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Exploring the Role of Natural Treatments in Wound Healing: An Update on Calendula

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EDUCATIONAL OBJECTIVES

Pharmacists

At the completion of this activity, the participant will be able to:

- Examine the process of wound healing and the role of natural alternative treatments
- Explore the use of calendula in dermatologic applications, such as wound healing and post-radiation dermatologic complications
- Compare the variety of topical dosage forms available for wound management
- Identify the pharmacist's role and opportunities for patient education in the treatment of wounds using natural alternative therapies

Pharmacy Technicians

At the completion of this activity, the participant will be able to:

- Discuss the role of natural alternative treatments in wound healing
- List the uses of calendula in dermatologic applications
- Describe the variety of topical dosage forms available for wound management
- Identify opportunities for patient education in the treatment of wounds using natural alternative therapies

TARGET AUDIENCE: Pharmacists and pharmacy technicians

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INTRODUCTION

Wounds and skin disease can be socially and financially burdensome to affected individuals. Skin ulcers and wounds ranked in the top 5 of the most economically burdensome skin diseases.[1] Wound care products and therapies can promote the healing process, reduce scar formation, and improve the new skin's properties. Certain natural compounds have demonstrated potential anti-inflammatory, antimicrobial, and cell-stimulating properties that may aid wound healing.[2,3] These complementary and alternative (CAM) or complementary and integrative medicine (CIM) therapies using plant extracts have been used in wound healing for centuries. Homeopathic treatments, as discussed here, are a branch of CAM therapy.

Approximately 33% of US adults use some form of CAM or CIM.[4,5] In addition, more than 15 million Americans use CAM (herbal products [including homeopathic] or high-dose vitamins) with their prescription medications.[4] Comparative clinical trials for homeopathic medications are increasing in number; however, the complexity of standardizing scientific methods for such therapies is difficult. Evidence-based data supporting the use of these therapies are lacking.[4] CAM or CIM therapies for wound healing are typically less expensive than prescription medications but have not been associated with bacterial resistance.[2,3] Several CAM or CIM therapies have been used historically for potential effects on skin healing; however, clinical trials have not shown clear benefits for many of these products. Some of

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these well-known products include aloe vera, ginkgo biloba, St. John's wort, and honey. Other plant extracts such as tea tree oil, oak bark, and calendula extract have also been used for wound healing. This article will focus on CAM in wound healing and, more specifically, the use of calendula.

WOUND HEALING

Skin disorders and wounds are generally defined based on the depth of injury, healing time, healing progression, underlying pathology, associated risk of mortality, and the effect on quality of life.[6,7] Surgical and traumatic wounds, burns, radiation dermatitis, and abrasions (including scrapes and microdermabrasion) are considered acute wounds, whereas venous and arterial leg ulcers, fungating wounds, pressure ulcers, and diabetic ulcers are classified as chronic wounds. Healing time and sequence also delineate acute versus chronic wounds. In general, acute wounds can repair themselves in an orderly and timely manner, unlike chronic wounds.[8]

Typical wound healing progresses through key phases. All phases occur in an overlapping sequence and progress until healing is complete.[9,10] Minor wounds are superficial, shallow, noninfected wounds that occur in patients without comorbid conditions that could complicate treatment (such as diabetes or immune deficiencies). Phase 1 of wound healing controls bleeding.[9,11] Vascular constriction, platelet migration, and fibrin clot formation reestablish hemostasis shortly after vascular injury and provide an extracellular matrix for cell migration.[9,11] Through this process, mediators of wound healing attract inflammatory cells to the area of injury, progressing into the next phase of inflammation.[10]

Phase 2 overlaps with the previous hemostasis and coagulation phase and begins within a few hours of injury. It is primarily defined by the accumulation of leukocytes and macrophages.[11,12] Macrophages enter the wound site and release growth factors, such as platelet-derived growth factor, which facilitate the formation of new connective tissue (ie, granular tissue).[11] Macrophages also help resolve inflammation and stimulate tissue regeneration, facilitating the transition from the inflammatory to reparative phases of proliferation and remodeling.[9]

Occurring from 3 to 21 days post injury, phase 3 (proliferation) is characterized by granulation tissue formation, re-epithelialization of the wound surface, and contraction of the wound margins.[9,12] Granulation tissue will contain macrophages, fibroblasts, and immature collagen, all of which stimulate granulation tissue formation. Concurrently, blood vessels will stimulate capillary growth. Fibroblasts within the wound bed stimulate the production of collagen, one of the key components of the extracellular matrix. The final phase of wound healing (phase 4) can last for years and involves the reorganization of collagen fibers to create new skin.[9,12] New skin may gain less than a quarter of its final strength in the first 3 weeks and rarely ever reaches the same strength as uninjured skin.[11]

STAR*

How do the CAM and homeopathic product regulatory pathways differ?

