The Topical Evolution: Free Ions, Orthomolecular Agents, Phytochemicals, and Insect-Produced Substances

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Significance: A variety of topical antiseptic substances have been used historically to treat open wounds with suspected tissue infection or that are slow to heal. However, the effectiveness of these substances in treating infected or recalcitrant wounds remains controversial.

Recent Advances: Newly formulated topical antiseptics delivered through differing dressing technologies, such as ionic substances, hold the potential to limit the development of and treat antibiotic-resistant microbes in open wounds. Other topically delivered substances, such as insect-derived substances, orthomolecular agents, and phytochemicals, also present opportunities to optimize wound healing by decreasing tissue bioburden and facilitating the wound healing process.

Critical Issues: Limited systemic perfusion of open wounds in individuals with certain diagnoses, such as peripheral arterial disease or necrotizing infection and the increasing number of antibiotic-resistant wound pathogens, suggests a continued role for topically applied antiseptic agents. Likewise, the failure of wounds to heal when treated with standard of care therapy opens the door to innovative treatment approaches that include the natural substances described in this article.

Future Directions: Evidence for the use of select topical antiseptic agents from each of the aforementioned categories will be discussed in this article. Additional well-controlled clinical studies are needed to provide definitive recommendations for many of these topical agents.

SCOPE AND SIGNIFICANCE

THE EFFECTIVENESS OF TOPICALLY applied substances such as antiseptic agents for treating chronic wounds continues to be controversial in the wound care community. Long-running debates have occurred routinely at conferences and in the literature as to the value of these topical agents in treating wound infections or for promoting wound healing.¹⁻⁵ However, research is beginning to produce evidence that topical antiseptics may indeed have utility in the treatment of localized wound infection.⁶ At the

same time, there is a growing acceptance for other topically applied substances in chronic wound care. These bioactive substances include insect-produced substances, orthomolecular therapy, and phytochemicals. Examples of these agents and evidence supporting their use will be discussed in this review.

TRANSLATIONAL RELEVANCE

Awareness of the evidence or lack thereof, supporting the value of topically applied substances in treating

slow healing or clinically infected wounds, provides translational researchers with the opportunity to design well-controlled clinical trials to address gaps in our current knowledge. This article provides a critical review of the current state of evidence for using select topical wound substances and identifies agents that require more study before definitive treatment recommendations can be made.

CLINICAL RELEVANCE

Understanding the evidence that supports the use of topical agents in the management of slow to heal or infected wounds informs the practice of wound care clinicians and ensures that the patient receives effective treatment. This article provides a critical review of the evidence for using select topical agents.

DISCUSSION

The role of topical antiseptics in chronic wound infection

The wound care community has debated the utility of using topical antiseptics in the treatment of chronic wound infections for decades (Table 1). The debate has stemmed primarily from the lack of evidence for their efficacy.^{1,2} It has been argued since 1919 when Fleming⁷ published his extensive work examining antiseptics that there is no evidence to support their use. Fleming demonstrated that antiseptics were unable to penetrate tissue, and later in 1985, Zamora *et al.*⁸ demonstrated that organic substances reduce the antimicrobial activity of the antiseptic, povidone–iodine. Clinically, evidence supporting the use of antiseptics has also been lacking. For example, a prospective, randomized controlled trial demonstrated that saline-soaked gauze treatment of infected pressure ulcers resulted in significantly less bacteria than povidone–iodine-treated pressure wounds.⁹

The argument against antiseptics is further supported by their documented detrimental effects on wound bed cells and tissues.^{3,10} The prolonged use and/or high concentration of antiseptics are

known to harm mammalian cells, delay healing, and produce a chronic inflammatory state. For example, *in vitro* testing of hypochlorites, hydrogen peroxide, chlorhexidine, and povidone–iodine have all been shown to kill cultured fibroblasts.^{10,11} *In vivo* studies have also demonstrated similar toxic effects on fibroblasts.¹² Examination of the effects of antiseptics such as chlorhexidine, povidone–iodine, Eusol, and chloramine T on blood flow in rabbit ears demonstrated detrimental effects. Tissue perfusion was immediately abolished with Eusol and chloramine T, whereas the effect of povidone–iodine was concentration dependent with 5% completely depressing the blood flow in small vessels.

