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Exploration on Traditional Uses of Herbal Medicines for Wound Healing in Different Animal Models

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Abstract

A wound is a bodily injury resulting in a break in the continuity of the soft tissues of animal and human beings. Wound healing is the most dynamic but complex mechanism of the body and is a continuous process. So far, various therapeutics are used to augment wound healing and organ regeneration without infection. Seemingly, ethnic groups mostly use several herbal medicines for the treatment of wounds, burns, and cuts. This review aims to elucidate the various herbal medicines that are used in-vivo or in-vitro in the experimental trial of wound healing. Moreover, herbal's extracts have an indispensable history and successful clinical track record as indigenous drugs for wound repairment. Because many herbal medicines show hemostasis, anti-inflammatory, antimicrobial and antioxidant properties to promote wound healing. The further scientific validation of herbal medicines with their toxicities assessment at the molecular level is necessary before it is extensively used in wound treatment.

Keywords: Wound Healing; Herbal Medicine; Ethnic Group

Introduction

Skin is a multilayer organ that covers the body of all mammals. It acts as an interface between the external environment and internal organs, forming a barrier to infection. It has been also considered as a thermoregulatory organ to prevent the body from dehydration [1]. As an external organ, it is highly vulnerable to various types of injuries, burns, wounds, etc. After wounding, the body's defense system initiates a complex cascade of biological processes toward the restoration of anatomic continuity and function. Wound healing is accomplished by several processes which involve overlapping of three phases i.e., inflammation, proliferation, and remodeling with complex series of events of repair and regeneration [2]. The healing processes are modulated up by the transforming growth factors, cytokines, mitogens, and chemotactic substances [3]. To stimulate the healing process, reduce the scar formation, and improve the strength of the new skin, several wound care products and ethno medicinal therapies have been devised and tested experimentally [3-14]. Due to expensiveness, hypersensitivity reaction, the emergence of multi-resistant organisms, and a lack of newer antibiotics wound care professionals still rely on traditional and alternative medicine for wound management [13,15]. Traditional therapies have been used in many centuries particularly by the rural populations of developing countries

including Nepal.

Overview on the Mechanism of Wound Healing

Wound healing is an intricate process that involves an array of biochemical and cellular processes. Immediately after injury, the platelets enter the area and play a crucial role in hemostasis and the inflammatory phase is characterized by the influx of polymorphonuclear cells followed by infiltration of macrophages [16,17]. Neutrophils and macrophages are the major cells that are responsible to secrete the transforming growth factor-beta (TGF-β), cytokines (interleukins, tumor necrosis factors alpha (TNF-α), and chemokines (CC-chemokine, CXC-chemokine, CX3C-chemokine, and C-chemokine) necessary for wound healing [18-20]. These complex signal networks stimulate the healing to evolve the proliferative phase, which constitutes fibroplasia, matrix deposition, angiogenesis, and re-epithelialization [21,22]. TGF-β regulates the proliferation of fibroblasts, collagen synthesis, production of granulation tissue (23), and differentiation of fibroblasts to myofibroblasts in granulation tissue [23,24]. Finally, the maturation stage comprises a dynamic phase in which the new extracellular matrix composed of proteoglycans, glycosaminoglycans, factor-alpha, and collagens are continuously deposited and degraded [17,25] (Figure 1). Fail or defects in this multifaceted biological process might destroy the delicate equilibrium of cells and soluble factors necessary for complete wound repair, resulting in fibrotic scars [26,27].

