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Herbal Therapy for Burns and Burn Scars

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<http://dx.doi.org/10.5772/intechopen.71665>

Abstract

Burn wound healing is a complex process including inflammation, epithelialization, granulation, neovascularization, and wound contraction. Modern therapies present a large number of options, while traditional therapies are promising effective choices. Plant-based products have been used in the treatment of wounds for centuries worldwide. Recently, the mechanisms behind many of these traditional therapies could be explained in detail. The most commonly found mechanisms behind the herbal source products supporting wound healing are mostly their antioxidant, anti-inflammatory, antimicrobial, cell proliferative, and angiogenic effects. However there is not much more studies demonstrated in patients except *Aloe vera* and *Avena* sp., herbal treatment still show a lot of promise in the future. It is important not to ignore possible toxic and allergic effects of plants and phytochemical agents, but the studies mostly resulted with antitoxic effects. Several herbs show efficient results with therapies of wounds also in burn wounds, which may be considered as an option for treatment. On the other hand, herbal treatment in burn wounds still needs to have more clinical and pharmaceutical studies to place in modern therapies safely.

Keywords: burn wound, herbal therapy, plant, phytochemical, wound healing

1. Introduction

Skin is the largest organ of the human body that protects the internal organs from the external environment and prevents body dehydration. It can be traumatized by burn injuries, chronic wounds, excision, tumors, and other dermatological conditions [1]. Burns are one of the most commonly seen trauma incidents and burn wounds need a meticulous care for progress, which causes major medical and economic costs [2]. Burns have extensive categories that may result from heat, cold, chemical, or radiation exposure causing acute cutaneous wounds [3]. Burn wounds are classified into three subgroups according to the depth as first

degree (superficial), second degree (partial thickness), and third degree (full thickness) [4]. Process of the wound healing has complicated pathways that do not occur in a linear way and can progress forward or backward during the phases depending on various intrinsic and extrinsic factors [5]. After the cutaneous injury, hemostasis is achieved with the activation of platelets resulting in clot formation, which essentially acts as a temporary wound closure mechanism [6]. Burn wound healing is a complex process including inflammation due to the disruption of blood vessels and extravasation of blood constituents, reepithelialization, formation of granulation tissue handled by macrophages and fibroblasts that are responsible for the recovery of the extracellular matrix (ECM), neovascularization as well as migration and mitogenic stimulation of endothelial cells and wound contraction as a result of the interaction between cells, ECM, and cytokines [7]. Neutrophils begin placing to the injury area within hours of the injury, by the effects of platelet-derived growth factors (PDGF), transforming growth factor-beta (TGF- β), and fibroblast growth factor (FGF), that are potent chemotactic agents for neutrophils [6].

Several biochemicals are involved in burn healing process including matrix metalloproteinases, superoxide dismutase, catalase, reduced glutathione, malondialdehyde, myeloperoxidase, vascular endothelial growth factor, hydroxyproline, hexosamine, ascorbic acid (vitamin C) and protein content in damaged and surrounding tissue, serum levels of aspartate transaminase, alanine transaminase, lactate dehydrogenase, blood urea nitrogen, creatinine as indicators of liver and kidney damage, and tumor necrosis factor (TNF) for the evaluation of generalized tissue damage [8]. Moreover, wound repair process has also a chronic progression because of oxygen free radicals. Oxidative stress causes delay in healing and concludes with secondary tissue damage. It is assumed that antioxidant therapy may have a defense effect by decreasing free oxygen radicals and strengthening cellular antioxidant mechanisms, which supports the healing process of the wound [9]. Consequently, compounds playing roles as free-radical neutralizers that include antimicrobial properties may have an important effect in enhancing wound healing. Several traditional herbal-based therapies have been shown to possess antioxidant activity and also enhance wound healing in *in vitro* studies [10].