However, closer inspection of the literature reveals that research has produced equivocal results. In the study described above by Brennan and Leaper¹² that examined the effects of antiseptics on rabbit ear perfusion, povidone–iodine had no detrimental effects on perfusion at a concentration of 1%. Other studies have also demonstrated either a lack of effect or a beneficial effect of povidone–iodine on wound healing processes. For example, application of a 1% solution of povidone–iodine to clean acute wounds did not affect fibroplasia or collagen cross-linking.¹³ Additionally, no difference was detected in tensile strength of these wounds. A study by Bennett *et al.*¹⁴ demonstrated that the application of an even greater concentration of povidone–iodine (10%) was associated with an increased number of proliferating fibroblasts and enhanced angiogenesis compared to untreated controls.

With the ever increasing number of antibiotic-resistant microorganisms, interest in iodine has been rekindled. Whereas the jury is still out on the use of povidone–iodine, a newer formulation of iodine has growing evidence to support its use in facilitating wound healing and controlling wound bioburden.^{15,16} Cadexomer iodine, like povidone–iodine, is an iodophor (Table 2). Iodophors are a complex of iodine and a carrier polymer that serves as a reservoir for the iodine ion. Cadexomer iodine became available ~25 years ago and appears to be less toxic, more stable, and to have an increased clinical efficacy.

Table 1. Topical antiseptic evaluation

	In Vivo Testing	In Vitro Testing
Hypochlorites	X	X
Hydrogen peroxide	X	X
Chlorhexidine	X	X
Povidone–iodine	X	X
Eusol	X	X
Chloramine T	X	X
Cadexomer iodine	X	X

X, testing has occurred.

Table 2. Comparison of cadexomer iodine and povidone–iodine

	Cadexomer Iodine	Povidone–Iodine
<i>In vitro</i> studies		
Fibroblasts	Nontoxic	Toxic
Reepithelialization	Enhances	Enhances
MRSA	Kills	Kills
Human studies		
Ulcer healing	> Standard of care	No difference than standard of care

MRSA, methicillin-resistant *Staphylococcus aureus*.

In vitro analysis of cadexomer iodine has demonstrated that concentrations as high as 0.45% are nontoxic to fibroblasts.¹⁷ Chronic wounds also demonstrate reepithelialization in the presence of cadexomer iodine.¹⁸ The cadexomer iodine formulation is different from povidone–iodine. Povidone–iodine is a combination of free iodine, molecular iodine, and a nonionic surfactant, whereas cadexomer iodine is composed of elemental iodine bound to a three-dimensional starch (polysaccharide) lattice that allows slow release of the iodine ion. To date, 10 clinical trials have been conducted to examine the effects of cadexomer iodine.¹⁶ A Cochrane Review by O'Meara *et al.*⁶ indicates that some evidence supports the use of cadexomer iodine in the treatment of chronic wounds. In a number of studies, cadexomer iodine was found to increase healing rates while also reducing symptoms often associated with infection such as exudates, erythema, edema, and pain.¹⁶ A recent, randomized controlled trial comparing cadexomer iodine to standard of care in venous ulcerations demonstrated increased healing rates in the cadexomer iodine treatment group.¹⁸ Moberg¹⁹ demonstrated a similar effect in pressure ulcers in 1983. In this study, cadexomer iodine was shown to reduce pus, debris, and pain in pressure ulcers while also promoting a 76% reduction in ulcer area compared to a 57% for ulcers receiving standard therapy. It should also be noted that six patients went on to complete wound closure in the cadexomer iodine-treated group compared to one in the standard therapy group.

Cadexomer iodine is just one example of a topical elemental antimicrobial. Others include silver, copper, zinc, and gold.²⁰ Of these elements, iodine and silver have been used for centuries in wound care (Table 3). Today, silver is available in a number of preparations that include topical creams and a variety of dressing products (alginates, film polymers, foams, hydrocolloids, hydrofibers, and polyethylene mesh).²¹ The release of silver cations from these products has a direct effect on bacterial

viability through cell wall disruption, inhibition of bacterial respiratory enzymes, and the electron transport, as well as interference with DNA and RNA synthesis.²²

