Current Trends in Biotechnology and Pharmacy
Vol. 17(4) 1506-1517,October 2023, ISSN 0973-8916 (Print), 2230-7303 (Online)
DOI: 10.5530/ctbp.2023.4.84

Herbs with Acute Wound Healing Potential: A Review

Jie Chen Chow [1*], Mogana Rajagopal [1*], Choo Shiuan Por [1]

[1]Faculty of Pharmaceutical Sciences, UCSI University, 56000 Cheras, Wilayah Persekutuan Kuala Lumpur, Malaysia
*Corresponding authors: 1001851067@ucsiuniversity.edu.

Abstract

Wound healing is a timely and orderly process comprised of coagulation, inflammation, proliferative, and remodeling. Any disruption in the physiological process will delay the healing process and result in chronic wounds. Wound cleansing is the standard management for acute wounds to provide an optimal environment for healing. Besides wound cleansers, topical antimicrobials are commonly used to reduce microbial load and prevent microbial infection. However, they are associated with adverse reactions and antibiotic resistance, resulting in delayed wound healing. To overcome the limitations of conventional wound treatment, herbal therapy as an alternative is implemented for wound management with antimicrobial, anti-inflammatory, and antioxidant properties. Following the increased demands of herbal therapy in wound management, the innovative polyherbal formulation has gained popularity and has been extensively studied to promote better wound healing. The combined use of multiple herbs is comparatively cost-effective in providing synergistic effects with minimal side effects. This review provides insight into the role and mechanism of diverse medicinal plants with wound healing potential for acute wound management.
Keywords: acute wound healing; herbs; polyherbal formulation; antimicrobial; antioxidant

Introduction

Skin is the largest organ in the human body that serves as a protective barrier against physical, chemical, and biological attacks (1). Damage and rupture to the skin layers, commonly known as wounds result in skin structural and functional dysregulation (2). Depending on the occurrence and healing period, wounds are classified into acute and chronic types. Burns, surgical, and traumatic wounds are categorized under acute injuries that occur suddenly and heal within 4 to 6 weeks through a coordinated healing mechanism (3, 4). In contrast, chronic wounds are wounds that fail to recover within the aforementioned period due to disruption in the normal healing process.

A retrospective cohort analysis conducted in the United Kingdom reported 40% acute wounds out of 11,200 total wounds were managed in 2012/2013 (5). The statistics from World Health Organization (WHO) revealed globally more than 14, 000 people experience wounds each day, ranging from cuts, violence, falls, and burns to road traffic accidents (6). Wounds are described as a “silent epidemic” and cause undefinable impacts to individuals, caregivers as well as the healthcare system (7).

Wound healing is a normal physiological process where tissue regeneration and repair occur in response to tissue and vascular injury (8). The healing process is complicated and overlapping which comprises hemostasis, inflammation, proliferative, and remodeling (9). Hemostasis, also known as coagulation, is the

first mechanism to stop and prevent further bleeding via vasoconstriction and platelet plug formation (10–13). Platelet plug formation, in turn, stimulates the release of pro-inflammatory mediators, including platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), fibroblast growth factor (FGF), epidermal growth factor (EGF), and interleukin 8 (IL-8) to activate innate immune system (14). Upon activation of innate immune system, neutrophils and macrophages travel to the injury site to perform phagocytosis (14, 15). In addition, macrophages are essential in promoting the transition to the proliferative phase (16). Proliferation is mainly characterized by three major events: re-epithelialization, angiogenesis, and granulation tissue formation. Re-epithelialization involves the migration and proliferation of keratinocytes regulated by calcium influx, matrix metalloproteinases (MMPs), FGF, EGF, TGF, and cytokines to restore the epidermis layer (15, 17, 18). Angiogenesis is the formation of new blood vessels stimulated by vascular endothelial growth factor (VEGF), PDGF, FGF, TGF-β, and angiopoietins to ensure an adequate supply of oxygen and nutrients (15, 19). Granulation tissue rich in collagen type III, proteoglycans, hyaluronic acid, glycosaminoglycans, and fibronectin replaces the fibrin matrix, leading to extracellular matrix (ECM) deposition (16, 20). Meanwhile, fibroblasts transform into myofibroblasts for wound contraction (20, 21). Finally, ECM remodeling occurs when MMPs degrade ECM rich in collagen type III and replace it with collagen type I, causing scar formation and skin tensile strength restoration (22).