Excessive tissue growing may result with aberrant patterns of wounds. Hypertrophic scars and keloids are deviant form results of wound healing that are also seen after burn wounds. Aberrant function of fibroblasts and exaggerate accumulation of ECM during wound healing with a dysregulated response to cutaneous injuries, result in an excessive deposition of collagen. Hypertrophic scars have a raised and firm surface with red or pink in color and usually limited to wound area, while keloids have raised firm and irregular surface usually dark red and pigmented in color that extends into the neighboring skin. Keloids are tougher lesions to treat because of not regressing, also difficult to manage surgically, that do not provoke scar contractures with time, contrary to hypertrophic scars [11, 12]. There are plant-based agents that may inhibit nuclear factor κ B (NF- κ B) and TGF- β 1 signaling in keloid fibroblasts and also decrease ECM production [3].

Various wound care products are used for the management of scars, like autografts and allografts, creams and solutions, wound dressings and alternative tissue-engineered skin

substitutes [1]. In recent years, a variety of commercially available wound dressings were launched. However, they possess certain critical limitations such as addition of antimicrobial agents, which might include cytotoxic effects, especially on prolonged treatment period, causing to delay wound healing. Some of the marketed dressings lose their moisturizing effect, which makes them adhere to the surface of the wound and damage the newly formed epithelium [13]. After burn damage, the treatment of skin needs the use of several drugs administered separately or combined, and it is a complex and painful process [14].

In traditional medicine, there are various phytochemicals that are used for wound healing supplying enhanced healing process via anti-inflammatory or antioxidant activity [3]. However, several herbal-sourced phytochemicals have shown some efficacy in animal models on the treatment of burn wounds; only a few herb-derived phytochemicals have been studied in human trials such as *Aloe vera* and *Avena* sp. More effective natural products are being studied to get over with the side effects of chemotherapeutics [8].

2. Herbal therapies

2.1. *Aloe vera*

Extensive study results showed that herbs especially *A. vera* has an effective anti-inflammatory and wound healing effect. *A. vera* belongs to the Liliaceal family, which is a perennial succulent plant [15]. It originates from South Africa, widely used in conventional therapy and of great interest for several biomedical, pharmaceutical, and cosmetic applications [1]. Studies are mostly about the anti-inflammatory and wound healing effects. The gel form of *A. vera* has demonstrated the progress in wound, burn, and frostbite healing, showing known as anti-inflammatory effects also antifungal, hypoglycemic, and gastroprotective effects [15]. Furthermore, due to the features of *A. vera* as anti-inflammatory, antibacterial, antiseptic, and its reliability to inducing collagen synthesis during the wound healing, its gel form is thought to be used for the treatment of skin disorders [1]. *A. vera* has an analgesic effect and also been used in a host of curative purposes including treatment of skin disorders and healing of wounds [16]. *A. vera* gel has a significant effect that improves the synthesis of collagen and the degree of collagen cross-linking, after topical and systemic administration in wounds created in a diabetic rat model. Also, it is mentioned that the oral administration of *A. vera* significantly induces the proliferation of fibroblasts, the collagen deposition, and angiogenesis in radiation-exposed rats [17].

A. vera is a choice for treating burns because the colorless gel that comes from the leaf parenchyma is a potent moisturizing agent; it also helps in the healing process of skin lesions and alleviates pain [16, 18]. In a review, no withdrawal or serious adverse reaction was reported. The unwanted symptoms reported were only irritation, itching, discomfort, and minimal transient pain; on the other hand, these symptoms were common signs in burns, and they were found in both the *A. vera* and the control groups. Contamination with anthraquinone while using topical fresh *A. vera* has a potential cause of the irritation [19]. The polymer film

formulation containing hyaluronate and alginate appears to be a promising approach for the application of substances, able to reduce damage and facilitate the healing process, like *A. vera* extracts and the antioxidant vitamin E acetate [16]. Burn healing and anti-inflammatory activity was observed in topical treatment with *A. vera* gel preparations [20]. A study of human demonstrated the efficacy of *A. vera* on second-degree burn wound patients [21–23]. In a study, it was reported that TNF- α , interleukin-6 (IL-6), and leukocyte adhesion were found to be decreased in a rat model of burn wound treated with *A. vera* gel. It was also showed to be an antibacterial effect against *Klebsiella pneumoniae*, a nosocomial pathogen in another study [8].

