Phytochemicals and Naturally Derived Substances for Wound Healing

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Background: Complementary and alternative medicines (CAMs) are widely used by the general public. Natural products including plant-derived extracts (phytochemicals) and naturally derived substances, such as honey, are an important component of CAM. Here, we review the evidence for their use in wound care.

The Problem: Wound healing is complex and disruption of this process can lead to considerable morbidity, including chronic wounds, infection, and scarring. Natural products have a long history of use in wound care, but there are only a few rigorous studies. With the growing interest in the use of natural products and the belief that they are safer than standard therapies, it is vital to understand the current knowledge of their efficacy and side effects.

Basic/Clinical Science Advances: Natural products possess antioxidant, anti-inflammatory, angiogenic, and cell synthesis-modulating components among many others. However, this complex composition of chemicals may increase the risk for irritant or allergic side effects.

Clinical Care Relevance: Natural products can be much cheaper than conventional treatments, but further study is needed to better understand their efficacy. The type of wound and the potential for side effects need to be carefully considered when choosing a treatment.

Conclusion: The research to date is supportive of the use of natural products in wound care. Patients need to be cautioned of potential side effects. Collaborative research between allopathic medicine and medical systems that frequently employ phytochemicals and naturally derived substances, such as Ayurveda and naturopathy, will provide a better understanding of how to integrate natural products into wound care.

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Abbreviations and Acronyms

CAM = complementary and alternative medicine

FDA = federal drug administration

MRSA = methicillin-resistant *Staphylococcus aureus*

BACKGROUND

AMERICANS FREQUENTLY USE complementary and alternative medicine (CAM) to treat their medical ailments, spending billions of dollars each year to do so. With the heightened awareness of “natural products” among the general population, it is especially essential that physicians become more familiar with them as they are an important part of CAM. Alternative medical

systems such as naturopathy and Ayurveda utilize herbal medications as an important part of therapy.

Naturally derived products have long been used in wound healing, but clinical investigation of these therapies is still in its infancy. These products have several advantages. Whole-plant extracts or naturally occurring substances may contain multiple helpful chemicals such as antioxidants, antimicrobials,

anti-inflammatory agents, and enhancers for re-epithelialization and collagen formation. This can have a synergistic effect for wound healing. However, plant and naturally derived substances may have side effects including irritation and allergic hypersensitivities.

TARGET ARTICLES

1. Davis SC and Perez R: Cosmeceuticals and natural products: wound healing. *Clin Dermatol* 2009; **27**: 502.
2. Jull AB, Rodgers A, and Walker N: Honey as a topical treatment for wounds. *Cochrane Database Syst Rev* 2008; CD005083.

CLINICAL PROBLEM ADDRESSED

Acute and chronic wounds are a widespread and common health issue, especially with the rise of obesity and diabetes. A delay in wound healing can lead to an increased risk for infection and worsened scarring, leading to increased morbidity and cost for continued medical care. Although wound dressings can prevent desiccation and provide a protective barrier, many of the other claims regarding improvement of wound healing are often not supported by evidence.¹ The introduction of “natural products” into the wound healing arena raises the possibility of applying complex chemicals and substances that may have several different benefits for wound healing at the same time. The public perception is that these “natural products” will have fewer side effects. Because this field is still in its infancy, it is important to scientifically test the efficacy of naturally derived substances including plant-derived products (phytochemicals) and how these products should be integrated into wound care.

RELEVANT BASIC SCIENCE CONTENT

As wound healing research involving phytochemical and naturally derived substances progresses, it is vital to understand several general concepts. (1) Do extracts provide more utility than a single purified substance? Naturally derived unpurified extracts are a complex mixture of many different chemicals that can individually have antioxidant, anti-inflammatory, angiogenic, and cell synthesis-modulating properties. This can lead to a myriad of beneficial effects over a single extract. (2) Does “natural” necessarily mean safer? The pres-

ence of a complex array of chemicals may lead to greater risk for irritant or allergic side effects. Testing for such allergies at the basic science level can become challenging when there are many potential chemicals that may act as a sensitizer or as an irritant. (3) The method of extraction can alter the composition of chemicals in the final extract. Extraction in an aqueous media will tend to extract hydrophilic substances; similarly, extraction in nonaqueous media will tend to extract hydrophobic substances. Therefore, the extraction media may significantly alter the final composition of chemicals in an extraction process.

