxicity is tender with bright erythema; patchy, moist desquamation or moderate erythema. Grade 3 skin toxicity is defined as having confluent, moist desquamation, other than skin folds, and pitting edema. Grade 4 skin toxicity exhibits ulceration, hemorrhage, and necrosis. Secondary measures included weekly assessments of pain using a visual analog scale (VAS), interruptions to treatment due to skin reactions from the ointments, patient satisfaction, and the quality of the study medication.

Grade 2 or 3 skin toxicity was experienced in 41% of the women in the calendula treatment group compared to 63% of women in the trolamine group ($p < 0.001$). Women in the calendula group also experienced significantly less grade 3 toxicity (7% using calendula vs. 20% using trolamine; $p = 0.034$). Less grade 2 or 3 skin toxicity was observed in women using calendula compared to women using trolamine in the submammary fold (34% vs. 50%, respectively; $p = 0.02$), armpit and tangential area (28% vs. 48%, respectively; $p = 0.004$), and the supraclavicular nodes (28% vs. 63%, respectively; $p < 0.001$). None of the women in either group experienced grade 4 toxicity. The VAS for pain was significantly less in the calendula group compared to the trolamine group (1.54 vs. 2.10, respectively; $p = 0.03$).

Volunteers using the calendula ointment did not experience any allergic reactions, while 4 patients using trolamine experienced itching and hives. Twelve treatment interruptions (9%), for a mean duration of 10 days each, occurred in the trolamine group due to skin toxicity. No interruptions for skin toxicity occurred in the calendula group. Thirty percent of volunteers rated application of the calendula ointment as "difficult" compared to 5% of volunteers using trolamine. (There was no explanation in the paper regarding the meaning of the term "difficult" so it is not possible to determine the significance of this finding.) Two patients discontinued using the calendula ointment due to this difficulty. Eighty-four percent of physicians rated adherence to application of the medications as "good" for calendula compared to 92% for adherence to trolamine ($p = 0.047$). Women in the calendula group used 1.62 times less ointment during the study period compared to women using trolamine (2.7 tubes vs. 4.4 tubes, respectively).

Comments/Opinions: This large clinical trial suggests that calendula ointment is a safe and cost effective treatment for prevention of mild to severe radiation-induced dermatitis in women being treated with radiation therapy for breast cancer. Although the trial lacks a placebo group (based on ethical concerns), the comparison to the control substance, trolamine, points to calendula as an interesting alternative for women not wishing to use steroid-based creams or other more aggressive treatment such as sucalfate or hyaluronic acid.

The reference drug, trolamine (a soap substitute used for burn patients), is widely recommended in France for radiation-induced dermatitis due to a small risk of side effects. The researchers note that it has been used for several years in their clinic. This trial suggests that not only is calendula superior for preventing acute dermatitis but it is also less likely to lead to side effects such as itching or hives. However, it is important to note that some studies have found that trolamine was no more effective in preventing

* The calendula product used in the study is obtained by incubation of calendula flowers (marigold) at 75°C in petroleum jelly to extract the liposoluble components.

radiation-induced dermatitis than supportive care or no treatment at all, although one study did suggest that trolamine might have curative properties.^{1,2} Other nonsteroidal topical agents (e.g., aloe vera, soy oil) have also failed to prevent dermatitis in smaller clinical trials.^{3,4} In a randomized, open-label, parallel group study with 156 patients with second and third degree burns, the effectiveness of topical calendula ointment was compared with Elase (a “proteolytic” ointment; Pfizer, New York, NY) and petroleum jelly.⁵ The calendula ointment was found to be better tolerated but only marginally better than petroleum jelly alone for healing. Randomized trials with more aggressive treatments such as corticosteroid creams and sucralfate have accrued few patients and the radiation sites were more numerous and not as uniform as those in the reviewed study with calendula.^{6,7} The results using calendula certainly point to a follow-up trial using corticosteroid cream or ointment as a comparison to calendula ointment.