**S = Stop; T = Think; A = Assess; R = Review*

CAM, HOMEOPATHY, AND REGULATION

CAM products are regulated differently depending on their classification as dietary supplements or homeopathic drugs.[4] The regulatory mechanism for dietary supplements is primarily postmarketing in nature and applies to most CAM products. Currently, the American regulatory system defines most of these products as dietary supplements. Compared with the FDA approval process for drugs and biologics, manufacturers can produce and sell dietary supplements without demonstrating safety before they market a product.[13,14]

Products designated "homeopathic," however, undergo a premarket regulatory process. Homeopathy is based on the principle of similars or "like cures like," and was established more than 200 years ago.[15] This concept theorizes that substances causing healthy people to experience symptoms of a disease can also cure diseases in dilute amounts. In other words, high doses of pharmacologically active substances may cause symptoms when administered to healthy individuals and, when prepared in very dilute forms, may relieve the same symptoms.[15] Homeopathic remedies are derived from substances that come from plants, minerals, or animals and are traditionally highly diluted. However, it is important to note that not all homeopathic remedies are diluted and may contain substantial amounts of active ingredients, contributing to adverse effects (AEs) and drug interactions as with any drug or dietary supplement that has chemical ingredients.[16]

Homeopathic drugs are subject to the Federal Food, Drug, and Cosmetic Act laws and FDA regulations. Manufacturing, labeling, marketing, and sales of homeopathic drugs are subject to FDA compliance rules.[16] Many homeopathic drugs are available over the counter (OTC) and may not claim treatment of a serious disease, such as cancer, but rather claim treatment of minor health problems that are self-limiting, such as a cold or headache.[16] Patients should be instructed that homeopathy is not a substitute for conventional care. However, it is still important for pharmacists to be familiar with homeopathic agents so that they may appropriately address questions from patients seeking consultation regarding natural remedies.

The Homeopathic Pharmacopoeia of the United States (HPUS), which is developed by the Homeopathic Pharmacopoeia Convention of the United States (HPCUS), a nongovernmental organization, provides a list of official homeopathic drugs that have monographs.[17] To be included in the HPUS, the HPCUS must determine the product to be safe, effective, and prepared according to the specifications of the HPUS general pharmacy section. Additionally, the drug must meet at least one of several

TABLE 1. CRITERIA FOR INCLUSION IN THE HPUS[18]

Clinical benefits must be demonstrated through clinical verification by the HPCUS
Published documentation indicating that the substance was in use prior to 1962 exists
Therapeutic use is established by at least 2 adequately controlled double-blind clinical studies using the drug as the single intervention; or by data gathered from clinical experience encompassing the symptom picture before and after treatment, including subjective and any available objective symptoms

HPCUS indicates Homeopathic Pharmacopoeia Convention of the United States; HPUS, Homeopathic Pharmacopoeia of the United States.

criteria listed in TABLE 1.[18] It is important to note that not all products have achieved all of these criteria but rather may have met one for inclusion. The HPUS monograph process is substantially different from the new drug approval process of clinical trials required for prescription medications. This difference reflects the clinical history of homeopathic drugs.

The Federal Trade Commission's 2016 policy statement titled *Enforcement Policy Statement on Marketing Claims for Over-the-Counter Homeopathic Drugs* holds efficacy and safety claims for OTC homeopathic drugs to the same standards as other non-homeopathic drugs making similar claims. Companies must have "competent and reliable scientific evidence" for homeopathic health-related claims.[19] Labeling of homeopathic OTC drugs that have not been substantiated by competent and reliable scientific evidence would have to include statements that acknowledge this or include a clarification that the theories of homeopathy are not supported by modern medicine. This additional marketing requirement is intended to prevent misleading claims to the public.[19]

TOPICAL DOSAGE FORMS FOR WOUND MANAGEMENT

Topical drug absorption is a passive process. Percutaneous absorption of medications (ie, the rate-limiting step) requires passage through the outermost layer of the skin.[20] Cutaneous drugs are absorbed systemically from the superficial capillary plexus (residing between the epidermis and dermis). When the stratum corneum is hydrated, more percutaneous absorption occurs. Heat and occlusion can also increase drug penetration. Clinicians should consider these factors, in conjunction with treatment goals and the type of skin irritation or wound, when considering a topical medication's delivery system.[20] Some of the most widely used dosage forms among the various topical delivery systems available include ointments, creams, gels, and foams.

