Herbal Therapy for Burns and Burn Scars
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ABSTRACT

Burns are one of the most common trauma occurrences. Burn wound healing are a complicated and highly susceptible to bacterial infection. In traditional medicine, there are various phytochemicals that are used for wound healing supplying enhanced healing process via anti-inflammatory or antioxidant activity. The purpose of this review is to summarize the current knowledge gained in preclinical and clinical studies on topical herbal products with burn wound healing activity. Electronic databases including PubMed, Scopus, and Google Scholar were searched for articles published from 2014 to the present. Total 480 studies, 199 reports were excluded because of duplication. After examining the full text of the 3 studies against the inclusion criteria. This study found that the topical antimicrobial therapy is one of the most important methods of burn wound care. The ideal antibacterial agent for wound infection prevention and control should directly kill pathogens and reduce local inflammation and tissue destruction by absorbing decay products and improved tissue nutrition. Among various herbal preparations, A. sativum, A. vera, C. asiatica and H. rhamnoides have the best wound healing effects through different mechanisms.

Introduction

Skin is the largest organ of the human body, which can protect the internal organs from the external environment and prevents dehydration of the body.1 Our skin is the key to our survival, sensing the environment, maintaining physicochemical and thermal homeostasis, acting as a reservoir of essential nutrients, providing passive and active defenses, and responding to trauma and injury.2 It can be traumatized by burn injuries, chronic wounds, resections, tumors, and other skin disease.1 Burns are one of the most common trauma occurrences, and burn wounds require precise care to improve, resulting in significant medical and economic expenses.3 In 2004, the incidence of severe burns was over 11 million persons, ranking fourth among all injuries, and was greater than the combined incidence of TB and HIV infection.4

Burn wound healing is a complicated process that includes inflammation, re-epithelialization, granulation, neovascularization, and wound contraction.5 Burn injuries are described as injuries induced by the application of heat, chemicals, electrical current, or radiation to the body's external or internal surface, causing tissue damage.6 Burns are a severe, unexpected, and destructive kind of trauma that affects both the victim's physical and psychological health.7 Burn wounds are highly susceptible to bacterial infection, particularly those caused by aerobic or facultative pathogens such as Staphylococcus aureus, Pseudomonas aeruginosa, and -hemolytic streptococci, which colonize in the first 24 hours after burn and are main causes of delayed healing.8,9

Scars are treated with a variety of wound care
treatments, including autografts and allografts, lotions and solutions, wound dressings, and alternative tissue-engineered skin replacements. In recent years, a number of commercially available wound dressings have been introduced. However, they have certain significant limitations, such as the inclusion of antimicrobial medicines, which may have cytotoxic effects, especially when used for a long length of time, causing wound healing to be delayed. Some commercially available dressings lose their moisturizing function, causing them to cling to the wound's surface and harm the newly created epithelium. Skin treatment after burn damage necessitates the administration of various medications, either alone or in combination, and it is a complex and painful process.

In traditional medicine, there are various phytochemicals that are used for wound healing supplying enhanced healing process via anti-inflammatory or antioxidant activity. Due to their effectiveness and safety, herbal drugs are most commonly used in traditional therapies and treatments of skin wounds. Reports on herbal products affecting various phases of the wound-healing process, such as coagulation, inflammation, epithelization, collagenation, and wound contraction, are abundant in the scientific literature. Herbal products with antibacterial activity can inhibit bacterial growth through different mechanisms and have important clinical value in the treatment of drug-resistant microbial strains. In addition, shortening the wound healing time is critical to the wound repair process and reduces the chance of bacterial infection. And reduce complications and costs. The use of herbal products to treat burns provides such an opportunity.

The purpose of this review is to summarize the current knowledge gained in preclinical and clinical studies on topical herbal products with burn wound healing activity. In addition, it will describe its antibacterial, anti-inflammatory and antioxidant mechanisms, as well as the penetration of herbal products through burned skin, and the adverse effects of herbal therapy.

Methods
For this purpose, electronic databases including PubMed, Scopus, and Google Scholar were searched for articles published from 2014 to the present. Search terms include “herbs for burn wound healing,” “topical herbal treatments for burn wound healing,” “herbal treatments in burn wound model,” and “herbs for bacterial burn wound infections.” References from reviews about herbal products and wound healing were searched for additional articles and case reports. A manual search was also conducted based on citations in the published literature. The inclusion criteria the results of the animal- and human-based studies on topically used herbal products in the burn wound healing comparing herbal products treatment versus control treatments (placebo or active therapy) were selected. This study excluded other ways of using herbal products in burn wound healing (eg, Oral, systemic) rather than topical administration. Also, publications published in languages other than English are not considered. In the second step, the researcher reads and evaluates the full-text research that meets the requirements.

