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WOUND HEALING ACTIVITY OF SOME MEDICINAL PLANTS: A REVIEW

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ABSTRACT

Wound is defined as the disruption of the cellular and anatomic continuity of a tissue. Wound may be produced by physical, chemical, thermal, microbial or immunological insult to the tissues. The process of wound healing consists of integrated cellular and biochemical events leading to re-establishment of structural and functional integrity with regain of strength in injured tissues. Naturally, the investigative curiosity to promote healing continues since ages. Plants and their extracts have immense potential for the management and treatment of wounds. The phyto-medicines for wound healing are not only cheap and affordable but are also purportedly safe as hyper sensitive reactions are rarely encountered with the use of these agents. These natural agents induce healing and regeneration of the lost tissue by multiple mechanisms. However, there is a need for scientific validation, standardization and safety evaluation of plants of the traditional medicine before these could be recommended for healing of the wounds.

INTRODUCTION

Wounds are physical injuries that result in an opening or break of the skin. Proper healing of wounds is essential for the restoration of disrupted anatomical continuity and disturbed functional status of the skin (Begum, 2000). Healing is a complex and intricate process initiated in response to an injury that restores the function and integrity of damaged tissues (Govindarajan *et al*; 2007). Wound healing involves continuous cell–cell and cell–matrix interactions that allow the process to proceed in three overlapping phases viz. inflammation (0–3 days), cellular proliferation (3–12 days) and remodeling (3–6 months) (Glynn; 1981, Clark; 1996, Martin; 1996). Healing requires the collaborative efforts of many different tissues and cell lineages (Martin; 1997). It involves platelet aggregation and blood clotting, formation of fibrin, an inflammatory response to injury, alteration in the ground substances, angiogenesis and re-epithelialization. Healing is not complete until the disrupted surfaces are firmly knit by collagen (Buffoni *et al;* 1993)

Wound healing is an intricate process whereby the skin (or another organ-tissue) repairs itself after injury. (Nguyen et al, 2009).In normal skin, the epidermis (outermost layer) and dermis (inner or deeper layer) exist in steady-state equilibrium and shield from the external environment. When the skin is broken, the normal (physiologic) process of wound healing begins. The classic model of wound healing comprises three or four sequential, yet overlapping, phases:

(1) Hemostasis (not considered a phase by some authors),
(2) Inflammation,
(3) Proliferation and
(4) Remodeling. Upon injury to the skin, a set of complex biochemical events takes place in a closely orchestrated cascade to repair the damage.

Within the first few minutes after the injury, platelets (thrombocytes) aggregate (join together) at the injury site to form a fibrin clot, which reduces active bleeding (hemostasis). The speed of wound healing depends on bloodstream levels of platelets, fibrin, and hormones such as oxytocin (Midwood *et al,* 2004). During the inflammation phase, bacteria and cell debris are phagocytes and removed from the wound by white blood cells. Blood factors are released into the wound that cause the migration and division of cells during the proliferative phase.

The proliferation phase is characterized by angiogenesis, collagen deposition, granulation tissue formation, epithelialization, and wound contraction. In angiogenesis, vascular endothelial cells form new blood vessels (Garg, 2000). In fibroplasia and granulation tissue formation, fibroblasts grow and form a new, provisional extra cellular matrix (ECM) by excreting collagen and fibronectin. Concurrently, re-epithelialization of the epidermis occurs, whereby epithelial cells proliferate and 'crawl' atop the wound bed, covering the new tissue (Enoch and Price,.2004). During wound contraction, myofibroblasts decrease the size of the wound by gripping the wound edges and contracting using a mechanism that resembles that of smooth muscle cells. When the cells' roles are close to complete, unneeded cells undergo apoptosis.

The phytomedicines for wound healing are not only cheap and affordable but are also purportedly safe as hypersensitive reactions are rarely encountered with the use of these agents. These natural agents induce healing and regeneration of the lost tissue by multiple mechanisms. However, there is a need for scientific validation, standardization and safety evaluation of plants of traditional medicine before these could be recommended for healing of the wounds. Plants or chemical entities derived from plants need to be identified and formulated for the treatment and management of wounds. In this direction, a number of herbal products are being investigated at present.

