Cosmeceuticals and natural products: wound healing

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Abstract Despite several technologic and strategic advances in the field, wound care has returned to the roots of medicine and embraced some of the remedies used millennia ago. Some of the many potentially beneficial natural products include the β-glucans, honey, aloe, cocoa, and oak bark extracts. There has recently been a surge of interest for their possible roles in wound healing.

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Introduction

In recent years, modern societies have become more cognizant of holistic or “natural” treatments to disease and are embracing the development of such products. Although some people view these ideas as somewhat primitive or ignorant, many of the remedies are the result of thousands of years of empiric observation. These remedies have their roots in the ancient civilizations of the East as well as those of the Native American and Native South American cultures. Several of the more “modern” treatments, such as penicillin, morphine, aspirin, and Taxol, are considered natural products; however, most natural products are considered dietary supplements in the United States, are not regulated, and the active ingredients are not standardized.

This lack of standardization has made it more difficult to determine the true efficacy of these products. Although many natural products have claimed to have healing effects, most do not have well-controlled scientific data to back their claims. Various preparations may actually have a therapeutic effect on compromised skin; however, the beneficial effect may be due to the vehicle and not the active agent. Many vehicles thought of as inert may have a significant effect on wound healing and can be used alone or as vehicles for active agents. One study, for example, found that various lots of United States Pharmacopeia petrolatum could either enhance or retard healing.

Honey

Control of the microbial flora of wounds is desirable in nearly every type of wound. There are also suggestions that a small amount of bacteria may be beneficial to the wound-healing process. This presents a dilemma for the clinician, who must balance between infection and minimal colonization of a wound. The situation may become dire in cases of chronic wounds where patients may be immunodeficient. Although honey has a long tradition of use within medical systems and has enjoyed a resurgence in its popularity within the last 15 years, some clinicians believe there is insufficient evidence to support its benefits, despite it being the oldest known wound dressing.

For years, researchers have believed that honey gains its broad antimicrobial activity from hydrogen peroxide generated by a glucose oxidase deposited into the honey by bees and by the high osmolarity due to the sugar...
content. These may, however, be just a couple of many sources of antimicrobial activity, because honey is a complex mixture of potentially beneficial natural products such as flavonoids and other phytochemicals. Almost all medicinal honey research has been conducted on manuka (Leptospermum scoparium) honey, which has little peroxide generation potential. The nonperoxide antimicrobial activity of this honey has been attributed, at least in part, to a yet uncharacterized “unique manuka factor.” Regardless of the source of the antimicrobial activity, manuka honey has been demonstrated to be effective against several human pathogens, including Enterobacter aerogenes, Salmonella typhimurium, Staphylococcus aureus, and methicillin-resistant S aureus (MRSA). Almost all medicinal honey research has been conducted even into various tissues and paper products. Most commercial preparations of aloe are derived from the internal gel of the aloe leaf and not from the aloe sap. Whole leaf aloe extracts have been shown to possess anti-inflammatory and antibacterial properties in vitro and in animals. Although whole leaf extracts are antibacterial to some human pathogenic bacteria, the activity depends on the amount of anthraquinones, which are found in the sap and not in the gel. These compounds have been used for millennia as purgatives due to their potent laxative nature.

There is some evidence that aloe may be beneficial to a healing wound. Molecular analysis of human liver and lung cell lines treated with a more than 99% pure carbohydrate extract of aloe demonstrated an up-regulation of granulocyte-colony stimulating factor and stem cell factor. Similar extracts have shown significant activity for the repair of radiation damage, pressure ulcers, and other wounds. Silver sulfadiazine is often used to control the microbiologic flora within burn wounds; however, silver sulfadiazine has been known to retard healing in some instances due to its cytotoxicity towards human keratinocytes and fibroblasts. These effects were reversed when silver sulfadiazine was used with aloe preparations. Aloe preparations have been shown to increase intercellular communication and proliferation of human fibroblasts. This is achieved by increases in the stimulatory effects of basic fibroblast growth factor-2 when combined with aloe extracts. These effects were minimal in fibroblasts cultured in the absence of fibroblast growth factor-2.

Like honey, aloe is an extremely complicated mixture of natural products. Fractionation of extracts and purification of compounds from aloe resulted in the identification of β-sitosterol, an angiogenic factor that may be beneficial to the healing process, because angiogenesis is a key step in the repair mechanism. The compound was shown to be angiogenic in the chorioallantoic membrane assay and to stimulate neovascularization in the mouse Matrigel plug assay. The compound also gave positive results in the human umbilical vein endothelial cell motility assay. These findings indicate that β-sitosterol may prove beneficial in the management and treatment of chronic wounds. Aloe has been used to treat wounds and burns for centuries. It is also thought to reduce tissue loss from ischemia owing to its ability to decrease thromboxane A2, thromboxane B2, and prostaglandin 2α, which produce platelet aggregation and vasoconstriction. Aloe also contains other ingredients that have anti-inflammatory and antipruritic activity, salicylic acid and magnesium lactate, respectively, which could easily influence the repair process.