In the healthcare setting, several approaches such as wound debridement and dressings are available to promote wound closure and healing (23). Wound debridement is the removal of dead tissues from the wound, whereas wound dressings are applied to the injury site to prevent infection and promote wound healing activity (24). In addition, antibiotic is often prescribed for the prevention and treatment of wound infections, however, antibiotic overuse and misuse had contribute to antibiotic resistance that is associated with increased morbidity and healthcare cost (25). Advanced technologies, including cell and platelet therapy, are gaining attention for the management of chronic non-healing wounds (26, 27). Despite the advancement and effectiveness of current wound care strategies, patient factors, wound assessment as well as the availability and selection of ideal management greatly affect the outcomes of wound management (28). Furthermore, the total cost of wound treatment is another dilemma, particularly for low-income families (29). In addition, the adverse reactions of conventional wound care, such as irritations, bleeding, and damage to healthy tissues, lengthen the recovery time (30, 31). Therefore, herbal therapy practiced since ancient time has gained important nowadays as an alternative to wound care management.

Herbs, as natural sources, consist of various bioactive compounds that give promising effects in treating and preventing diseases. Several studies showed that herbal extracts are as effective as drug therapy with fewer side effects (32). Unlike conventional drug therapy, herbal therapy is a comprehensive approach to maintaining good physical, mental, emotional, and spiritual health and supporting body systems rather than treating primary conditions (32).

Method

Literature search was conducted through databases such as google scholar, PubMed, and Springer Link to obtain references up to December 2022. The keywords “herbs”, “extract”, “polyherbal formulation”, “cutaneous wounds”, “acute wounds”, and “wound healing” were used alone or in combination with the Boolean operators such as “AND” and “OR” to facilitate the searching process. A total of 30 articles were included in this review that met the following inclusion criteria. The inclusion criteria include acute cutaneous wounds, herbs or phytochemicals for wound healing, topical herbal

preparations, have undergone either preclinical or clinical studies, and were published in English language. Studies being excluded include chronic wounds, internal wounds, and oral herbal formulation. Single herbal therapy as alternative for acute wound management

Calendula officinalis L.

Calendula officinalis L., commonly known as marigolds, is traditionally used for the treatment of minor skin inflammations and wounds. A randomized clinical trial (n=40) showed that 2% of standardized Calendula officinalis extracts accelerate the healing speed by 3.3% per day by shortening the inflammation phase (33, 34). In this study, diabetes control and smoking habit were considered and reported no significant difference in terms of healing speed. Yet, the severity of diabetes and daily smoking frequency were not assessed which might underestimate the outcome on wound healing.

A pre-clinical study using excised rats showed significant reduction in interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) level, while increased epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) level (34). It is remarkable that low proinflammatory cytokines reduce the release of reactive oxygen species (ROS) that will further injure the cells and delay the healing, while promote the transition to the subsequent healing phase. On the other hands, EGF and PDGF are essential to promote the proliferation of keratinocytes and fibroblasts through the activation of a disintegrin and metalloproteinases (ADAMs) on EGF receptors.