Medicinal plants having wound healing activity:

Aegle marmelos

The wound healing effect of methanolic extract of the root of aegle marmelos was evaluated in the form of an ointment with two different concentrations (5% and 10% w/w in simple ointment base) in excision wound model and incision wound model in rats. In both the concentrations, the extract ointment produced a significant response in both the wound types tested, as evidenced by its wound contracting ability, wound closure time and increase in the tensile strength. The results were also comparable to those of a standard drug nitrofurazone.(Jaswanth *et al*.,1994).

Aloe vera

Aloe vera improves wound healing and inhibits inflammation. Since mannose-6-phosphate is the major sugar in the Aloe gel, the authors examined the possibility of its

being an active growth substance. Mice receiving 300 mg/kg of mannose-6-phosphate had improved wound healing over saline controls. This dose also had anti-inflammatory activity. The function of mannose-6-phosphate in A. Vera is discussed.(Ahmad oryan *et al.*,2010).

Azadirachta Indica

The wound healing effect of the aqueous leave extracts of *Azadirachta indica (neem tree)* was investigated on adult male wistar rats. The aim of this study is to scientifically determine if the aqueous leave extracts of *Azadirachta indica* has wound healing abilities. Twenty male wistar rats (two groups of 10 control and 10 experimental rats)of average weight 150-200g were used for this study. A 2cm by $2cm^2$ area of wound was made at the dorsolateral aspect of the rats and an aqueous leave extract of *Azadirachta indica* was applied on the wound of experimental rats while normal saline was used on the control rats. All animals had their wound dressed every three days, wound dimension measured and morphometry assessed. Wound biopsy was collected by random selection in each group on day 9 and on the day of complete reepithelialization. Tissue processing was done using paraffin wax method. Slides were stained with haematoxilin and eosin for histological assessment of fibroblast, neovascularization, granulation and end scar tissue profile. Results showed significant wound contraction at day 6 ($p<0.05$).The mean percentage wound contraction for experimental rats was 72.34± 2.49 while the control group was 62.39± 7.94. Mean percentage wound contraction for experimental group at day 9 was 92.20± 6.66 while that of the control group was 85.19± 7.84. The mean of the percentage wound contraction on day 9 was insignificant ($p>0.05$). The extracts of *Azadirachta indica* significantly increased ($p<0.05$) the day of complete wound closure in experimental group compared to control group. Aqueous leave extracts of *Azadirachta indica* promotes wound healing activity through increased inflammatory response and neovascularization.(Osunwoke Emeka *et al.*,2013).

Beef Cattle

Eleven heifers of the Purunã cattle breed were used to evaluate wound healing by second intention. An experimental wound excision model in bovines was created by means of a

skin punch of diameter 2cm. The animals were topically treated for 17 days with a saline control or decoctions of ***Schinus terebinthifolius*** Raddi (Aroeira mansa), ***Tabebuia avellanedae*** Lorentz ex Griseb (Ipê Roxo), and ***Casearia sylvestris*** Sw.(Guaçatonga) mixed with carboxymethyl cellulose. Centripetal retraction, clinical, and histological aspects of the wounds were observed until complete healing. Decoctions of ***T. avellanedae*** and ***S. terebinthifolius***, but not ***C. sylvestris***, had a beneficial effect on wound healing by second intention (Lipinsk *et al.,* 2012).

Cassia occidentalis

To evaluate the healing activity of an extract from the leaves of ***Cassia occidentalis*** on skin wounds induced by the venom of ***Bothrops moojeni*** in mice. A total of 24 Swiss albino mice were divided into 4 groups: Group 1 animals were treated for 7 days with lanette cream; Group 2 animals were treated for 7 days with 10% leaf extract of ***Cassia occidentalis*** in lanette cream; Group 3 animals were treated for 14 days with lanette cream; and Group 4 animals were treated for 14 days with 10% leaf extract of ***Cassia occidentalis*** in lanette cream. To induce wounds, the animals were anesthetized intramuscularly after the dorsum cervical region was shaved and inoculated intradermally with 4 µg ***Bothrops moojeni*** venom. The gross and histological evaluations were assessed 7 and 14 days after inoculation of the poison. Extract from the leaves of ***Cassia occidentalis*** decreased inflammation and epidermal hyperplasia and increased the vascular proliferation and reepithelialisation of wounds induced by ***Bothrops moojeni*** venom. These data suggest that the leaves of ***Cassia occidentalis*** stimulated the healing of wounds induced by the dermal venom of ***Bothrops moojeni*** in mice, and they can be considered an alternative product to treat wounds caused by these snakebites.(Maraísa *et al.,*,2013).