In a systematic review published by the Department of Veterans Affairs Health Service Health Services Research & Development Service in November of 2012, the effectiveness of silver on chronic wound healing was assessed.²¹ In one study, silver ointment produced a 23% increased healing rate over standard care.²³ A study comparing a silver-releasing foam and foam dressing without silver found no difference in days to healing.²⁴ Additionally, two studies that compared silver products to other wound care products (iodine, calcium-based dressings) showed no significant differences in healing rates.^{25,26} Evidence for the use of silver dressings was rated low overall in this review. A review produced by Vermeulen *et al.*²⁷ in 2010 and by O'Meara *et al.*⁶ in 2014 for the Cochrane Collaboration also found insufficient evidence to support the use of silver dressings or topical therapies in the treatment of infected chronic wounds. However, the findings of these systematic reviews contrast with those of a meta-analysis by Lo *et al.*,²⁸ in which silver dressings were found to increase wound healing rates and decrease odor, exudates, and dressing wear time.

Orthomolecular therapies in wound healing

Orthomolecular therapies (Table 4) are biologically based alternative or complimentary therapies that focus on the use of vitamins, minerals, amino acids, or trace elements in the treatment of a variety of health conditions.²⁹ The term was originally coined by Linus Pauling, Nobel laureate in chemistry, in reference to treating mental health disease states with varying levels of substances normally found in the human body.³⁰ Whereas Pauling's work examining the potential role of vitamin C as a cancer therapy³¹ was controversial during his lifetime, the use of micronutrients in the treatment of illness or disease has since become a more widely researched treatment approach.

Today, the role of nutritional deficiencies and malnutrition in individuals with chronic pressure wounds is well recognized.³² Several clinical studies demonstrate a correlation between malnutrition and the development of pressure ulcers.^{33–35}

Table 3. Comparison of cadexomer iodine and silver

	Cadexomer Iodine	Silver
<i>In vitro</i> studies		
Bioburden	Decreases	Decreases
Fibroblasts	Enhances migration	Enhances migration
	Nontoxic	Toxicity Concentration Dependent
Human studies		
Ulcer healing	> Standard of care	Mixed results to no difference than standard of care
Clinical signs of infection	Decreased	Decreased

Table 4. Examples of orthomolecular therapies

Vitamins
Minerals
Amino acids
Micronutrients

Research evidence from two clinical studies also indicates a positive role for oral nutritional supplementation with protein and micronutrients (arginine, zinc, ascorbic acid, and vitamin E) in facilitating pressure ulcer healing.^{36,37} In one double-blind clinical trial, topical application of zinc oxide was shown to promote wound cleansing and reepithelialization in 37 leg ulcer patients with low serum zinc levels. These individuals also experienced fewer skin infections and ulcer deterioration. Animal studies provide evidence to support a role for the topical application of vitamin E, L-arginine, and omega-3 fatty acids in facilitating wound healing.³⁸ However, to date, no strong clinical studies provide evidence to support a role for topical application of these orthomolecular agents to stimulate wound healing.

Phytotherapy in wound healing

Phytochemicals or plant-derived compounds have been used to treat wounds for centuries but have been frowned upon in modern day medicine.²⁹ Recently, a renewed interest in the use of phytochemicals has occurred in western medicine. Traditional compounds such as sugar and aloe vera are under investigation once again to examine their potential benefit in chronic wounds. Other plant-derived compounds of interest include calendula, hypericum, oak bark, and Tea tree oil (Table 5).

Aloe vera contains approximately 75 active chemical agents. These include the following: vitamins, enzymes, minerals, sugars, anthraquinones, fatty acids, amino acids and hormones. The growth hormone, gibberellin and the polysaccharide, glucomannan stimulate healing, while c-glucosyl chromone and bradykinase decrease inflammation.³⁹

Two clinical studies have examined the effectiveness of aloe vera on wound healing rates.⁴⁰ Wound healing was more rapid in a controlled clinical trial involving 17 patients who had undergone dermabrasion. Time to epithelialization was 72 h quicker in individuals treated with polyethylene oxide gel saturated with aloe vera compared to the gel alone. At 48 h, the individuals treated with the aloe vera-containing gel experienced a decreased level of edema and at 4 days, they exhibited decreased exudates and crusting. In comparison, a nonblinded, ran-

domized controlled trial of 40 women treated for postgynecological surgery wounds demonstrated significantly faster healing in individuals receiving conventional therapy compared to a wound gel containing aloe vera.⁴¹