EXPERIMENTAL MODEL OR MATERIAL: ADVANTAGES AND LIMITATIONS

The great advantage of studies involving phytochemicals or other naturally derived substances is that the tested extracts have a plethora of chemicals that may augment wound healing. At the same time, the presence of numerous chemicals limits the ability to discern the specific action of the individual chemicals within the extract.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Phytochemicals

Aloe vera. Aloe vera has long been used to treat various ailments of the skin. The derivative of many commercial aloe preparations comes not from the aloe sap but from the internal gel of the whole aloe leaf. Extracts of aloe vera can stimulate the release of several growth factors; they also have antimicrobial and anti-inflammatory factors. Several clinical studies have evaluated the role of aloe vera in the healing of acute surgical wounds,^{2,3} burn wounds,⁴ and pressure ulcers.⁵ In acute wounds, one randomized, blinded, placebo-controlled study found that aloe vera accelerated healing,² whereas another appropriately powered, randomized, unblinded study in the healing of cesarean incision by secondary intent found that it delayed it.³ However, the study of healing of the cesarean incisions did not have an appropriate control group and the gel formulation for the aloe vera gel may have inhibited the healing rather than the aloe vera itself. In a randomized, placebo-controlled study involving second-degree burn wounds where patients were used as their own control, aloe vera was found to be superior to silver sulfadiazine in the rate of wound closure and there was no reported difference in infection rate.⁴ A randomized, controlled, unblinded trial using aloe

vera-based cream was not found to be significantly different than saline-moistened gauze in the healing of pressure-induced ulcerations.⁵ In these studies, there were no side effects reported with the use of topical aloe vera, although one study noted that the granulation tissue appeared more fibrotic and pale in the aloe vera treatment group.³ Overall, in clinical trials, aloe vera appears to be helpful in acute wounds, but more controlled clinical studies will be needed to better assess its role in chronic wounds.

Banana leaf. Banana leaves have been studied as low-cost dressings for partial thickness burn wounds and donor sites.^{6,7} Unrandomized, controlled studies showed that sterilized banana leaf dressings showed a greater rate of re-epithelialization in comparison to Vaseline gauze in donor site healing.⁷ The studies report that the sterilized banana leaves must be used within 3–4 days as fungal overgrowth can occur after 1 week. There were no reports of allergic or irritant reactions.

Cocoa. Cocoa has a long history of use for various ailments including cutaneous burns and cuts; however, its effects on wound healing have not been well studied under rigorous methods. The topical use of cocoa has been shown to improve re-epithelialization in second-degree burns in a porcine model,⁸ but there have been no clinical studies that have assessed its utility in human wounds. Cocoa is not without side effects, because it can contain enough nickel to elicit a systemic contact dermatitis from consumption.⁹ Whether topical cocoa can elicit the same result will need to be assessed in future clinical studies.

Tree barks. Bark extracts are a rich source of plant polyphenols and tannins that have antimicrobial, anti-inflammatory, antioxidant, and astringent properties. Several different bark extracts have been studied in wound healing. Aqueous bark extracts from *Choerospondias axillaris* (Nepali Hog Plum) were studied in an open, randomized, controlled trial of second-degree burn wounds and were shown to have accelerated wound closure time and lower wound infection rates when compared with saline gauze treatment.¹⁰ Aqueous bark extracts of *Rhizophora mangle* (Red mangrove) have been studied in single-blinded, randomized, controlled trials and shown to improve healing times of acute surgical wounds and aphthous ulcers with no infections noted in either study.^{11,12} No power analysis was noted in any of these studies. A proprietary ointment (Bensal HP) that contained

extracts from *Quercus rubra* (oak bark) was superior to sulfadiazine in healing of diabetic ulcers in a randomized, controlled trial.¹³ This study also showed clearance of *Staphylococcus aureus* after treatment with Bensal HP in wounds that initially exhibited growth of the bacteria. This corroborates previous studies in wound infection models that showed that Bensal HP can lower methicillin-resistant *Staphylococcus aureus* (MRSA) carriage.⁸ Studies with Bensal HP should be interpreted with caution as it is composed of a mixture of oak bark extract, benzoic acid, and salicylic acid and all three of the agents have antimicrobial activity and can potentially augment wound healing.^{8,13} Therefore, it is not possible to isolate the effects of oak bark extracts in these studies.

β -Glucans. Found in the cell walls of fungi, yeast, and cereal plants, β -glucans are glucose polymers that have been touted for boosting the immune system, antioxidant properties, and their potential for wound healing. One retrospective study found that a β -glucan/collagen-based hybrid dressing was well tolerated by children with partial-thickness burn wounds.¹⁴ However, because this study was retrospective, a causal interaction cannot be assessed. Further, the lack of a control group eliminates the ability to assess the efficacy of this treatment to a standard treatment regimen. Although this retrospective study is encouraging, prospective clinical studies will be needed to better assess the role of β -glucans in wound healing.

Turmeric. Turmeric is a natural spice that is derived from the Ayurvedic medical system in India. Turmeric contains curcumin as one of its components, which has been found to be a potent antioxidant, anti-inflammatory, and antimicrobial agent. Animal studies have shown that curcumin improves healing of excisional wounds, but there have been no human clinical studies to evaluate its role in wound healing.