Catharanthus roseus

Wound healing activity was determined in rats, after administration (100 mg kg^{-1} day^{-1}) of the ethanol extract of ***C. roseus*** flower, using excision, incision and dead space wounds models. The animals were divided into two groups of 6 each in all the models. In the excision model, group 1 animals were topically treated with carboxymethyl cellulose as placebo control and group 2 received topical application of the ethanol extract of ***C.***

roseus at a dose of 100 mg/kg body weight/day. In an incision and dead space model group 1 animals were given normal saline and group 2 received the extract orally at a dose of 100 mg kg^{-1} day^{-1}. Healing was assessed by the rate of wound contraction, period of epithelization, tensile strength (skin breaking strength), granulation tissue weight, and hydoxyproline content. Antimicrobial activity of the flower extract against four microorganisms was also assessed.The extract of ***C. roseus*** significantly increased the wound breaking strength in the incision wound model compared with controls ($P < 0.001$). The extract-treated wounds were found to epithelialize faster, and the rate of wound contraction was significantly increased in comparison to control wounds ($P < 0.001$), Wet and dry granulation tissue weights, and hydroxyproline content in a dead space wound model increased significantly ($p < 0.05$). ***Pseudomonas aeruginosa*** and ***Staphylococcus aureus*** demonstrated sensitivity to ***C. roseus*****(Nayak *et al.*,2006).**

Centella asiatica

The efficacy of Centella asiatica for incision and burn wounds are not fully understood. Here, we report the wound healing activities of sequential hexane, ethyl acetate, methanol, and water extracts of Centella asiatica in incision and partial-thickness burn wound models in rats. Male Sprague-Dawley rats weighing 250-300 g were randomly divided into incision and burn wound groups. Each group was stratified into seven subgroups: (1) untreated; (2) NSS-; (3) Tween 20®- (vehicle control); (4) hexane extract-; (5) ethyl acetate extract-; (6) methanol extract-; and (7) aqueous extract-treated groups. The test substances were applied topically once daily. The tensile strength of the incision wound was measured on the seventh day after wound infliction. The general appearance and degree of wound healing of the burn wound were assessed on Days 3, 7, 10 and 14 after burn injury and prior to histopathological evaluation. On the seventh day after wound infliction, the tensile strength of incision wound in all extract-treated groups was significantly higher than that of the vehicle control (Tween 20®), but comparable to the NSS-treated group. The degrees of healing in the burn wound with the four extracts were significantly higher than that of the control on Days 3, 10 and 14. Histopathological findings on Day 14 after burn injury revealed prominent fibrinoid necrosis and incomplete epithelialization in the control and untreated groups, whereas fully developed

epithelialization and keratinization were observed in all extract-treated groups. Analysis by thin layer chromatography demonstrated that the phyto-constituents β-sitosterol, asiatic acid, and asiaticoside and madecassocide were present in the hexane, ethyl acetate and methanol extracts, respectively (Somboonwong *et al*.,2013).

Heliotropium Indicum

Extracts of *Heliotropium indicum* (*H.indicum*) are used traditionally in Ivory Coast for the treatment of tumors, asthma, wounds and inflammatory diseases. The purpose of the present study was to evaluate the in vitro wound healing activity of the butanol, ethyl acetate extracts from *H.indicum*.

Wound healing activity was studied using incision wound models in cell culture (H292). All the fractions showed a wound healing effect. But n-butanol and ethyl acetate extracts showed possessed wound healing activity. Their activity was better than the effect of residue extract ($p<0.5$). There was no significant difference between the wound healing effect of butanol and ethyl acetate ($p<0.5$).H.indicum possesses significant in vitro dose-dependent wound healing; this supported in vivo study and traditional claims for the plant as a wound healer. (Dodehe Yeo *et al*.,2011).

Mimosa pudica

Mimosa pudica, commonly known as touch-me-not, is used in folklore medicine in arresting bleeding and in skin diseases. There was no scientific evidence justifying the use of Mimosa pudica, therefore the present study was aimed at evaluation of wound healing activity of the plant. In the present study the roots of Mimosa pudica were studied for wound healing activity by incorporating the methanolic and the total aqueous extract in simple ointment base B.P. in concentration of 0.5% (w/w), 1% (w/w) and 2% (w/w). Wound healing activity was studied in three types of model in rats viz. excision, incision and estimation of biochemical parameter. In case of the excision wound model wound contraction and period of epithelization was studied while in incision wound model was evaluated by determining tensile strength and hydroxyproline content in the scab. Treatment of wound with ointment containing 2% (w/w) the methanolic and 2% (w/w) the total aqueous extract exhibited significant ($P<0.001$) wound healing activity. The methanolic and total aqueous extracts were analyzed for total phenols content equivalent