2.2. Curcumin

Curcumin is a polyphenol compound, diferuloylmethane, responsible for the yellow pigmentation. Curcumin is a chemical compound present in the Asian spice named turmeric or *Curcuma longa*. It is used in Indian and Chinese cuisine; also, it has been used topically for cutaneous wounds including ulcers, traditionally in the Indian subcontinent [24, 25]. It has antiproliferative, anti-invasive, and antiangiogenic effects; also, it is a therapeutic agent in wound healing. Curcumin-incorporated collagen sheets were designed for dermal wound healing. These membranes supply higher antioxidant activity, hydrothermal stability, and faster wound reduction compared to collagen-treated wounds. For effective infection control, curcumin-included membranes could be used by means of prolonged antimicrobial activity [15]. Curcumin is a phytochemical candidate for the treatment of hyperinflammatory burn wounds by the mechanism of suppression of TNF- α and IL-1 production by human macrophages anti-inflammatory properties [3].

In hypertrophic scarring and keloids, there is an abundance of TGF-B1 expression, fibroblast proliferation, and excess collagen and ECM synthesis [26]. In scleroderma, which is another fibrotic skin disease, curcumin has also been shown to inhibit TGF-B1 signaling [27]. Curcumin is a potent inhibitor of NF- κ B, inhibits TGF-B1 signaling in keloid fibroblasts, and also decreases ECM production [3]. In vitro, it is showed that curcumin also suppresses the proliferation cascades of keloids and hypertrophic scar-acquired fibroblasts [28].

2.3. Honey

Honey is a nutritious thick carbohydrate-rich syrup, which was effectively known and used since ancient times in traditional medicine. Today, honey has a broad area being used due to its evidenced therapeutic effects. It is a well-known antibacterial, antiparasitic, pain reliever, and it has proven efficient against respiratory tract infections [13]. Honey has been used as a topical treatment for chronic wounds and burns in traditional medicine by diverse parts around the globe [29]. It has been used for burns in various ancient societies such as Greek and Roman physicians, and also for the treatment of burn wounds [30]. It was shown in a study that Leptospermum honey was potently active against antibiotic-resistant clinical pathogens [31]. Antibacterial features of honey are about its high osmolality, low pH, and hydrogen peroxide production that accelerate the wound healing process [13]. Since chronic wounds and burns are particularly vulnerable to infections, honey's antibacterial effect attracts to be a

therapy method [3]. The phytochemical components, such as flavonoids and phenolic acids, act as antioxidants due to their free radical removing activities, which save cells from the damage due to free oxygen radicals and decrease the inflammatory response [13]. Its immunomodulatory effects are useful for the management of chronic wounds. Honey is also shown to promote angiogenesis and fibroblast proliferation in human clinical trials [3]. It is shown in rat models of partial-thickness burn injuries, honey usage shortened the period of epithelialization and increased wound contraction compared to vehicle controls [32]. Honey carries protease enzymes that help debridement cleaning out of the wounds [33]. Honey overcomes the hyperinflammatory microenvironment on chronic wounds via its anti-inflammatory effects by the inhibition of cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), TNF- α , and IL-6 expression [34]. Also honey contains various compounds including flavonoids, phenolic acids, catalase, peroxidase, carotenoids, and ascorbic acid, which possess antioxidant properties that can neutralize the abundance of free radicals found in chronic wounds [35, 36].