Calendula officinalis tincture (CDOT) was prepared using 41% ethyl alcohol showed increased proliferation and migration of fibroblasts (35). The possible mechanism of CDOT was related to the activation of phosphatidylinositol 3 kinase (PI3K) pathway via the phosphorylation of protein kinase B (Akt) and focal adhesion kinase (FAK) at serine 473 and tyrosine 397, respectively. The author predicted that PI3K activation result in upregulation of connective tissue growth factor (CTGF) and alpha-smooth muscle actin (α-SMA) in Calendula officinalis hydroethanol extracts (CEE) and water fraction of CEE (WCEE), however, the actual mechanism that one causing another still unknown (36). Study reported that water fraction of extract promotes wound healing, but not in ethyl acetate and hexane fraction, hence, this proven the phytochemicals responsible for wound healing effects are mainly polar compounds. However, there is still lack of relevant biomarkers for standardization to assure the pharmacological effects.

Hippophae rhamnoides

Hippophae rhamnoides, or sea buckthorn, is a herbal plant used extensively in Europe and Asia with anti-inflammatory, antimicrobial, immunomodulatory, anticancer, antiulcer, and wound healing properties (37). In a randomized clinical trial, Bates-Jensen Wound Assessment Tool (BWAT) illustrated that 40% sea buckthorn cream showed faster healing (6.7±2.1 days) compared to 1% SSD cream on second-degree burn (38). Sea buckthorn was rich in polyunsaturated fatty acids to increase cytokine production in regulating cell function (39). Additionally, increased fibroblast proliferation, collagen synthesis, MMP-2 and MMP-9 expression, and VEGF stimulation contribute to quicker healing process (39, 40). Lacking negative control in the clinical trial unable to detect confounding and extraneous factors for assessing causal inference as burn wounds vary widely among individual patients (41).

Incorporating nanotechnology in the preparation of modern and herbal drugs will further enhance the efficacy of the formulated products as smaller particles can easily penetrate and retain at the targeted sites for their actions. The nanoemulsion gel of sea buckthorn seed oil showed an increased collagen formation and neovascularization with a low number of macrophages compared to sea buckthorn seed oil alone (42). This implicated that nano-

emulsion gel shortens the inflammatory phase and promotes the later stages of wound healing to accelerate the healing period. The promising effect of the combination of nanotechnology with herbal extract warrant the use in wound management.

Arnebia euchroma

Arnebia euchroma, commonly known as pink arnebia is a traditional Iranian plant rich in alkannin, shikonin, and anerbin-2 with anti-inflammatory, antibacterial, and antioxidant properties to promote wound healing. A randomized, single-blind study (n=49) formulated 10% A. euchroma ointment (10g A. euchroma roots, 20g goat fat, 15g cow butter, 20g glycerin, and 35g Eucerin) to evaluate the burn wounds healing effect against SSD cream at two different sites (43). Arnebia euchroma ointment (AEO)-treated sites showed better healing with a high general wound appearance score within a shorter period (13.9±5.3 days) than the 1% SSD (17.5±6.9 days). Pre-clinical studies by creating burn wounds model on rats showed a high wound contraction and shorter re-epithelialization time with higher satisfaction score on the AEO-treated sites in terms of pain, warming and burning sensation (44, 45). Moreover, Arnebia euchroma not only showing effect on burn wounds, while it also enhance fibroblast proliferation and collagen synthesis in excisional wounds (46). Though Arnebia euchroma effectively improve wound healing, the findings were inferior where the nurses were the only blinded in this study, as well, the study participants were informed of the treatment option with different colours of formulation.

Centella asiatica

Centella asiatica, or gotu kola is a perennial plant that rich in asiaticosides and madecassic acid. A study reported that asiaticosides and madecassic acid enhance collagen type I synthesis via phosphorylation of the Smad 2 and 3 pathway and activation of the TGF-β receptor I kinase-independent Smad pathway (47). Other mechanisms promoting wound healing include stimulating fibroblast proliferation, extracellular matrix synthesis, and tissue function restoration through the activation of several growth factors such as VEGF, FGF, and EGF (47, 48). A randomized trial showed 3% of Centella asiatica ointment significantly a significantly shorter the re-epithelialization period with better Vancouver scar scale and scores for dryness, itching, and irritation indexes in treating partial thickness burn wounds (49). Another clinical trial using 0.05% w/w standardized Centella asiatica extract (ECa 233) gel containing 51% madecassoside and 38% asiaticoside improved scar appearance in post-laser resurfacing on the face(50). The findings proved that Centella asiatica is effectively to improve healing in different wound types, however, more well-designed clinical trial is warranted.