Ointments

Ointments are oil based (water in oil; less than 25% water content) and are moderately to highly occlusive (form a hydrophobic film on the skin surface).[18] Due to their occlusive nature, ointments tend to have greater drug absorption and slower evaporation of water than creams. Ointments are generally greasy and may stain clothing, which may reduce medication adherence. Application of ointments to intertriginous areas (2 skin areas that may rub together) can lead to maceration (breakdown of epidermis) and folliculitis (increased bacterial growth leading to infection); therefore, it should be avoided. Ointments are an ideal vehicle to increase drug concentrations and moisturize skin, but they may aggravate skin conditions such as acne.[21]

Creams

Creams are oil-in-water emulsions (31%-80% water content) that are easily applied, useful on most areas of the skin, and deliver concentrated drug to the skin surface.[20] Some creams have emollients added to them that can help to reduce transepidermal water loss.[21] Additionally, a humectant can be added to a cream to draw water from the dermis to the epidermis. Creams are not generally occlusive or greasy.[21,22] Creams leave the concentrated drug on the skin's surface and are also easily removed.[20] Preservatives must be added to creams to maintain stability and extend product shelf life. Patients may experience irritation, stinging, or allergic reactions because of these additives, which can further aggravate the skin condition. Creams are typically selected for skin conditions that do not need occlusion, are often of a lower potency than ointments, and can have a drying effect on skin.[21]

Gels and Foams

Gels and foams are water-soluble emulsions that concentrate drug on the surface of the skin after they have evaporated. These tend to be greaseless and nonstaining.[20] Unlike creams and ointments, gels and foams are ideal for hairy skin because they are quickly and easily absorbed without leaving any residue. However, gels and foams have a high alcohol content and can be drying, which can further aggravate the skin condition. Also, gels and foams need preservatives and tend to be more expensive than creams or ointments (as are shampoos and mousses).[21]

CAM OR CIM TO PROMOTE WOUND HEALING

CAM or CIM therapies have shown mixed results for use in general wound healing. Standardized clinical trials are needed to determine their place in therapy before routine use can be recommended.[3] Aloe vera, tea tree oil, St. John's wort, ginkgo biloba, oak bark, honey, and calendula have been used topically for many years. A review of each of these products follows.

Aloe vera

Aloe vera is a cactus-like succulent plant that is native to hot climates (but often grown as a house plant in other climates) and has been used for wounds, skin infections, burns, and numerous other dermatologic conditions for centuries. Aloe vera gel, available in many products, is the colorless, mucilaginous gel obtained by splitting open the fresh, meaty leaves of the plant.[23,24] Topical aloe vera exerts an anti-inflammatory effect by stimulating bradykinase

activity and inhibiting thromboxane B2 and prostaglandin F2α production.[25,26] It also modulates macrophage activity, which improves wound healing.[27]

Although topical aloe vera is widely used as an OTC remedy for minor burns, there is little evidence to support its use for general wound healing. An aloe gel extract (Carrington Dermal wound gel) was applied to surgical wounds (N = 21) after cesarean delivery or laparotomy for gynecologic surgery; all incisions had opened spontaneously or had been drained to treat a seroma, hematoma, or wound abscess before referral to the outpatient clinic. The researchers compared aloe vera dermal gel plus standard wound care with standard wound care alone. In this study, patients treated with aloe vera gel and standard wound care took 30 days longer to heal than those treated with standard wound care only (P = .003).[28] In another study, a hydrogel containing acemannan, an aloe constituent, did not improve wound epithelialization or pain control in patients with biopsy wounds as compared with standard therapy.[29]

Molazem et al (N = 90) found that applying aloe gel (Carrington Carrasyn Hydrogel Wound Dressing) plus dry gauze to a post-cesarean delivery wound improved wound healing over the first 24 hours compared with dry gauze alone (P = .003). However, no difference in the wound healing score was noted at day 8 post surgery (P = .283).[30]

A randomized, double-blind trial compared placebo with an aloe gel powder 0.5% (Zarband) mixed with a cream. The cream was applied to posthemorrhoidectomy wounds by patients 3 times per day for 4 weeks.[31] Compared with placebo, application of an aloe-gel cream to posthemorrhoidectomy wounds reduced postoperative pain, healing time, and pain medication requirements with most significant differences noted in the days following surgery. The data supporting aloe vera's utility in wounds are conflicting. Rigorous, comparative clinical trials of aloe vera as monotherapy are needed.