Using honey over burned area supplies an advantage of wetter environment. It saves the burned surface entirety; also, it is nonadherent and provides a bacterial barrier that prevents cross infection and prevents infecting bacteria [13]. In a systematic review of randomized controlled trials of eight studies in humans comparing the efficacy of honey to silver sulfadiazine-impregnated gauze demonstrated that honey had a superior healing effect, yet burn characteristics were limited to superficial and partial thickness only [37]. Honey debrides the wound, inhibits scar formation, and induces wound healing by stimulating tissue regeneration process so that it reduces the need for skin grafting. There are no adverse effects reported from using honey in burn healing [13]. Honey also has been shown to be protective against hypertrophic scarring as a result of burn wounds. In a randomized controlled trial, the effects of honey were compared to silver sulfadiazine in 104 patients with superficial burns. Hypertrophic scarring and postburn contracture in the honey-treated group have significantly lower incidence in comparison to the silver sulfadiazine-treated group [38].

2.4. *Terminalia* genus

Some *Terminalia* species have been reported to have wound-healing properties, antioxidant and antimicrobial activity with anti-inflammatory effects. *Terminalia chebula* extract, chebulagic acid (CA), is an antioxidant compound, when cultured with macrophages in vitro, significantly suppressed NF- κ B activation as well as TNF- α and COX-2 expression. These results show the possibility of topical application of *T. chebula* that would be beneficial in hyperinflammatory wounds such as chronic diabetic wounds or burns. In burn wounds, the extracts of *T. chebula* accelerate wound healing in comparison to 1% silver sulfadiazine in rat models [39, 40]. *Terminalia sericea* antimicrobial activity against *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Pseudomonas aeruginosa* has also been reported [3].

2.5. *Avena* sp.

Avena sp. used in shower and bath oil containing 5% colloidal oat meal in patients with partial-thickness burn showed significant decreasing in itch in comparison with control group [41].

2.6. *Zanthoxylum bungeanum*

Z. bungeanum maxim seed oil (ZBSO) was found to be effective in wound-healing activity on experimentally burned rats. It is thought to be the increased antioxidant activity as evidenced by the increase in superoxide dismutase level and decrease in malondialdehyde level, anti-inflammatory action through NF- κ B signaling pathway, and accelerated collagen synthesis through the decrease of Matrix metalloproteinase-2 and Matrix metalloproteinase-9 expressions. These effects of ZBSO might result with the early reepithelialization and faster wound closure [2].

2.7. *Hippophae rhamnoides*

Oral and topical administration of *H. rhamnoides* seed oil showed progression in tissue regeneration, matrix metalloproteinase (MMP) 2 and 9, vascular endothelial growth factor (VEGF), collagen type-III, DNA, total protein, hydroxyproline and hexosamine content in the granulation tissues, as well as decrease in reactive oxygen species and edema. Omega 3 and omega 6 fatty acids, tocopherols, and carotenoids are probable active components of the oil [42]. Moreover, the leaves of *H. rhamnoides* were showed in vivo burn healing effect by increasing epithelialization, MMP-2 and 9, VEGF, hydroxyproline, hexosamine, collagen type-III, and antioxidant function. In vitro study in chick chorioallantoic membrane also demonstrated the angiogenic effect of the plant extract [43].

2.8. *Calotropis procera* Aiton

C. procera Aiton, named as *Calotropis*, is native to South-west and South-East Asia and Africa and also grows in the Caribbean Islands, in Central and South America. *Calotropis*' latex contains tannins known to advance wound healing with their astringent and antimicrobial properties providing wound contraction and increased rate of epithelialization. In complementary and alternative medicine, the whole plant of *Calotropis*, leaves, barks, and its latex have been employed in the treatment and management of many health conditions for dressing fresh skin burns. In a trial study with rabbits, *Calotropis* latex was shown to have dual effects on wound healing. It induces florid granulation tissues, inhibiting exaggerated response of fibroblasts and aberrant collagens in the matrix that might be supportive of its potential antikeloidal activity. It is demonstrated that reduction in the quantity and width of the broad band collagens in the group treated with *Calotropis* latex means in collagen is inhibited by *Calotropis*' latex. The result of this study suggests that *Calotropis*' latex can be a potential source of therapeutic agents that can be used in the treatment of keloid [11].