Naturally derived substances

Propolis. Used by bees as a sealant and containing both antioxidant and antimicrobial properties, propolis is derived from the hives of honeybees. There has been one clinical study that assessed propolis for second-degree burn wounds in a single-blinded, controlled trial where each subject served as their own control. Propolis was superior to silver sulfadiazine in achieving wound closure with no difference in infection rates.¹⁵ Propolis rarely causes contact dermatitis or severe allergic responses.¹⁶

Honey. Honey is commonly used for wound healing purposes. Though honey has an extended history in the treatment of burns, wounds, and ulcers since ancient times, the validity of its benefits have recently come under more rigorous investigation. Honey has many theoretical advantages for wound healing, including its anti-inflammatory, antioxidant, antimicrobial, and osmotic properties.^{8,17} Unlike other naturally derived products and phytochemicals, honey has been more extensively studied in clinical settings. Most of the studies primarily utilize Manuka honey that is derived from bees that generate their honey from *Leptospermum scoparium*, a flower localized to New Zealand. In particular, Manuka honey shows greater activity against MRSA and vancomycin-resistant *Enterococcus* than other forms of honey.¹⁸ However, there are other forms of honey, such as Ulmo honey, that may be superior to Manuka honey in activity against MRSA.¹⁹ In 2007 MEDIHONEY®, a Manuka honey-derived product, received Federal Drug Administration (FDA) approval for the treatment of wounds. This marks the first naturally derived substance that has been approved for wound care. A systematic review of all the available well-done randomized, controlled clinical studies revealed that honey was beneficial in the treatment of acute burn wounds in comparison to conventional dressings such as Vaseline gauze, but offered no benefit in healing time when compared with silver sulfadiazine.²⁰ A similar benefit for acute wounds due to lacerations, abrasions, or acute toenail removal wounds was not found. For chronic wounds, honey was found to be beneficial for pressure-induced wounds, infected postsurgical wounds, and Fournier's gangrene.²⁰ However, honey was not found to provide any further benefit when added to physical compression in the treatment of chronic venous leg ulcers.²⁰ Overall, honey seems to be helpful in some acute and chronic wounds, but it does not seem to be helpful for venous leg ulcers. This is not surprising as the pathophysiology of the delayed wound healing rests in the underlying vascular compromise rather than local factors.

One of the most concerning features of honey is that it may house spores of *Clostridium botulinum*. Although commercially available dressings, such as MEDIHONEY, are sterilized prior to use, the possibility of persistent spores precludes their use in young children to avoid the potentially devastating effects of botulism.

INNOVATION

Research into phytochemicals and other naturally derived substances are in the early stages and there are many discoveries yet to be made. Within medical systems that rely on phytochemicals, such as traditional Chinese medicine, Ayurveda, and naturopathy, there are many herbs and plants that have to be yet explored for their therapeutic potential. The increased research and use of phytochemicals and other naturally derived substances indicates that the field is now moving toward a more complex approach to the treatment of wounds, which have a complex physiology and pathophysiology.

SUMMARY ILLUSTRATION

Schematic of the proposed advantage of obtaining extracts from natural products. Multiple components within an extract may have several different properties that can help with wound healing.

CAUTION, CRITICAL REMARKS, AND RECOMMENDATIONS

The general population is expecting safer, economical, and effective treatments with more emphasis driven toward “natural products.” The challenge

TAKE-HOME MESSAGE

Basic science advances

- Natural product extracts are a complex mixture of several components that have antioxidant, anti-inflammatory, angiogenic, and cell synthesis-modulating properties.

Clinical science advances

- Although in its early stages, data are accumulating on the benefits and risks with the use of natural products for wound healing. Natural product extracts seem to have a beneficial role in wound healing with a more pronounced effect on acute wounds.

Relevance to clinical care

- Natural products have a role in wound healing therapy and potential side effects must be considered. The field is still in its early stages and more studies are needed to better understand their role in acute and chronic wound care. An integrated approach between allopathic medicine and other medical systems will be needed for more rapid and greater understanding of how natural products can be used in wound therapy.

of wound healing is no exception. As such, it is imperative that this demand be met with rigorous research in this arena. Early research has shown that naturally derived products can have beneficial effects, but they are not free of side effects either. The wound needs to be carefully considered, in terms of an acute versus a chronic wound, and the appropriate research studies should be conducted. Further, because naturally derived materials may have a higher risk for contamination with infectious agents, proper sterilization and bacterial testing is of the utmost importance before their use in a wound. All of these factors need to be discussed with a patient when considering treatment with naturally derived products, as the FDA has not evaluated most of them.

Alternative diagnoses must be entertained for nonhealing wounds such as a malignancy, a deeper infection, or an autoimmune process and the appropriate workup must be performed. For example, a malignancy would be better treated with surgery and an autoimmune process may be better treated with immunosuppression.

FUTURE DEVELOPMENTS OF INTEREST

The introduction of phytochemicals and naturally derived substances is an exciting inno-

vation for wound healing. More prospective, well-controlled studies are needed to assess the role of these naturally derived products for wound care. Studies are needed to better define the influence of the extraction technique on the final composition of the extract and the value of this knowledge is currently underappreciated. Unlike allopathic medicine, naturopathic medicine, Ayurvedic medicine, and homeopathic medicine, frequently use plant/herbal extracts and naturally derived substances. Collaborative efforts will be needed to develop future rigorous and thoughtful investigations into the role of naturally derived products for wound healing.

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