Recently, a team of researchers conducted a comprehensive review of medicinal claims related to aloe vera. With reference to wound healing, the researchers cite a number of studies (many of them older) that may explain how aloe vera works. Possible mechanisms of action include increasing wound moisture and epithelial cell migration, accelerating collagen maturation, and reducing inflammation. They note that researchers propose that aloe vera's biologic and pharmacologic activities might be related to polysaccharides found in the leaf gel, demonstrating that individual polysaccharides having specific therapeutic properties is a formidable endeavor. Thus, more well-structured studies are needed. Numerous trials using aloe vera in an assortment of conditions are underway, including wound management.[32,33]

Patients using aloe vera should be cautioned about its contraindications and AEs. Patients should avoid aloe if allergic to plants of the *Liliaceae* family (garlic, onions, or tulips).[34] Aloe vera should not be applied to open skin, surgical wounds, or pressure ulcers.[24]

Tea tree oil

The tea tree, *Melaleuca alternifolia*, is a small tree or tall shrub in the myrtle family, Myrtaceae. Native to Australia, it grows along streams and on swampy flats. It has a strong medicinal odor. Steam distillation of tea tree leaves produces tea tree oil.[35-37] Based on its purported antiseptic properties, tea tree oil has been used historically to prevent and treat infections. Tea tree oil may be used topically for cuts and abrasions, burns, insect bites and stings, and boils. Fourteen of the almost 100 elements that make up tea tree oil have been standardized.[36] A quasi-experimental design was used to assess the efficacy of a tea tree oil wound dressing (2 drops of 100% tea tree oil on a pad or gauze) changed every 3 days compared with standard wound care in 10 patients with abscesses infected with *Staphylococcus aureus*. All but 1 patient treated with tea tree oil had reduced healing times. This was a small convenience study with a number of limitations. The authors did not perform a statistical analysis.[38]

A recent review of the antimicrobial properties of tea tree oil raises the proposition that this herbal, alone or in combination with heavy metals, may play a potential role in addressing the growing number of drug-resistant wound infections. The authors highlight that the amount of active compound included in the botanical extracts has differed a great deal.[35] The final concentration reflects the plant's adaptation to its environment and harvesting period as well as the manufacturer's extraction process, dehydration procedures, and purification and storage methods.[35] These concerns are not solely associated with tea tree oil but are germane to all plant-based products.

When used topically, tea tree oil is generally well tolerated. The most common AEs observed with topical tea tree oil include contact dermatitis and skin irritation.[36] Further research is needed to determine if tea tree oil is effective for wound healing.

St. John's wort

St. John's wort is a flowering plant native to Europe.[39] Both the hyperforin and hypericin constituents of St. John's wort are believed to have anti-inflammatory effects. It is thought to stimulate collagen synthesis and promote epithelial cell proliferation and migration.[40] St. John's wort preparations are used for a variety of purposes, such as bruises and abrasions, inflammation, and wound healing.[32] In a randomized, double-blind clinical trial, 144 women received St. John's wort extract (20% ointment) 3 times daily for 16 days, placebo, or no treatment for post-cesarean delivery incisions. Those treated with St. John's wort demonstrated significantly improved wound healing time and reduced scar formation compared with placebo. However, many limitations to this research reduce its applicability to practice, with the most prominent being the use of a topical preparation that is not commercially available (the investigators compounded the study drug from *Hipericum perforatum* plants).[40] Limited efficacy and safety information exist for the use of St. John's wort in wound healing. More evidence is needed to support its use.[39]

Ginkgo biloba

Similarly, ginkgo biloba liquid extracts have been used therapeutically for wound healing for centuries.[3] Ginkgo biloba is a large tree with fan-shaped leaves native to Asia but now grown around the world.[41] When used topically in wound dressings, ginkgo leaf and seed may be beneficial in increasing skin circulation and for skin sores, respectively. Radioskin 2, a cream product containing ginkgo extract, aloe vera, and metal esculetina, has been used for radiation dermatitis. It is applied 2 or 3 times daily at least 3 hours before and after radiation treatment, beginning 15 days prior to and for 1 month after radiotherapy.[42] In a pilot experimental study, 100 patients with breast cancer receiving radiation therapy were divided into 5 groups, and each was treated with a different type of topical treatment including Radioskin 2. The investigators were unable to differentiate among the products because the sample size was too small.[42] The effect of ginkgo biloba in wound healing may be attributed to its antioxidant properties as well as its ability to increase the breaking strength of granulation tissue.[2] The safety of topical ginkgo is unknown.