to Gallic acid. The content of total phenols was 11% (w/w) and 17% (w/w) in methanolic and total aqueous extract respectively. The methanolic extract exhibited good wound healing activity probably due to phenols constituents. All extracts of Centella asiatica facilitate the wound healing process in both incision and burn wounds. Asiatic acid in the ethyl acetate extract seemed to be the most active component for healing the wound.(Kokane *et al*., 2001).

Prosopis farcta

Wound healing in diabetes is one of the challenges in the medical science. Accordingly, new quick wound-healing compounds are welcomed. It is likely that Prosopis farcta - indigenous to southeastern Iran – accelerates regenerating process for its anti-inflammatory, antimicrobial and antidiabetic effects. This study is aimed at examining the local effect of the fruit dusk powder and root extract of Prosopis farcta on diabetic healing. Twenty-four male Wistar rats were randomly divided into 4 groups of intact, diabetic control, Experimental group 1(diabetic treated with fruit powder) and Experimental group 2 (diabetic treated with root extract). Diabetic groups were injected streptozotocin (STZ). Then, three holes (4 mm diameter) were made on both dorsal sides of the rats in all groups. Experimental groups were treated by fruit dusk powder and the plant root aquatic extract and the control groups were treated by normal saline. The area of the holes was continuously measured till they were completely closed. In the treatment groups using fruit dusk powder and plant root aquatic extract, the whole area had significantly decreased ($p< 0.05$).

It seems that local administration of Prosopis farcta fruit dusk powder and root aquatic extract probably accelerates healing in diabetic rats. Regarding the antidiabetic, anti-inflammatory and healing effects of this plant, we are hopeful that Prosopis farcta plant finds an appropriate status in traditional medicine and pharmacology.(Azadeh Ranjbar *et al.*,2012)

Sesbania grandiflora

Sesbania grandiflora Linn belonging to family *Leguminosae* is well known medicinal plant in various region of india. Flower extract used in various disease like nasal catarrh, headache, laxative, aperitif, gout, ozoena,bronchitis, pain. Present study is concern

mainly with evaluation of wound healing activity of flower ethanolic extract in wistar rats using excision and incision wound model in the form of ointment using two concentration (2 and 4 % w/w ointment) of flower extract in simple ointment base. Both concentration of ethanolic extract showed significant response in both the wound type tested when compared with control group.Nitrofurazone ointment (0.2%w/w) was used as standard drug.

Vernonia arborea

To investigate the comparative wound-healing potency of aqueous and methanol leaf extracts of *Vernonia arborea* Hk. Excision, incision and dead space wound models were used to evaluate the wound-healing activity of *Vernonia arborea* Hk., on Swiss Wistar strain rats of either sex. In excision wound model, treatment was continued till the complete healing of the wound, in incision and dead space wound models the treatment was continued for 10 days. For topical application, 5% w/w ointment of aqueous and methanol leaf extracts was prepared in 2% sodium alginate and for oral administration suspensions containing 30 mg/ml of each of the extracts in 1% gum tragacanth were prepared. In excision and incision wound models, the control groups of animals were left untreated and in dead space wound models the animals were treated with 1 ml of 1% gum tragacanth / kg, b.w. The healing of the wound was assessed by the rate of wound contraction, period of epithelialisation, skin breaking strength, granulation strength, dry granulation tissue weight, hydroxyproline estimation and histopathology of the granulation tissue. Aqueous and methanol leaf extracts promoted the wound-healing activity significantly in all the wound models studied. High rate of wound contraction, decrease in the period for epithelialisation, high skin breaking strength and granulation strength, increase in dry granulation tissue weight, elevated hydroxyproline content and increased collagenation in histopathological section were observed in animals treated with methanol leaf extract and aqueous leaf extract when compared to the control group of animals. Methanol and aqueous leaf extracts of *Vernonia arborea* Hk. promote wound-healing activity. Methanol extract possesses better wound-healing property than the aqueous extract.(Pradhan et al.,2009).

CONCLUSION

Plants and their extracts have immense potential for the management and treatment of wounds. Various herbal products have been used in the management and treatment of wounds over the years.

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