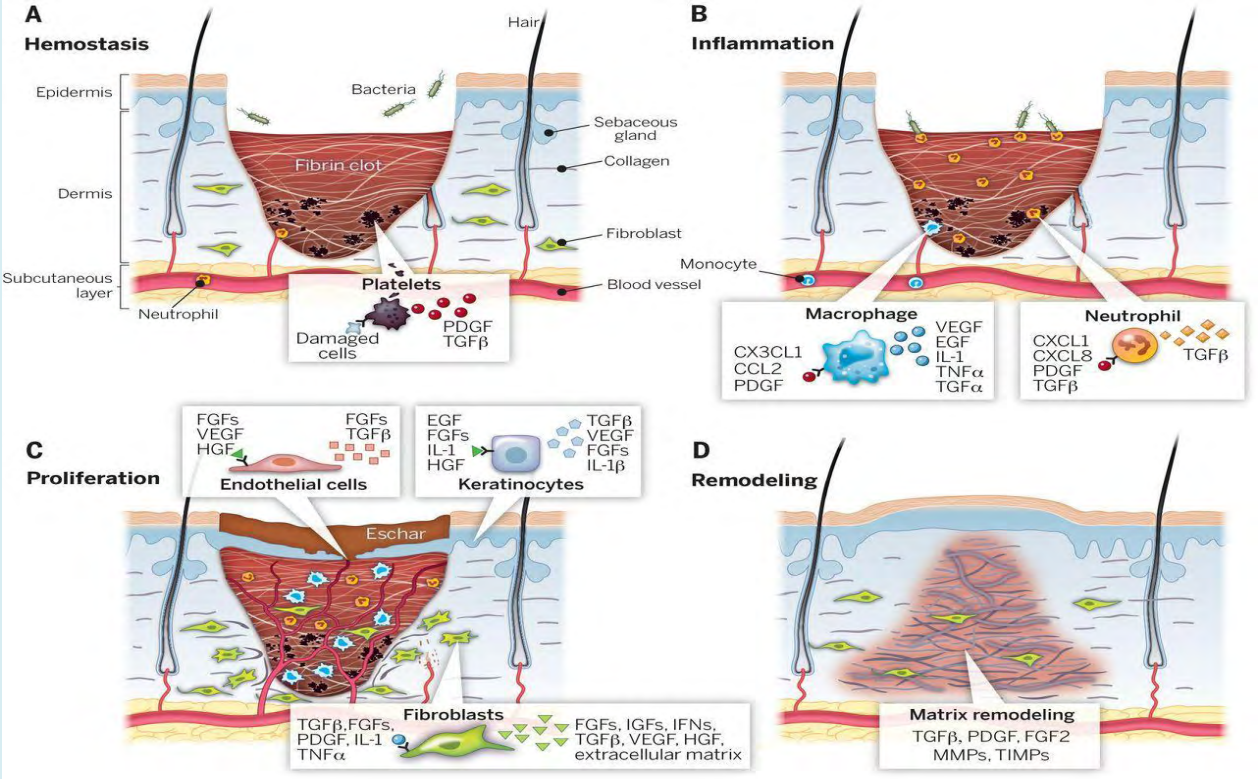

Figure 1: Stages of wound healing. It is classically divided into four stages: (**A**) hemostasis, (**B**) inflammation, (**C**) proliferation, and (**D**) remodeling. Each stage is characterized by key molecular and cellular events and is coordinated by a host of secreted factors that are recognized and released by the cells as a wounding response. Representative subsets of major factors are depicted. CCL_2, chemokine (C-C motif) ligand 2; CX3CL1, chemokine (C-X3-C motif) ligand 1; CXCL1, chemokine (C-X-C motif) ligand 1; CXCL8, C-X-C Motif Chemokine Ligand 8; EGF, Epidermal growth factor; FGF2, basic fibroblast growth factor; FGFs, fibroblast growth factors; HGF, hepatocyte growth factor; IFNs, interferons; IGFs, insulin-like growth factors; IL-1, interleukin-1; IL-1β, interleukin-beta; MMPs, matrix metalloproteinases; PDGF, platelet-derived growth factor; PDGI, platelet-derived growth inhibitor; PGF2, Prostaglandin F2; TGFα, transforming growth factor-alpha; TGFβ, transforming growth factor-beta; TIMPs, tissue inhibitor of metalloproteinases; TNF-α, tumor necrosis factor alpha; VEGF, vascular endothelial growth factor (28).

The aim of wound treatment is to promote tissue repair and regeneration in a shorter time with adequate tissue perfusion and oxygenation, proper nutrition, and minimum undesired consequences (29).

Ethno-Medicinal Plants Used in Wound Healing

Ethno-medicinal plants are presumed to play a central role in remedies of wound healing since ancient times. A huge number of plants/plant extracts/decoctions or pastes are equally used by tribal and folklore traditions in Nepal, India, Bangladesh for the treatment of wounds and burns. It is important to note that about 80% of the Asian and African population still relies on the use of traditional medicine as primary health care [30]. However, the innovation of allopathic medicine retarded the utilization of ethno medicine. Due to various side effects of allopathic drugs, the uses of complementary and alternative medicines are gaining popularity for the treatment of wounds throughout the world [31]. These therapies have been proved cost-effective and efficacious for the treatment of diverse and difficult-healing wounds such as ulcers, burns, and infected wounds by stimulating the healing process and improving the strength of the new skin [32]. In this review, we elucidated the healing properties of various ethnomedicinal plants used in studies and outlined the information that might be useful to design the novel experiment for their scientific validation. Table 1 provides a general idea of the most important curative plants and their properties, with recognized effects on wound healing.