Result
From total 480 results, 199 reports were excluded because of duplication. After reviewing the titles and abstracts from 281 studies, 3 studies were identified for possible inclusion in the review. After examining the full text of the 3 studies against the inclusion criteria. The first study discussed evaluate herbal preparations and their phytochemical constituents for burn wound management. While the second study the chemical compositions, purity, efficacy, minimal active concentration, and toxicity of herbal formulations. Third study discusses establish experimental model of thermal injuries and to evaluate the effects of topical agents on healing of the burn wounds.
<table>
<thead>
<tr>
<th>Article</th>
<th>Ref.</th>
<th>Design Study</th>
<th>Sample</th>
<th>Main Results</th>
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<tr>
<td>Medicinal plants and their natural components as future drugs for the treatment of burn wounds: an integrative review</td>
<td>Bahramsolatni R et al</td>
<td>Observational</td>
<td>3 human studies and 62 in vivo and in vitro studies</td>
<td>Among single herbal preparations, Allium sativum, Aloe vera, Centella asiatica and Hippophae rhamnoides showed the best burn wound healing activity. Flavonoids, alkaloids, saponins and phenolic compounds were active constituents present in different herbs facilitating wound closure. Glycosides including madecassoside and asiaticoside and proteolytic enzymes were among the main active components. Phytochemicals represented positive activity at different stages of burn wound healing process by various mechanisms including antimicrobial, antiinflammatory, antioxidant, collagen synthesis stimulation, cell proliferative and angiogenic effect.</td>
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<tr>
<td>Herbal Products for Treatment of Burn Wounds</td>
<td>Herman A et al</td>
<td>Observational</td>
<td>30 studies</td>
<td>Topical applications of herbal products with antimicrobial, anti-inflammatory, and antioxidant activity seem to be a good alternative for the treatment of burn wounds. However, the chemical compositions, purity, efficacy, minimal active concentration, and toxicity of herbal formulations need to be further investigated. Nevertheless, herbs may be considered as an important support during conventional therapy or even as a substitute for synthetic drugs burn treatment.</td>
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<tr>
<td>Topical Treatment of Standardised Burn with Herbal Remedies in Model Rats</td>
<td>Bečić F et al</td>
<td>Experimental</td>
<td>Forty female wistar rats</td>
<td>The result of treatment application was a significant reduction of burn wound diameters. Herbal topical preparations expressed positive therapeutic effects on the parameters of burn wounds. The efficiency of silver sulfadiazine cream in burn wound healing was significantly more expressed in comparison to healing process in control group of animals (p&lt;0,001). We conclude that herbal topical preparations efficiently caused the completion of burn wound healing process without scar formation.</td>
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Table 1. Summary of studies
**Discussion**

The main stages of the recovery process for burned skin include the migration of blood cells from deep within the burn wound, the promotion of local inflammation, the removal of cellular debris and pathogens, the proliferation of connective tissue and extracellular matrix, the neovascular network (angiogenesis) and tissue remodeling. (Granulation tissue). Therefore, the ideal medicine for burn patients should not only have great wound healing potential, but also show positive effects at different stages of wound repair. The antioxidant activity seems to be a good option for treating burns.\textsuperscript{18,19}

The topical antimicrobial therapy is one of the most important methods of burn wound care. The ideal antibacterial agent for wound infection prevention and control should directly kill pathogens and reduce local inflammation and tissue destruction. Therefore, herbal products can be used successfully to treat wounds. The application of herbal preparations can enhance the anabolic phase of burn wound healing simply by absorbing decay products and improved tissue nutrition. Achillea millefolium alcohol extract,\textsuperscript{20} a mixture containing aloe vera gel and sea cucumber extract,\textsuperscript{1%} Cleistocalyx operculatus essential oil,\textsuperscript{21} sliced fresh kiwifruit,\textsuperscript{22} and Sanguisorba officinalis extract against Gram-positive bacteria (S. aureus, S. pyogenes) and Gram negative bacteria (E. coli, P. aeruginosa) planting burns. Methanolic extracts from Amaranthus spinosus, Anogeissus leicarpus, Spondia monbin, Corchorus olitorius, and Mallotus oppositifolia were found to inhibit the growth of pathogenic microorganisms (Staphylococcus aureus, Escherichia coli, Klebsiella pneumonia) and clinical isolates of Citrobacter.\textsuperscript{23} In contrast, 10% hydroalcoholic licorice extract\textsuperscript{24} and Cucurbita moschatu husk\textsuperscript{25} are not active against Staphylococcus aureus and Pseudomonas aeruginosa.

An increasing number of burn wound infections are made by fungi, especially yeast Candida sp.\textsuperscript{26,27} Burn patients who require prolonged courses of antibiotic or broad-spectrum antibiotic treatments should be carefully monitored for the development of Candida and should have prophylactic administration of antifungals considered.\textsuperscript{28} Moreover, it was revealed that Pseudomonas sp., alone or in combination with other bacterial species, invariably inhibited Candida sp. growth in burn wounds.\textsuperscript{29} What is more, Achillea millefolium extract\textsuperscript{20} showed activity against yeast C. albicans.