Aloe

Preparations of aloe vera (Aloe barbadensis) have been used since ancient times for various ailments, especially those of the skin. Today, a multitude of products contain aloe preparations of varying compositions and potencies. These are incorporated into various gels and creams for a range of skin disorders, hair products, and even into various tissues and paper products.
β-Glucans

The β-glucans are a structural component of the cell walls of bacteria, fungi, and plants. The long-chain polysaccharide polymers consist of glucose monomers in a β(1,3)(1,6) linkage. The polymers have been incorporated in bioartificial skins by combination with gelatin or collagen. Although these products have enjoyed some success, they have been used traditionally as vehicles for fibroblast formulations or as bandage-like coverings for burns or autograft sites."40,39

β-Glucans are not found in mammalian systems and are considered to be pathogen-associated compounds. As such, they are capable of inciting immune responses in animals and humans.41 One study found that β-glucans extracted from beer yeast (Saccharomyces cerevisae) were capable of potentiating leukocyte functions in human whole blood and monocytic cell cultures without inducing cytokine production.41 Furthermore, β-glucans have been shown to lack pyrogenic properties in humans at therapeutic levels.42

In a rat wound model, β-glucan increased the cellular response to the injury, resulting in double the number of leukocytes in the wound at 6 hours after treatment, and 3.5 times the amount 18 hours after treatment when compared with an untreated control and a negative control (dextran). The effects were similar for bacterial infection in a rodent pneumonia model. In addition, the animals treated with β-glucan had a 60% reduction in pulmonary bacteria.43 These results are interesting, because little progress has been made in well-defined pharmacologic interventions to improve neutrophil or macrophage function. Such an intervention may prove to be an indispensable tool to the wound care clinician, because early migration of these cells into a wound area is essential for prompt and healthy healing.44

Cocoa

External application of cocoa has been reported to have a variety of benefits, including soothing burns, disinfecting skin wounds, and acting as a moisturizer for the skin.45 Ingestion of cocoa has also been associated with photoprotection against ultraviolet (UV)-induced erythema and improved dermal blood circulation and skin hydration.46 Research has shown that flavanoids, which are secondary plant metabolites found in cocoa and a variety of fruits and vegetables, have antioxidant attributes.47 Topical application of green tea polyphenols has also been shown to decrease UVB-induced erythema.48

Although several studies have investigated the beneficial effects of nutritional cocoa, including a recent study showing consumption of flavanol-rich cocoa acutely increased microcirculation of the skin,49 there are limited studies on its use topically. The beneficial antioxidant effects of cocoa and its ability to enhance vascularity may be important in the wound-healing process (Figure 1). In a preliminary study (unpublished), the authors investigated the effect of hydrolyzed and pure cocoa butter on 180 second-degree burn wounds, using a well-established porcine model.50,51 From past experience, the authors assessed burns for complete epithelization starting on day 7, because they seldom see any of the wounds completely epithelized at this early assessment time. In the cocoa butter study, however, the authors observed that all wounds treated with pure and hydrolyzed forms were 40% and 100% completely epithelized, respectively. Using this model for the past 20 years, the cocoa treatments have appeared to be one of the best treatments the authors have examined to date; however, additional studies are needed to determine the significance of this pilot study.

Oak bark extracts

Tree bark extracts, including that of Quercus rubras, have been used traditionally by the native elders of Vancouver Island to treat illnesses ranging from digestive tract ailments to dermatologic complaints.52 Oak bark contains tannin and has a significant astringent property that is thought to coagulate surface proteins of cells, which causes a reduction in permeability and secretions.53 One study demonstrated that Quercus rubra had the most antistaphylococcal activity of eight chosen plant extracts.54

Wound infection is known to impair the repair process in both acute and chronic wounds.55 Most of the infections are polymicrobial,56 and most of these bacteria are aerobic gram-positive cocci (predominately S aureus and the hemolytic streptococci).5 Wound infections, especially those associated with S aureus, are a major concern for health care providers (Figure 2). The incidence of MRSA has continued to grow throughout the years.57 High rates of MRSA isolated from outpatient skin and soft-tissue specimens have been found, especially in the United States and France.58 Using a wound infection model,59,60 the authors studied the effect of an oak bark extract product (Bensal HP, 7Oaks Pharmaceuticals) on its ability to kill MRSA and also examined its wound healing
properties. The Bensal HP product consists of benzoic acid (6%), salicylic acid (3%), and extract of oak bark, *Quercus rubra* (3%).

The authors found that wounds treated with the oak bark formulation had approximately a log and half reduction of MRSA colonies at 24 hours compared with all other treatment groups. At 48 and 72 hours, at all assessment times, a log CFU/mL reduction in MRSA counts was seen with the oak bark formulation compared with the other treatments. It is possible that the benzoic and salicylic acids that are found in the oak bark extract may have contributed to its antimicrobial effects, because both have been shown to have antimicrobial activity.61-63

Conclusions

Natural compounds contain a wealth of interesting and possibly beneficial pharmaceutically active compounds. The use of these natural compounds has been increasing dramatically in the United States, with other countries now requiring standardizations of herbal therapies of dermatologic disorders.1 This is due to the complexity of the sources, complexity of isolating the active components, and being able to study them in a well-controlled setting. Studies have shown that honey, aloe vera, β-glucan, cocoa, and oak bark extracts can be used fairly effectively in various *in vitro* and *in vivo* settings. Although *in vitro* studies are extremely important to help determine the initial appropriate dose of potential agents, additional *in vivo* studies are necessary to take into account the effect of the antimicrobial agent in the presence of wound fluid, growth factors, and antimicrobial peptides, among others.64 With only a few clinical trials warranting their use for pharmaceutical intervention in wound care, additional studies are needed with controlled extract formulations that are reproducible. Unfortunately, this may prove difficult, further delaying the application of these potentially beneficial agents in a clinical setting.

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References


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**Fig. 2** Effect of an oak bark extract formulation on methicillin-resistant *Staphylococcus aureus* (log CFU/mL).