Species/ plant's name	Scheme	The extract used and formulation	Clinical properties	Wound model	Results	Refer ence
Achyranthe saspera		An ointment containing 5% methanol extract	Wound healing activity and antioxidant potential	Burn wound in a rat	It exhibited wound healing not only via wound contraction, fibroblast proliferation, epidermis formation, and collagen deposition, but also through the elevation of Na^+, catalase, vitamin-C, and hydroxyl proline and the up-regulation of the expressions of matrix metalloproteinases (MMP-2 and MMP-9).	[33]
Aloe vera		Blended fibrin/Aloe gel film	Wound healing	Streptozotocin-induced diabetic rats	The application enhanced wound healing by enhancing hydroxyproline, fibroblast, and collagen.	[34]
Becium grandiflorum		5% and 10% (w/w) ethanol leaf extract	Antibacterial, anti-inflammatory, and wound healing activity	Excision and incision wound models in mice	Ointments showed an increase in wound contraction, shorter epithelization time, and higher skin tensile strength along with considerable deposition of collagen, fibroblast proliferation, and vascularization. The plant extract also inhibited the inflammation.	[35]

Buteamon osperma (Palas)		The alcoholic bark extract of *Buteamono sperma*	Cutaneous wound healing and antioxidant properties	Excision wound model of rat	The extract showed the increase in DNA, total protein, and collagen content of granulation tissues with more epithelialization and contraction.	[36]
Caesalpinia mimosoides		Aqueous and ethanolic extract ointment 5% (w/w) of shoots and leaves	Antimicrobial, wound healing, and antioxidant activities	Circular excision and linear incision wound models in adult Wistar albino rats	Complete wound healing was noted with ethanol and aqueous extract on day 15.	[5]
Calendula officinalis		*n*-hexanic and the ethanolic extracts from *Calendula* flowers	Wound healing	*In vitro* studies in human immortalized keratinocytes	Extracts influenced the inflammatory phase by activating the transcription factor NF-κB and by increasing chemokine IL-8, both at transcriptional and protein level.	[37]
Calotropis procera		Topical application of 20 ml of 1.0% sterile solution of the latex of *C. procera* twice daily	Wound healing	Full-thickness excisional wounds of 8.0 mm diameter were inflicted in a guinea pig.	It resulted in wound area reduction by increasing collagen, DNA, protein synthesis, and epithelization.	[38]
Carica papaya		Ethanol extract of seeds (50 mg/kg/day)	Wound-healing activity, antimicrobial activity	Excision wound model in Sprague-Dawley rats	The papaya seed extract (1:1 ratio) showed 86% wound contraction on day 13. It also exhibited antimicrobial activity against *Salmonella choleraesuis* and *staphylococcus aureus*.	[39]
Centella asiatica		Asiaticoside isolated from *Centellaasiatica gum. T*opical applications of 0.2% solution of Asiaticoside.	Healing activity	In-vivo study in guinea pig in punch wound model and in-vitro study in chick chorioallantoic membrane model	Asiaticoside produced a 56% increase in hydroxyproline, 57% increase in tensile strength, increased collagen content, and better epithelization.	[40]
Daucu scarota		Paraffin-based cream containing 1%, 2%, and 4% w/w of ethanolic extract of root topically.	Wound healing activity	Excision wound model and incision wound model	It increased the hydroxyproline, 57% increase in tensile strength, increased collagen content,,t and better epithelization.	[12]

Deloni xelata		Ethanolic extract (DSE)	Wound healing activity	Excision, incision, and dead space wound models	The complete wound contraction was found at 16 days. An increased expression of Col 1α (I) was observed in the wound tissue treated with DSE.	[10]
Entadap haseoloides (L.) Merr.		Total *Entadaphaseoloides (L.) Merr*. tannins (TEPT) are used topically.	Wound healing activity	Excision wound model in rats	It promoted the wound shrinkage, rate and augmented the healing of infected wounds in rats with antimicrobial activity too.	[41]
Globularia alypum		Methanolic extract	Burn wound healing process, inflammation, antibacterial and antioxidant activities	Burn wound of 177 mm^2 area	Wound area contraction on day 12.	[42]
Heliotropium indicum		Ethanolic extracts 10% w/v	Wound healing activity	Excision and incision wound models in rats	Complete healing of wounds was noted at 14 days.	[43]
Hypericum patulum		5% and 10% w/w ointment of methanol extract of leaves	Wound healing	Excision and an incision wound models in rats	Both concentrations of ointment enhanced wound healing.	[44]
*Jatrophaneo pauciflora*pax		Two groups of treatment: Oral administration of latex (250, 500, and 750 mg/ kg) and topical administration of latex.	Antimicrobial, anti-inflammatory activities, and wound-healing	Anti-inflammatory activities in Wistar rats	It showed higher antioxidant activity, anti-inflammatory potential in oral administration of latex, and antimicrobial properties to promote wound healing.	[45]
Lavandula aspic l.		Lavender oil	Antioxidant and wound healing activity	Excision wound model in rats	The biopsied skin showed fibrous connective tissue regeneration on day 14.	[46]
Morinda citrifolia l.		Ethanolic extract of the leaf at a rate of 150 mg /kg/day orally	Wound healing activity	Excision and dead space wound models in rats	It enhanced wound contraction, decreased epithelialization time, and increased hydroxyproline content and histological characteristics.	[11]