2.9. *Punica granatum*

P. granatum L., is also known as pomegranate. In Traditional Chinese and Indian Medicine, it is used for traumatic hemorrhage, ulcers, nose bleeds, and aphthae. The therapeutic properties of pomegranate include ellagitannins represented by ellagic acid (EA), gallic acid, and punicalagin. Mo et al. showed that in an antioxidant assay-guided extraction of pomegranate peel,

ellagic acid (EA) was found to be the marker compound and major antioxidant. It was found to be in vitro and in vivo anti-inflammatory activities. *P. granatum* is a potential antioxidant therapy for burn wound healing [44, 45].

2.10. *Chromolaena odorata*

C. odorata is a plant in southern Asia and western Africa, and has been traditionally used for the treatment of wounds in Vietnam for many years [3]. *C. odorata* presents its wound healing property using multiple mechanisms. The extract of *C. odorata* contains many antioxidant compounds that progress wound healing process. It reduces the bleeding and clotting time as the first-line function of wound healing. It also has an anti-inflammatory effect that provides protection for the cells from destruction. *C. odorata* has antibacterial activities against both gram-positive and gram-negative bacteria, suggesting that it may reduce the wound infections [46]. It has been shown that *C. odorata* promotes wound contraction in in vitro models, and also promotes fibroblast proliferation. Moreover, *C. odorata* has been demonstrated to have protective effects on human fibroblasts and keratinocytes against the oxidative damage of hydrogen peroxide [3].

Herbal therapies	Healing mechanisms in burn wounds
<i>A. vera</i>	Anti-inflammatory [1, 15] Antibacterial [1] Antifungal [15] Analgesic [16] Antikeloidal effect [17]
Curcumin	Antiproliferative, antiangiogenic [15] Antikeloidal effect [28]
Honey	Antibacterial, antiparasitic, analgesic, antioxidant [13] Immunomodulatory effect [3] Antikeloidal effect [38]
<i>Terminalia</i> genus	Anti-inflammatory [39] Antibacterial [3]
<i>Avena</i> sp.	Antipruritic [41]
<i>Zanthoxylum bungeanum</i>	Antioxidant [2]
<i>Hippophae rhamnoides</i>	Antioxidant [42, 43]
<i>Calotropis</i>	Antibacterial, antikeloidal effect [11]
<i>Punica granatum</i>	Antioxidant, anti-inflammatory [44, 45]
<i>Chromolaena odorata</i>	Antioxidant [3, 46] Anti-inflammatory, antibacterial [39, 46]
<i>Centella asiatica</i>	Increasing reepithelialization and keratinization [47]

Table 1. Healing mechanisms in burn wounds of herbal therapies.

2.11. *Centella asiatica*

C. asiatica extracts of aerial parts were investigated for burn wound healing activity, and being the most potent one, ethylacetate extract, also all types of the extracts had positive effect on wound healing by increasing reepithelialization and keratinization [47]. *C. asiatica* extracts, madecassoside, and asiaticoside and their corresponding aglycones (madecassic acid and asiatic acid) isolated from were shown to be stimulatory action on synthesis of collagen type I and III by activating fibroblasts via TGF- β in human skin fibroblast cells. Moreover, wound contraction in mice was demonstrated by means of madecassoside and asiaticoside [48]. Oral administration of madecassoside increased proliferation of fibroblasts and granulation tissue, hydroxyproline content, collagen synthesis, and angiogenesis in burn wounds of ICR mice [49] (Table 1).

3. Other herbal sources of burn wound care

Ficus asperifolia, *Bridelia ferruginea*, *Gossypium arboreum* [3], *Cucurbita moschata* [50], *Linum usitatissimum* L. [51], *Sesamum indicum* L., *Pistacia atlantica* Desf., *Cannabis sativa* L., *Juglans regia* L. [52], *Scutellariae* (altissimae, galericulatae, hastifoliae) [53].

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