Murandu⁴² examined the effects of two different granulated sugars on necrotic wounds in 22 individuals. Patients reported less wound pain with the sugar-based dressing. Murandu and Dealey⁴³ also reported in a case study that white granulated sugar enhanced autolytic debridement, pain control, odor reduction and prevented wound contamination in a patient with two infected pressure ulcers. Knudson *et al.* reported that over almost a 5-year period, 605 patients with open wounds were treated with granulated sugar and povidone-iodine.⁴⁴ A reduction in healing time, bacterial contamination, and debridement of eschar was reported along with reduced use of antibiotics and skin grafting. An animal study has provided evidence for increased fibroblast and keratinocyte activity with sugar and povidone-iodine treatment.⁴⁵ Topical application of sugar and povidone-iodine treatment has also been shown to be effective against methicillin-resistant *Staphylococcus aureus* (MRSA) in diabetic mice and to promote reepithelialization.⁴⁶

Another plant that has been used in wound care for centuries is calendula or English marigold.³⁸ Terpenoids are an example of phytochemicals in this plant that may facilitate wound healing. In animal studies, terpenoids have been shown to stimulate collagen production and granulation tissue formation.^{45,47} A single-blind, randomized controlled trial provided evidence that the calendula cream reduced the development of grade 2 or higher skin reactions in women receiving radiation therapy compared to standard of care therapy.⁴⁸ Pain was also decreased in the women treated with the calendula cream. The topical effects of Calendula were also examined in 50 patients with slow healing wounds.⁴⁹ In this poorly described trial, Calendula treatment was associated with reduced pain during dressing changes and rapid granulation development. In another small and poorly described clinical trial, two separate Calendula preparations were examined in 38 patients with either venous ulcers, burns, or other skin lesions.⁵⁰ Cleansing wounds daily with a Calendula solution followed by application of a 2% Calendula gel produced a more rapid healing rate (reduction in median time to heal) compared to wounds cleaned daily with 2% Calendula tincture. A more recent controlled trial involving 34 patients demonstrated a 27% quicker healing rate in Calendula-treated venous ulcer wounds compared to saline controls.⁵¹

Table 5. Botanical phytochemicals

Botanical Substances	Proposed Influencing Phytochemicals
Aloe vera	Glucomannan, gibberellin, C-glucosyl chromone
Calandula	Terpenoids
St. John's wort	Hypericin, hyperforin
Oak bark	Terpenoids, salicylates
Tea tree oil	Terpenoids
Honey	Methylglyoxal, leptosin, bee defensin

White oak bark, St. John's wort (hypericum), and Tea tree oil have also been used to treat wounds.^{38,52} Both White oak bark and St. John's wort contain substances with anti-inflammatory effects. Hypericin from St. John's wort and the terpenoids and salicylates in White oak bark have anti-inflammatory properties. Hypericin along with Tea tree oil has an antibacterial activity that may contribute to enhanced wound healing. However, clinical studies are lacking at this time to support the above uses.

Insect-derived substances in wound healing

Honey is a natural product produced by bees. It has been used for wound healing since ancient times in a variety of wound types.⁵³ Whereas honey had fallen out of favor for use in wound healing, it has enjoyed a comeback in recent years. Honey has documented the antibacterial activity with some 60 or more microorganisms reportedly susceptible to its effects.⁵⁴ *In vitro* studies of honey have demonstrated an antibacterial effect against antibiotic-resistant microbes, including MRSA and vancomycin-resistant enterococci.⁵⁵ Similar to the ionic form of iodine, microorganisms have not demonstrated resistance to honey. The physical mechanisms of action (hyperosmotic conditions, acid conditions, generation of hydrogen peroxide) are not thought to easily lend themselves to generation of resistance. The presence of phytochemicals in honey may also be responsible for its antimicrobial effects. Honey also appears to be beneficial in odor control because its metabolism by bacteria produces lactic acid rather than other odiferous substances such as ammonia, amines, and sulfur. One honey that is currently used in the treatment of chronic wounds, Manuka (*Leptospermum scoparium*) honey from New Zealand, has an unidentified phytochemical(s) that is antibacterial.⁵⁶ Manuka honey is approved by the US Food and Drug Administration and dressings formulated from this honey are commercially available. It has been shown *in vitro* to have an antibacterial action that includes MRSA.