Oak bark

White oak (*Quercus alba*) is found primarily in North America.[43] The inner bark and the galls (growths produced in reaction to fungi or insects) may have medicinal properties. Oak bark has been used for inflammation associated with skin conditions. It should not be used topically for longer than 2 to 3 weeks, in weeping eczema, or on large areas of skin damage. It should not be taken orally due to potential renal or hepatic dysfunction. Oak bark has a high tannin content and many drug–disease interactions.[43] Data are lacking on the use of oak bark for wound healing.

Honey

Topical honey, when used appropriately, is considered safe and possibly effective.[44] Honey has been used for burns and wound healing. It is available as impregnated dressings and commercially as an FDA-approved medical device called MediHoney. Containing manuka honey, MediHoney is thought to have antibacterial activity.[45] In a Cochrane Library meta-analysis of acute wounds, it appeared that honey may improve healing times in superficial and partial thickness burns compared with conventional treatment. There are currently low-quality data to guide treatment in other wound areas. Some evidence also suggests that honey is more effective in healing wounds infected after surgery as compared with antiseptics.[45] In general, honey is well tolerated but can cause excessive drying, which can delay wound healing.

A meta-analysis published in 2019 looked at the growing body of literature examining medical-grade honey.[46] Although the authors initially identified hundreds of studies, ultimately, just 11 met their inclusion criteria. These researchers found that, in general, use of honey dressings effectively shortened the wound debridement, wound healing, and bacterial clearance times; the wound healing rate increased, whereas the bacterial clearance rate during the initial 1 to 2 weeks of use decreased. Limitations to their findings include the presence of studies that were not blinded and the fact that the honey products used in various studies were not uniform.[46]

Several herbal products have been proposed as potential wound healing products. However, rigorous scientific research to assess the efficacy and safety of these products may be lacking and routine use should be avoided.

Calendula officinalis

Calendula officinalis, commonly known as the marigold plant, has been used in many forms for centuries as an herbal remedy.[47] It is native to Asia and southern Europe but can be found in gardens around the world. Calendula's therapeutic effects can be attributed to the major chemical components of the natural extracts from the yellow-orange *Calendula officinalis* flower petals. The chemical components include triterpenoids, saponins, flavonoids, carotenoids, fatty acids, polysaccharides, and essential oils. Concentrations of these compounds vary depending on geographic area, although topical calendula's observed physiological effects appear to be consistent.[48,49] There is no known standard formulation of calendula. Calendula is available in various formulations including creams, lotions, ointments, and gels. For general use, calendula 2% to 5% ointment may be applied 3 or 4 times daily as needed.[47]

Mechanism of Action and Beneficial Effects

Calendula has demonstrated anti-inflammatory, antiviral, antioxidant, and antibacterial effects.[3,48] The active components of calendula's anti-inflammatory, antioxidant, and anti-infective activity are thought to be the triterpenoids.[47-49] Analgesic effects have also been anecdotally documented from calendula, but it is unclear if these are due to innate properties of the plant or a result of improved wound healing. Although the exact mechanism of action of *Calendula officinalis* is unknown, recent in vitro and animal studies suggest that calendula may up-regulate and increase proliferation of fibroblasts and other endogenous factors involved in wound healing after incisions.[50-52] Additionally, calendula may help to induce granulation tissue formation, which is necessary for phase 3 of the wound healing process.

STAR

What are the proposed therapeutic uses of Calendula officinalis*?*

Therapeutic Uses of Calendula Officinalis

MINOR WOUNDS, BURNS, AND ABRASIONS

Historically, topical calendula was used to treat minor wounds, burns, and abrasions; however, few clinical trials have been conducted to assess its efficacy and safety for these indications. Although an animal study suggests that calendula is beneficial for wound healing, such conclusions cannot be reasonably extrap-

olated to humans.[53] Currently, more clinical studies need to be conducted in humans for this specific indication.[48]

VENOUS ULCERS

Venous ulcer or stasis ulcer is the most common etiology of lower extremity ulceration and affects approximately 1% of Americans.[54] Venous ulcers are irregular, shallow, and usually recurrent. Treatment typically includes leg elevation, compression therapy, wound dressings, pentoxifylline, and aspirin.[54] Calendula has been studied as a possible treatment for venous leg ulcers.