Among various herbal preparations, A. sativum, A. vera, C. asiatica and H. rhamnoides have the best wound healing effects through different mechanisms. Also, among the compound herbal preparations, ampucare is the most effective, which can stimulate wound contraction and antioxidant defense mechanisms. A. sativum can reduce biomarkers of infection and organ damage. Several studies support the anti-inflammatory and antibacterial effects of A. vera gel. Glycosides from C. asiatica, including Madecassoside and asiaticoside, showed improvement in the biochemical and histological markers of burn wounds in vitro and in vivo. The preparation of different parts of H. rhamnoides increased collagen synthesis and angiogenesis. In some plants, including actinides and papaya species, proteolytic enzymes are active ingredients with cleansing properties.\textsuperscript{25}

Wound healing process consists of inflammation, reepithelialization, granulation and neovascularization, which result in wound contraction. In the inflammation phase, neutrophils and macrophages are attracted into the injured tissue. This process involves the release of numerous cytokines (interleukin [IL] 1β, IL-6, and tumor necrosis factor [TNF-α]), chemokines, and growth factors (especially platelet-derived growth factor and basic fibroblast growth factor).\textsuperscript{18} Following, and overlapping with the inflammatory response, the proliferative phase is characterized by keratinocyte and fibroblast activation by cytokines and growth factors.\textsuperscript{30} In this phase, keratinocytes migrate over the wound to assist in closure and restoration of a vascular network, which is a vital step in the wound-
healing process.\textsuperscript{31} Zanthoxylum bungeanum seed oil decreased TNF-α, IL-1β, and IL-6 levels in serum, upregulated IkBa, and downregulated p-NF-κB p65 and p-IκBα expressions in vivo, indicating the anti-inflammatory action of this oil.\textsuperscript{3} Also, A. vera-based extract of Nerium oleander (NAE-8\textsuperscript{®}) caused the significant downregulation of burn-related increases in TNFα and IL-1β expressions.\textsuperscript{32} In addition to abnormal cytokine levels, burn-related significant increases in myeloperoxidase activity were reduced by NAE-8\textsuperscript{®} treatment, referring to its inhibitory effect of tissue neutrophil infiltration.

In the inflammation phase, neutrophils and macrophages eliminate wound debris that results in the generation of free radicals such as reactive oxygen species (ROS).\textsuperscript{33} At high concentrations, ROS can cause tissue damage and further hinder the healing process by causing damage to cell membranes, DNA, proteins and lipids. Lipid peroxidation overexpressed by malondialdehyde (MDA) (an indicator of the level of oxidative stress in living organisms) is considered one of the most devastating events that occur after burns. Inhibition of subsequent ROS production has proven to be critical not only for accelerating wound healing, but also for preventing bacterial infections after burns.\textsuperscript{34,35} Therefore, topical applications of herbal products with antioxidant activity should protect tissues from oxidative damage and significantly improve the wound-healing process in burn patients. It was observed that treatment of burn wound with 20% C. moschata peel\textsuperscript{25} and NAE-8\textsuperscript{®}\textsuperscript{32} significantly decreased lipid peroxidation and supports the maintenance of cellular integrity as a potent antioxidants. The 5% ointment of Achyranthes aspera showed significant burn wound healing, which was evident by wound contraction and elevation of various antioxidant enzymes such as SOD, CAT, and vitamin C.\textsuperscript{36} The mastic extract of Pistacia atlantica affected wound healing by significant increase in the concentrations of SOD, CAT, and GPX.\textsuperscript{37} Also, Pistacia atlantica resin oil treatment significantly increased SOD and GPX as well as reduced MDA levels.\textsuperscript{38}

According to traditional medicine in different countries, including Iranian traditional medicine, there are many medicinal plants that have potential healing effects on burns. Malva spp., Althaea of ficinalis, Sambucus ebulus, Olea europaea, Cupressus sempervirenc, Pinus sp., Tragopogon graminifolius, Hypericum perforatum, Iris spp., Cucurbita maxima, Cucurbita pepo, Plantago major and Arnebia are mentioned in the book Examples.\textsuperscript{Text. Traditional Iranian medicine.\textsuperscript{39} Previously, anti-ulcer function of these herbs have been verified in various experimental studies, and it is exhibited that their healing activity on gastrointestinal ulcer is via several mechanisms of action including antioxidant, wound healing, antimicrobial, anti-secretory, immunomodulatory, cytoprotective and angiogenic effect.\textsuperscript{40,41} Further modern studies in order to exploring their wound healing mechanisms of action and responsible active components are suggested to be done.

\textbf{Conclusion}

Herbal products have been used for burn wound care for many centuries. A large number of animal studies and few clinical trials have confirmed the activity of herbal products in promoting burn healing. Several herbs have an effective effect in treating wounds (especially burns) and can be considered as an alternative source of treatment. Furthermore, various phytochemicals exhibit wound healing functions. Phytochemicals showed their positive activity at different stages of burn wound healing process by various mechanisms including antimicrobial, anti-inflammatory, antioxidant, collagen synthesis stimulation, cell proliferative and angiogenic effects. However, the chemical composition, purity, efficacy, minimum active concentration and toxicity of herbal preparations need to be further studied. Herbal medicine can be considered as an important support in conventional treatments, and can even be used as a substitute for synthetic drugs to treat burns. It is recommended to
conduct advanced clinical and pharmaceutical research to produce new natural medicines for the treatment of burn wounds.

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