As mentioned above, keratinocytes migration and proliferation are vital to restore the epidermis layer. Improving keratinocytes migration and proliferation through the activation of focal adhesion kinase (FAK) and ATP-dependent tyrosine kinase (Akt) pathway leads to the upregulation of the expression of Ras-related C3 botulinum toxin substrate 1 (Rac1) and Ras homolog gene family, member A (RhoA) that accelerates wound healing process (51). In addition, the extracellular signal-regulated kinases 1 and 2 (ERK1/2) and p38 phosphorylation significantly increase, which further promotes the proliferation of the keratinocytes.

Allium sativum

Allium sativum, or garlic, is an important spice used widely in many countries. The pungent smell enhances the flavour of dishes due to the presence of volatile organosulphur compounds upon crushing. Besides providing a pleasant aroma, the organosulphur compounds also give rise to medicinal benefits. A study using 30% garlic ointment showed improvement in wound appearance with a thinner, flatter, less erythematosus scar after three weeks of application (52). Garlic ointment consists of antibacterial effect to prevent the development of infec-

tion in regard to allicin with high potency against Staphylococcus aureus (53). The study was superior to evaluate the scar appearance over a follow-up period of up to 2 years. Nevertheless, the unblinded researchers had possess degree of bias, along with, confusion and misinterpretation with the use of common name in place of species name in the study.

Besides antibacterial effect, allicin also stimulates the proliferation of fibroblasts which shorten the inflammation period and promote the transition to the proliferative phase (54, 55). Adequate inflammatory response is crucially important for wound healing, however, prolonged inflammation will cause non-healing wounds. Other possible mechanism of garlic includes promoting angiogenesis, enhancing collagen deposition, and upregulating the intracytoplasmic carbohydrate ratio (56).

Camellia sinensis

Camellia sinensis, or tea plants including green tea, white tea, and black tea are commonly consumed as a beverage as well as supplements with pleasant aromas and health benefits. Epigallocatechin-3-gallate (EGCG), the major constituent in tea plants has been reported with anti-inflammatory, antioxidant, antimicrobial, anticancer, and antidiabetic properties (57). Figure 1 illustrates the chemical structures of phytochemicals with wound healing effect in herbs.

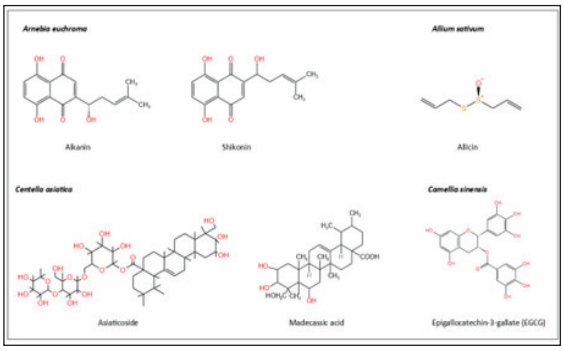

Figure 1. Phytochemicals reported with wound healing activity in herbs.

Hyaluronic acid, a major component in the extracellular matrix encoded by hyaluronan synthase gene to maintain the integrity and structure of skin. Wound treatment with green tea extract showed upregulation of hyaluronan synthase 2 gene expression to stimulate the proliferation and migration of keratinocytes (58). Shahrahmani et al. showed that 1% green tea ointment improved wound healing with less pain experienced after episiotomy by improving the Redness, Edema, Ecchymosis, Discharge, Approximation (REEDA) scale (59). In contrast, Kazemi et al. showed that 1% green tea ointment effectively reduce episiotomy pain with no significant change in wound healing (60). Nevertheless, the findings are yet to be proven as standardization of green tea ointment was not conducted to ensure the quality and quantity of phytochemicals contributing to wound healing (61). Moreover, lack of standard wound treatment as positive control produces less valid and reliable results as the extent of effectiveness is underdetermined, in addition, the treatment adherence was not assessed where non-compliance might be a cause of poor wound healing activity.