In an open, comparative clinical trial, 34 patients with venous leg ulcers were treated with either an ointment containing 7.5% marigold extract in a neutral petrolatum base (from a source in Serbia and Montenegro) applied twice daily for 3 weeks or saline solution dressings applied for 3 weeks.[55] At the end of the 3-week study period, patients treated with the calendula ointment had a statistically significant reduction in the aggregate ulcer surface area compared with those in the placebo group (–41.71% vs –14.52%, respectively; P <.05). The number of wounds achieving complete epithelialization was similar in both groups (7/21 calendula vs 4/13 placebo). AEs were not reported. Despite the positive results, this study lacked an adequate control group, was not blinded, and had a small study population. Further clinical trials are warranted to explore the described benefit.[55]

A similar study in Brazil enrolled 38 active treatment participants and 19 controls with venous leg ulcers.[56] Active treatment consisted of *Calendula officinalis* extract. In the treatment arm, 74% of participants experienced complete epithelialization compared with 32% in the control arm. The average healing time was approximately 13 weeks among active treatment participants, and 22 weeks with standard therapy. The researchers noted that treatment with *Calendula officinalis* increased healing approximately 4-fold, and they reported no AEs. This study's primary limitation was a small, nonrandomized study population.[56]

RADIATION DERMATITIS IN PATIENTS WITH BREAST CANCER

Radiation dermatitis is a cutaneous repercussion of the external beam ionizing radiation used to treat malignancies.[57] Also called "radiation skin damage" or a "radiation burn," it affects approximately 95% of patients receiving radiotherapy. Skin changes after radiotherapy may be minor, reversible, and self-limiting, but can be serious and lead to ulceration, infection, or permanent skin damage in some patients. Protective agents have been investigated. Controlled studies have not shown conclusive results in favor of specific agents, but patients have anecdotally noted satisfaction with ointments.[57] Calendula has also been studied in the prevention of radiation dermatitis.

Calendula was evaluated in an open, phase 3, single-center clinical trial for the prevention of radiation dermatitis following radiotherapy for breast cancer.[58] Women (N = 254) were randomized to be treated with calendula extract in petroleum jelly (Pommade au Calendula par Digestion; n = 126) or trolamine (the standard of care; n = 128) applied by patients at least twice daily. Patients with more pain or erythema applied the products more frequently. At the end of the study, Radiation Therapy Oncology Group (RTOG) grade 2 or higher dermatitis occurred less frequently in patients receiving calendula compared with those in the trolamine group (41% vs 63%, respectively; P <.001). Fewer patients treated with calendula versus trolamine experienced grade 3 toxicity (7% vs 20%, respectively; P = .034), required treatment interruption (1 vs 15 patients), or had an allergic reaction to the cream (0 vs 4 patients). Despite better overall outcomes, patients reported that it was more difficult to use the calendula formulation than trolamine (30% vs 5%, respectively), and more physicians believed patients were less likely to adhere to calendula than trolamine (84% vs 92%, respectively).[49] Study limitations include a lack of treatment blinding and the use of petroleum jelly (which itself may have beneficial effects) in the calendula formulation.[58]

A randomized phase 3 study compared a 10% calendula cream with an aqueous cream (moisturizer) without parabens (standard of care) applied twice daily before, during courses of, and after radiation therapy for breast cancer.[59] Each treatment was applied starting with the initial radiotherapy session and was continued until 2 weeks after the last session or until any acute radiation skin reaction was healed. The researchers enrolled 390 patients, with 194 receiving calendula cream and 196 receiving aqueous cream. No difference was observed between the use of calendula cream compared with aqueous cream for the incidence of RTOG grade 2 or greater dermatitis (23% vs 19%, respectively; P = .39). In addition, no differences were reported for other efficacy outcomes, including patient-reported symptoms such as itchiness and pain. However, patients reported that the calendula product was more difficult to apply and had worse absorption quality than the aqueous cream.[59]

CESAREAN WOUND HEALING

A small study (N = 72) examined calendula's effect on wound healing after cesarean birth.[60] The researchers randomized women to 2 arms: (1) use of a commercially prepared calendula ointment twice daily for 10 days, or (2) routine care. The researchers assessed wound healing on days 3, 6, and 9 after surgery. They noted that in 63.9% of study participants treated with the calendula ointment, the wound was "completely improved" on day 3. In the control arm, this level of healing was not observed until day 6. Pharmacists should note this study's small size as a limitation.