Clinical studies have also provided some evidence to support honey's role in facilitating wound healing in a variety of wound types across age groups.⁵³ However, a variety of uncharacterized honeys were used in these studies. Manuka honey, a well-characterized honey, has been shown to stimulate healing in a number of case studies.^{53,57} In a systematic review of the literature by The Cochrane Collaboration in 2008,⁵⁵ it was concluded that evidence existed to support the use of topically applied honey to burn wounds. Results of two open-labeled controlled trials comparing the effects of

honey to standard of care on venous ulcers showed honey to be at minimum equivalent to other standard wound care dressings.^{58,59} In two other trials, honey was found to enhance healing in pressure ulcers (First study—Stage I and II; Second Study—Stage II and III).^{60,61} Honey was also found to be equivalent to an iodine dressing in treating Wagner type II diabetic foot ulcerations.⁶² Overall, a review of the literature reveals a positive trend for honey in the treatment of pressure wounds (decubiti and diabetic type). Evolving evidence supports the use of honey in treating chronic wound types.

SUMMARY

"Everything old is new again."—Peter Allen

Review of the literature surrounding the use of topical agents from antiseptics to phytochemicals brings to mind the quote "Everything old is new again" by Peter Allen. The substances discussed in this article, in most cases, have been used for hundreds of years. In fact, they are substances that many of us in wound care practice have either seen used or used ourselves. A number of these substances were also on our do not use list in wound not so long ago. However, substances such as honey and iodine seem to be receiving a strong second look due to new formulations (iodine) for delivery and specific insect-derived substances. Recently, while attending a local bee keepers club meeting at the county extension office, a physician presented results of using Sourwood honey on a variety of chronic lower extremity ulcers. Needless to say, the results were quite impressive, but the case studies were without scientific rigor. The physician stated that the honey-treated (honey derived from wild American honey bees) wounds were chronic and had previously failed to heal with modern treatment approaches. Honey application appeared to reduce inflammation and to decrease overt tissue infection with wounds progressing to closure. Interestingly, at the end of his presentation, he revealed that he has since adopted the use of Manuka

Table 6. Current supporting evidence for selected topical substances

Topical Preparation	Area Examined	Supporting Evidence
Cadexomer iodine	Wound bioburden; promote wound healing	Strong
Silver-based therapies	Wound bioburden; promote wound healing	Moderate
Honey	Chronic wounds with promise in burn and pressure ulcers	Mixed
Orthomolecular preparations	Chronic wounds	Unsupported
Phytochemical preparations	Chronic wounds	Unsupported

honey with much success. Again the quote, “Everything old is new again” came to mind.

Time and again in this article, topically applied substances that have been used historically in wound management are being revisited and their use reexamined in a scientific manner. Whereas some substances such as the reformulated iodine treatment, known as cadexomer iodine, have evidence to support their use clinically others such as Tea tree oil are under active investigation.

The potential for these substances and others from their respective categories appears promising. The value of finding effective, inexpensive, and accessible treatments that are not outsmarted by bacterial superbugs or that enhance healing cannot be overstated. These substances if proven scientifically to be efficacious have the potential to provide cost-effective treatments to those in impoverished rural and urban America, as well as developing countries, who cannot afford other expensive, less accessible, and technologically advanced wound healing therapies. However, only time will tell if the many substances described in this article will be proven effective. Because of the potential effectiveness (Table 6) of these universally accessible agents (*i.e.*, iodine, silver, honey), it

TAKE HOME MESSAGES

- Strong clinical evidence supports the topical use of cadexomer iodine to control wound bioburden and promote wound healing.
- Clinical evidence for the use of silver-based topical applications is less clear, but a number of moderate level studies indicate a role for silver-based therapies in promoting wound healing and bioburden control.
- Clinical evidence for the topical use of honey in chronic wounds is promising.
- No strong evidence exists for the use of topical orthomolecular agents or phytochemicals in chronic wounds.

is imperative that the scientific and clinical community continues to study these agents.

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Abbreviation and Acronym

MRSA = methicillin-resistant *Staphylococcus aureus*