*Musa sapientum*var. *para*disiaca		Aqueous and methanolic extract of *Musa sapientumb (100 mg/kg)* orally.	Wound healing activity	Excision, Incision and dead space wound models in rats	Both extracts increased the levels of hydroxyproline, hexuronic acid, hexosamine, superoxide dismutase, reduced glutathione in granulation tissue, and decreased the wound area, scar area, and lipid peroxidation.	[47]
Ocimum sanctum Linn		Alcoholic and aqueous extract 0f 400 mg/kg and 800 mg/kg body weight of each.	Antioxidant and wound healing effects	Incision, excision, and dead space wounds in Wistar albino rats	Both alcoholic and aqueous extract increased wound breaking strength, hydroxyproline, hexuronic acid, hexosamines, superoxide dismutase, catalase, reduced glutathione, and significantly decreased wound contraction and lipid peroxidation.	[48]
Pereskia aculeate		5 % of each methanol extract (me) and hexane fraction (hf) of leaves	Wound healing and anti-inflammatory potential	Excision wound	Hexane fraction followed by methanol extract markedly accelerated the wound closure.	[49]
Plumbago zeylanicum		Ethanolic extracts 10% w/v	Wound healing activity	Excision and incision wound models in rats	Wound completely healed on day 18.4	[43]
Plumeria rubralinn		0.5 % w/w *Plumeriarubralinn* (protease from the latex) ointment in the hydrophilic base was applied topically once a day	Inflammatory activities and wound-healing	Excision wound model in rats	It reduced the carrageenan-induced edema and resulted in 81% wound contraction at 16 days.	[50]
Pongamia pinnata		Methanolic extracts of leaf	Wound healing, antimicrobial and antioxidant potential	Excision and an incision wound models in rats	Itdecreased the wound size (30 mm^2) on day 16.	[51]

Rhuschinensis		Hydroalcoholic 5% and 10% w/w leaf extract	Wound healing potential is also used to treat hemoptysis, inflammations, laryngitis, snakebite, stomachache, and fractures.	Incision wound, excision wound, and dead space wound	10 % w/v extract had greater wound healing abilities than others but less than povidone-iodine.	[52]
Sambucu sebulus		Alcohol preparation of powder of leaves and aerial parts of plants	Wound healing	Full-thickness excision wound model in rat	*S. ebulus* (2%) and its 2% combination enhanced wound healing.	[53]
Stevia rebaudiana		Aqueous crude extract of leaves	Wound healing potential	Excision and incision wound model in mice	Stevia treated mice showed a significant reduction in the wound area, the faster rate of epithelialization with moderately higher hydroxyproline.	[54]
Thevetiaper uviana		Leaves hexane extraction (lh) and fruit water extraction (fw)	Wound healing with antimicrobial, antioxidant, and anti-inflammatory potentials	Incision, excision, and dead space models in rats	Complete wound contraction was noted at 14 days.	[55]
Wedelia chinensis		Ethanolic leaf extract	Wound healing activity	Excision, incision and dead space wound models in rats	Ethanolic extract retarded the period of epithelialization, increased the wound contraction, skin breaking strength, granulation tissue dry weight, and breaking strength.	[56]

Table 1: shows the medicinal plants that are used for different models of the wound healing.

Areas of Interest for Researchers

In this world, nature gifted us a huge number of plants that are being used traditionally for medicinal purposes by various ethnic groups. Since ancient times, the plants, their extracts or paste have been consistently used to treat various types of wounds and tissue-related diseases. Further validation regarding the therapeutic uses of medicinal plants for healing wounds through scientific investigation seems imperative. The study on the underlying wound healing mechanism behind the use of medicinal plants could be a novel research area. Still, the several challenges such as identification, isolation, targeting, and mechanism of action of bioactive components of the medicinal plants are underexplored for developing the suitable herbal medicine for wound healing formulations. The combination of plant extracts with allopathic medicines may have synergistic potentials to promote wound healing capability and could be of recent research interest.

Conclusion

Wound healing is a complex process of the body self-defense mechanism. The topical or oral uses of herbal

medicine result in augmenting the wound contraction, epithelization rate, granulation tissue dry weight, and its breaking strength, preventing infection with proper activities of different growth factors, and collagen, etc. Although traditional and complementary medicines were used as therapeutics in the ancient period, still some ethnic groups are using them regularly. The various clinical trials in animal models, as well as in-vitro studies, proved its potentiality for wound healing purposes. The ethnomedicinal plants also possess superior wound healing abilities even in diabetic wounds. Further molecular investigations on medicinal plants are imperative for the invention of novel drugs for wound healing with minimal side effects.

Conflict of Interest

The authors declare that there is no conflict of interests.

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