DIABETIC FOOT ULCERS

Researchers in Brazil conducted a prospective, descriptive pilot study using *Calendula officinalis* hydroglycolic extract to treat diabetic foot ulcers.[61] They enrolled patients aged 18 to 90 years diagnosed with an uncomplicated, stable neuropathic ulcer of less than 3 months' duration. Patients applied *Calendula officinalis* hydroglycolic extract spray solution to their ulcers twice daily and covered the wounds with saline-moistened, sterile, nonadher-

TABLE 2. PATIENT INFORMATION TO OBTAIN WHEN RECOMMENDING A WOUND CARE PRODUCT

Chief complaint
A detailed medical history including concurrent illnesses
Allergies and past medical conditions
Medication history, including CAM or CIM and nutritional supplements
Use of self-care products
Current diet
Tobacco use, alcohol consumption, and exercise routine
Social interactions, hobbies, and motility

CAM or CIM indicates complementary and alternative or integrative medicine.

ent gauze and bandages. They also had weight-bearing restrictions and wore protective footwear. Although 84 participants enrolled, 43 withdrew, with the majority lost to follow-up. At 30 weeks, 78% of patients attained complete wound closure and the number of colonized wounds decreased from 29 at baseline to 5. The number of odorous wounds decreased from 19 to 1. Study participants reported no AEs. One limitation of this study is that it was observational. The researchers suggest randomized controlled studies using *Calendula officinalis* hydroglycolic extract are needed.[61]

STAR

What are some important counseling tips for the treatment of common skin conditions and minor wounds?

ROLE OF THE PHARMACIST IN THERAPY

When recommending a topical product for wound care, one should consider the proper dosage and frequency of application, patient age and weight, and the physical form of the preparation to be applied. Various drug vehicles have specific advantages and disadvantages, as described previously.[20]

Patient assessments and histories are necessary to develop a plan of care for any skin condition. Items identified through a patient interview, listed in TABLE 2, should guide treatment and identify areas of additional need, such as patient and family support, education, goals of care, and individual preferences.

Safety risks, such as allergic reactions, exist with any product but may be increased with herbal products. In addition, a lack of regulation in the production of herbal and CAM products could result in products having unidentified additives and preservatives.[62] To address these concerns, pharmacists and other health care practitioners should always recommend using products from trusted manufacturers and, in the case of supplements taken by mouth, ensure that they are US Pharmacopeia (USP) verified. The USP Verified Mark on the label indicates that the product[63]:

- Contains the declared potency and amount of the ingredients listed
- Does not have specified contaminants present in harmful levels
- Meets dissolution standards
- Has been manufactured according to FDA and USP guidelines for safe, sanitary, and well-controlled manufacturing practices

Advise patients to know and watch for symptoms of an allergic reaction and discontinue using the product if allergy symptoms appear.

For minor skin wounds and abrasions, pharmacists may help patients select self-care products for appropriate wound dressing and infection prevention. Pharmacists and clinicians can help patients navigate the multitude of available preparations and recommend appropriate delivery systems that are best suited for particular skin conditions (as described previously). As frontline health care providers, pharmacists may also identify patients with more serious or nonhealing wounds that require a physician's care. These patients should be referred immediately.

CONCLUSION

Wound healing is a complex process. Health care practitioners should have an understanding of the use of CAM or CIM therapies for wound healing to assist patients seeking self-care. The goal of this educational activity is to provide pharmacists with the information needed to answer patient questions on these therapies appropriately. Although herbal wound care products, such as topical calendula, have been historically used to treat minor wounds, skin irritations, minor burns, and insect bites and stings, data from large, comparative clinical trials are needed before routine use can be recommended.[64] Pharmacists and clinicians can effectively address patient questions about wound care and homeopathic therapies to help promote good wound care practices that encourage wound healing and minimize poor outcomes, such as infection or scarring.