Fibrosis, the overproduction of collagen has been a concern that causes scarring and suboptimal wound healing. The antifibrogenic effect from EGCG is prominent to reduce scarring by inhibiting the phosphoinositide 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway (62). In addition, suppressing the overexpression of transforming growth factor beta (TGF-β) receptor I and II will further inhibit the transcription of alpha-smooth muscle actin (α-SMA) and differentiation from fibroblasts to myofibroblasts, hence resulting in reduced type I collagen production (63, 64). The supplementary antifibrogenic effects in addition to wound healing activity warrant the use of green tea extract in clinical practice to promote wound healing and minimize the wound complications.

Polyherbal formulation as alternative for acute wound management

Polyherbal formulation (PHF) is a blend of herbs in specified ratios to produce optimized therapeutic effects. The increasing trend of PHF is due to the synergistic effects and side effects minimizing properties (65). Bioactive compounds in the PHF work together to exhibit a potentiating effect that is inadequate by an individual herb (66). In addition, combining various herbs in a single formulation improves patient adherence and avoids taking multiple herbal formulations at a time. PHF confers a better benefit-to-risk ratio with a wide therapeutic range that is effective at a low dose and safe at a high dose (67).

Jatyadi taila

Jatyadi taila (JT) is a classical Ayuverdic formulation made up of 15 herbs, including Jasminum officinale, Azadiracta indica, Trichosanthes dioica, Picrorhiza kurroa, Berberis aristate, Hemidesmus indicus, Rubia cordifolia, Curcuma longa, Glycyrrhiza glabra, Pongamia pinnata, Saussurea lappa, Prunus cerasoides, Symplococus racemosus, Terminalia arjuna, and Nymphaea stellata in wound management. JT illustrated a dose-dependent effect in reducing the wound area with the most efficacious dose at 0.75mL/wound (68). Biomarkers such as hydroxyproline, protein, and hexosamine were significantly increase suggested the synthesis of collagen at the wound site. In addition, topical application of JT on radiation-induced wounds showed accelerated re-epithelialization where the inflammation period is shorter with less neutrophils infiltration (69). Reduced inflammatory cells downregulate the TGF-β1 signaling and type I collagen deposition to prevent fibrosis and impaired healing. Besides the immunomodulatory effects, JT demonstrated radical scavenging activity by increasing the superoxide dismutase, reduced glutathione, and catalase levels, where high free radicals formation and oxidative stress are known to causing cell damage and halt wound healing. Pre-clinical studies showed promising effects in the improvement of wound healing process, however, there is still lack of clinical trials to prove the efficacy and safety on human study.

Bhallatakadi ghrita

Bhallatakadi ghrita is a cow ghee-based polyherbal Ayurvedic formulation used for wound management. Plant extracts include Semecarpus anacardium, Argemone Mexicana, Cocculus hirsutus, and Woodfordia fruticose in equal ratio were mixed with water and cow ghee in a ratio of 1:16:4 for wound healing activity. Applying Bhallatakadi ghrita onto incision and excision wound model showed significantly increase in wound contraction on day 3 ($p < 0.05$) and day 9 ($p < 0.001$) with a shorter full re-epithelization period of 15.17 ± 0.04 days(70). Besides, the polyherbal ointment showed better healing activity with increased granulation tissue formation and collagen deposition compared to the cow ghee (control) and povidone-iodine-treated group. Wayal et al. prepared Murcchita ghee with equal propotion of Terminalia chebula, Emblica officinalis, Terminalia bellirica, Cyperus rotundus, Curcuma longa Linn, and Citrus medica var. acidica to replace plain ghee showed faster full re-epithelialization by 13.50 ± 0.22 days(71). In addition, the antioxidant activity is more potent in this formulation herbs due to the synergistic effect of Murcchita ghee and Bhallatakadi ghrita(71). The Murcchita-based Bhallatakadi ghrita demonstrated better shelf-life and high acceptability (72). A well-developed formulation deems to promote wound healing while increasing consumer satisfaction to increase treatment compliance.