In addition to its potential use for radiation-induced dermatitis, healthcare practitioners should also be aware that topical calendula has been reported to reduce pain associated with post-mastectomy lymphedema.⁸ However, one study was unable to support this claim.⁹

Traditionally, calendula (pot marigold) has been used both externally for treating superficial wounds and burns, and internally for stomach ulcers and liver complaints.¹⁰ The German Commission E approves the topical use of flower preparations for the treatment of poorly healing wounds.¹¹ While the wound-healing and anti-inflammatory actions have been demonstrated, the active principles that promote wound healing have yet to be clearly identified.¹² The renowned German phytotherapy expert, Rudolf Fritz Weiss, MD, warned that the potent stimulation of granulation tissue by calendula may result in a later risk of keloid formation when using it for more severe wounds.¹³ Warnings for the topical use of the herb also extend to allergic reactions, particularly in those individuals with known hypersensitivity to plants of the family Asteraceae.¹⁴

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Practice Implications: This trial suggests that calendula ointment is an effective option in the prevention of acute dermatitis in women receiving radiation therapy for breast cancer. While topical treatments such as corticosteroid cream are often used for the treatment of acute radiation-induced dermatitis, there are no standard treatments for prevention of the condition—one that affects approximately 80% of women receiving radiation therapy. Hopefully, manufacturers of calendula ointments will take a close look at the issue of application difficulties and work on topical forms that are easier to apply. 🌱

References

1. Fenig E, Brenner B, Katz A, et al. Topical Biafine and Lipiderm for the prevention of radiation dermatitis: A randomized prospective trial. *Oncol Rep.* 2001;8:305–309.
2. Fisher J, Scott C, Stevens R, et al. Randomized phase III study comparing best supportive care to Biafine as a prophylactic agent for radiation-induced skin toxicity for women undergoing breast irradiation: Radiation Therapy Oncology Group (RTOG) 97-13. *Int J Radiat Oncol Biol Phys.* 2000;48:1307–1310.

3. Williams MS, Burk M, Loprinzi CL, et al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *Int J Radiat Oncol Biol Phys.* 1996;36:345–349.
4. Fenig E, Brenner B, Katz, A, et al. Topical Biafine and Lipiderm for the prevention of radiation dermatitis: A randomized prospective trial. *Oncol Rep.* 2001;8:305–309.
5. Lievre M, Marichy J, Baux S, et al. Controlled study of three ointments for the local management of 2nd and 3rd degree burns. *Clin Trials Metaanalysis.* 1992;28:9–12.
6. Bostrom A, Lindman H, Swartling C, et al. Potent corticosteroid cream (mometasone furoate) significantly reduces acute radiation dermatitis: Results from a double-blind, randomized study. *Radiother Oncol.* 2001;59:257–265.
7. Maiche A, Isokagnas OP, Grohn P. Skin protection by sucralfate cream during electron beam therapy. *Acta Oncol.* 1994;33:201–203.
8. Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines: A Guide for Healthcare Professionals.* London: Pharmaceutical Press; 2002:103–106.
9. Casley-Smith JR. The effect of “Unguentum lymphaticum” on acute experimental lymphedema and other high protein edemas. *Lymphology.* 1983;16:150–156.
10. Ellingwood F. *American Materia Medica, Therapeutics and Pharmacognosy.* Portland, OR: Eclectic Medical Publications; 1983.
11. Blumenthal M, Busse WR, Goldberg A, Gruenwald J, Hall T, Riggins CW, Rister RS, editors. Klein S, Rister RS, translators. *The Complete German Commission E Monographs—Therapeutic Guide to Herbal Medicines.* Austin (TX): American Botanical Council; Boston: Integrative Medicine Communication; 1998:100–101.
12. Schulz V, Hänsel R, Blumenthal, M, Tyler VE. *Rational Phytotherapy: A Physicians' Guide to Herbal Medicine.* 5th ed. Berlin: Springer-Verlag; 2004:310.
13. Weiss RF, Fintelmann V. *Herbal Medicine.* Stuttgart, Germany: Thieme; 2000:312.
14. Barnes J, Anderson LA, Phillipson JD. *Herbal Medicines: A Guide for Healthcare Professionals.* London: Pharmaceutical Press; 2002:103–106.

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