ADDITIONAL RESOURCES	
The Wound Institute	thewoundinstitute.com
Association for the Advancement of Wound Care	aawconline.memberclicks.net
OncoLink Homeopathy	oncolink.org/blogs/2015/07/homeopathy-what-you-should-know
The Homœopathic Pharmacopoeia of the United States	hpus.com

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Begin the activity by reading the content in its entirety.
For Pharmacists, go to **www.pharmacytimes.org/go/wound-healing** to access the online posttest and activity evaluation form.
For Pharmacy Technicians, go to **www.pharmacytimes.org/go/wound-healing-techs**.
Click "Proceed," then complete the online pretest.
Once completed, click "Next" until reaching the activity posttest.
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POSTTEST QUESTIONS

1. **Which statement is TRUE regarding wounds?**
   - **a.** Inflammation is the first phase of wound healing.
   - **b.** New skin reaches the strength of uninjured skin after completion of the wound healing phases.
   - **c.** Minor wounds are superficial, shallow, and heal within a few days.
   - **d.** Wound healing phases do not overlap but rather occur in succession.

2. **What characteristic is TRUE about creams?**
   - **a.** Should be left on top layer of skin
   - **b.** Can stain clothing
   - **c.** Can be greasy
   - **d.** Are difficult to apply

3. **Which statement is TRUE regarding the homeopathic regulatory process?**
   - **a.** It is similar to the prescription drug regulatory process.
   - **b.** Manufacturing, labeling, marketing, and sales of homeopathic drugs are subject to FDA compliance rules.
   - **c.** All complementary and alternative or complementary and integrative medicines have approved monographs.
   - **d.** It is similar to the over-the-counter (OTC) medication regulatory process.

4. **What compound within calendula is thought to contribute to the anti-inflammatory, antioxidant, and anti-infective properties of the agent?**
   - **a.** Triterpenoids
   - **b.** Cyclooxygenase
   - **c.** Prostaglandins
   - **d.** Psyllium fiber

5. **Based on clinical trial evidence, calendula topical therapy has shown a potential benefit in which specific clinical situation?**
   - **a.** Venous ulcers
   - **b.** Pressure ulcers
   - **c.** Sunburn
   - **d.** Diabetic foot infections

CASE-BASED QUESTIONS:

A 56-year-old woman undergoing radiation therapy for breast cancer approaches you and asks about topical therapies that can be used to prevent radiation dermatitis. She would like to avoid using topical corticosteroids because of adverse effects (AEs) that she has encountered with them in the past. Her physician instructed her to solicit your recommendation as you are familiar with OTC product availability. The patient reports no known drug allergies, and she does not have a significant medical history other than her malignancy. She is skeptical of herbal and homeopathic products, but she has heard about possible therapies from other women in a support group she attends. Her current medications include loratadine 10 mg by mouth daily as needed for seasonal allergies, famotidine 20 mg by mouth twice daily as needed for gastric reflux, and acetaminophen 650 mg by mouth as needed for pain.

6. **Which topical product has been shown in clinical trials to benefit patients with breast cancer and radiation dermatitis?**
   - **a.** Trolamine
   - **b.** Calendula
   - **c.** Aloe vera
   - **d.** St. John's wort

7. **What counseling points can be emphasized to this patient to address her concerns over the use of herbal and homeopathic products?**
   - **a.** Herbal products come entirely from nature, so they do not cause any of the AEs that are seen with typical drug therapies.
   - **b.** Homeopathic products do not require clinical trials to determine efficacy because the dilution process imparts special properties.
   - **c.** Because homeopathic therapies may cause AEs and interact with prescription medications, it is important to mention them to your clinician and pharmacist.
   - **d.** Herbal products require the same testing and clinical trials as prescription drugs in order to be marketed in the United States.

8. **What is a potential advantage of ointments over creams?**
   - **a.** They are more occlusive and increase drug absorption.
   - **b.** They can be applied to hairy skin.
   - **c.** They have greater water content.
   - **d.** They can be applied to intertriginous areas.

9. **Which role in wound healing would be the most appropriate for the pharmacist?**
   - **a.** Daily dress changing
   - **b.** Nutritional support and consult
   - **c.** Recommendation of appropriate topical vehicle
   - **d.** Recommendation to discontinue offending agent such as radiation therapy

10. **What should be recommended for a patient with diabetes or an immune deficiency disorder who asks about self-care for a wound?**
    - **a.** Refer patient to a physician for wound management.
    - **b.** Recommend an herbal product to aid wound healing.
    - **c.** Recommend wound care self-care products.
    - **d.** No recommendation is needed at this time; the wound should heal on its own.