Danggui Buxue Extract

Danggui Buxue (DB) is a traditional Chinese medicine made up of Angelica sinensis and Astragali radix for the rejuvenation of Qi and the improvement of Xue. A study on the individual herb of Astragali radix (root of Astragalus membranaceus) showed a dose-dependent increase in fibroblast proliferation with increased growth factors such as epidermal growth factor (EGF), basic fibroblast factor (bFGF), and TGF-β1 (73). Besides, cell cycle progression was reported by upregulating cyclin D1 in S and G2/M phases and downregulating I-kappa-B-alpha phospho-

rylation and nuclear factor-kappa-B p65 subunit translocation. On the other hand, wound treatment using Angelica sinensis illustrated high collagen secretion and cell proliferation through Erk and Akt pathways (74). In addition, peroxiredoxins and Parkinson's disease protein 7 are upregulated to scavenge free radicals in fibroblasts, suggesting the antioxidant effect of Angelica sinensis. Loaded both Angelica sinensis and Astragali radix in liposome with a ratio of 1 to 5 and demonstrated an accelerated healing process with fewer inflammatory cell infiltration and higher neovascularization and fibroblast proliferation via the activation VEGF/PI3K/Akt and TGF-β/Smads Signaling Pathway (75). Combining more than one herb in a single remedy provides synergistic effect, as well, the novel delivery system provides better penetration and release patterns to further enhance the wound healing activity.

The mechanism of actions of herbal therapy in different wound healing phases were summarized in figure 2.

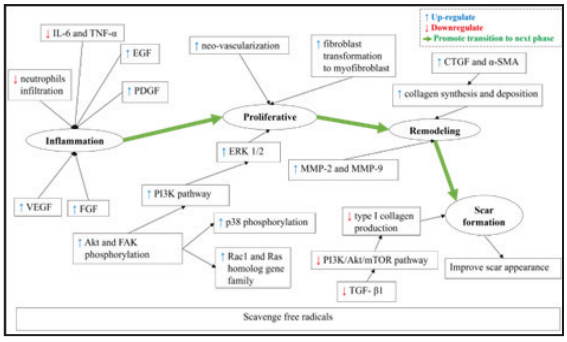

Figure 2. Summary of mechanism of action of herbal therapy in wound healing.

Conclusion

Nowadays, single herbal therapy as well as polyherbal formulation are increasingly used as an alternative treatment for wound management. The phytochemicals present in the plants provide synergistic therapeutic effects with minimal adverse effects to promote wound healing. Several pre-clinical and clinical studies showed that herbal formulation accelerate wound healing and prevent wound complications such as bacterial infections. Despite the effectiveness, the available clinical trials are still limited to validate the long-term efficacy and safety. Small sample size, short follow up period, high dropout rate and improper research design generate less convincing findings to support herbal formulation in the clinical setting. Therefore, more well-designed randomized clinical trial should be conducted to examine the long-term efficacy and safety of the herbal formulation. Additionally, standard assessment tool and grading system should be implemented and applied according to wound types for more accurate evaluation. More importantly, the selection of appropriate chemical biomarkers for standardization of herbal formulations is essential to ensure the reproducible effects and minimize batch-to-batch variation. Future study can implement nanotechnology in the formulation of herbs-containing dressings to facilitate and maximize the wound healing activity.

Acknowledgement

The authors would like to express their gratitude to the Ministry of Higher Education Malaysia for funding this research project through Fundamental Research Grant Scheme (FRGS) with project codes: FRGS/1/2021/SKK0/UCSI/03/1 and FRGS/1/2021/WAB03/ UCSI/03/1.

Disclosure of Interest

The authors report no conflict of interest.

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