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Scientific Documentation of Wound Healing Efficacy of Herbal Drugs - A Review

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ABSTRACT

Wound is simply a loss of cellular and functional continuity. Its healing is natural process as long as wound environment and health status of the individual is optimum. Delayed healing besides causing morbidity and loss of function of the particular part inflicts heavy economic loss to the individual. Early healing of a wound therefore has been the field of attraction for research workers. Various workers in past have tried number of wound healing agents to enhance the wound healing process. The demand for plant based medicines, health products, pharmaceuticals, food supplement, cosmetics etc are increasing in both developing and developed countries, due to the growing recognition that the natural products are non-toxic, have less side effects and easily available at affordable prices. These herbal drugs need to be standardized and their mode of action studied. Many herbal drugs have been proved to have wound healing efficacy and others are under trial nowadays. This review has therefore been an attempt to documents the scientific validation of proven herbs having wound healing efficacy.

Keywords: Herbal medicine, rhubarb, wound healing

INTRODUCTION

Wound healing has got high priority among body functions. Despite tremendous advancement, an effective wound management continues to be a challenge to the clinician. In addition to conventional allopathic medicines including antibiotics,

analgesics, anti-inflammatory drugs many medicinal plant preparations and biological dressing materials have been used to enhance the wound healing rate. Mostly the wounds are managed by topical medicaments, but action of many such common preparations are often discouraging because of ensuing destruction of leucocytes and other cellular elements of the wound (Tyagi and Singh, 1993). Common pathogens causing wound infection like *Staphylococcus aureus, Streptococus pyogenes*, *Escherichia coli*, *Klebsiella pneumonia* have been reported to have developed resistance against the targeted antibiotics. Such antibiotics are also showing adverse effects to the individuals (Mertz and Ovigten, 1993). Use of medicinal plants or their parts, either in whole form, or their extracts seems thus indispensable ((Essawi and Shour, 2000). Herbal medicine is still the mainstay of about 75 80% of the world population, mainly in the developing countries for primary health care because of better cultural acceptability, better compatibility with the human body and lesser side effects. Herbal drugs constitute only those traditional medicines which primarily use medicinal plant preparation for therapy. Furthermore plants are considered more potent healers because they promote the repair mechanism in the natural way. The chemical constituents present in them are a part of the physiological functions of living flora and hence they are believed to have better compatibility with the human body (Kamboj, 2000). The demand of herbal drugs is increasing day by day in developed as well as developing countries because they are safer and well tolerated as compared to allopathic drugs (Rawat *et al.,* 2012).

However in most of the cases mode of action studies, standardization based on chemical and activity profile and their safety and stability has not been documented (Kamboj, 2000). This review is an attempt to document the clinical trial of many medicinal plants used specifically for wound enhancing purpose.

Wound healing

Wound healing is a complex and dynamic process with the wound environment changing with the changing health status of the individual. Wound healing involves continuous cellcell and cellmatrix interactions that allow the process to proceed in three overlapping phases namely, inflammation (03 days), cellular proliferation (312 days) and remodeling (36 months) (Glynn, 1981; Clark, 1996; Martin, 1996). Healing is not complete until the disrupted surfaces are firmly knit by collagen (Buffoni *et al.,* 1993). The inflammatory phase prepares the area for healing and immobilizes the wound by causing it to swell and become painful, so that movement becomes restricted. At the tissue level, increased vascular permeability and the sequential migration of leukocytes into the extravascular space characterize inflammation (Cohen *et al.,* 1999). Migrating monocytes transform into macrophages as they migrate into the extravascular space in a process that is stimulated by chemotactic factors such as fibronectin, elastin derived from damaged matrix, complement components, enzymatically active thrombin, TGF-b, and serum factors (Fukai *et al.,* 1991). After activation, macrophages and neutrophils initiate cellular wound debridement by phagocytosing bacteria and foreign material (Newman *et al.,* 1982). Macrophages also initiate the development of granulation tissue and release a variety of proinflammatory cytokines and growth factors (Kondo and Ishida 2010). The angiogenic process becomes active from day 2 after wounding (Grotendorst, 1984). In the first week post acute injury three processes epithelialisation, wound contraction and collagen production occur simultaneously to achieve coalescence and closure. Within hours of injury, the release of EGF, TGF-a, and FGF act to stimulate epithelial cell migration and proliferation through the acts of reproduction and mitosis, resulting in the start of reepithelialization. The formation of granulation tissue starts at the wound space approximately 4 days after injury. Numerous new capillaries endow the new stroma with its granular appearance. Macrophages, fibroblasts and endothelial cells

move into the wound space at the same time. Macrophages not only augment inflammatory response but also promote angiogenesis. Neovascularization is essential for the synthesis, deposition and organization of new extracellular matrix (Konda and Ishida, 2010). The remodeling phase is most essential phase. The remodeling phase envisages replacement of granulation tissue with a frame work of collagen and elastic fibres with revascularization. The final outcome of all these events is repair of damaged tissues by formation of scar (Guo and DiPietro, 2010). A successful contraction results in a smaller wound that needs to be repaired by scar formation. A specialised cell called a myofibroblast is involved in this contraction process. Myofibroblasts attach to the skin margins, pull the entire epidermal layer inward, Control of wound contraction and scar formation at the time of wound formation is useful in order to control the direction of wound contraction and thus prevent distortion (Zitelli, 1987).

Historical background and current scenario of herbal drugs

The use of plants for healing purposes predates human history and forms the origin of much of the modern medicine. The earliest evidence of human's use of plant for healing dates back to the Neanderthal period (Winslow and Kroll, 1998). Many conventional drugs originated from plant sources. A century ago, most of the conventional effective drugs were plant based. The earliest recorded evidence of their use in Indian, Chinese, Egyptian, Greek, Roman and Syrian texts dates back to about 5000 years (Pal and Shukla, 2003). The classical Indian texts making mention about the use of herbal drugs include Rigveda, Atharvaveda, Charak Samhita and Sushruta Samhita. The herbal medicines / traditional medicaments have therefore been derived from rich traditions of ancient civilizations and scientific heritage (Kamboj, 2000). Traditional Chinese medicine has been used by Chinese people from ancient times. About 5000 traditional remedies, including mostly herbs are available in China. They account for approximately one fifth of the entire Chinese pharmaceutical market (Li, 2000). Many herbal remedies found their way from China into the Japanese systems of

traditional healing. Herbs native to Japan were classified in the first pharmacopoeia of Japanese traditional medicine in the ninth century (Saito, 2000). Ayurveda (Indian traditional medicine) is a medical system primarily practised in India that has been known for nearly 5000 years. It includes diet and herbal remedies, while emphasizing the body, mind and spirit in disease prevention and treatment (Morgan, 2002).

Worldwide, herbal medicine received a boost when the WHO encouraged developing countries to use traditional plant medicine to fulfill needs unmet by modern systems (Winslow and Kroll, 1998). In one survey it was estimated that 39% of all 520 new approved drugs in 1983-1994 were natural products or derived from natural products (Cragg *et al.,* 1997) and 60-80% of antibacterial and anticancer drugs were derived from natural products (Harvey, 1999). The wide spread use of herbal medicine is not restricted to developing countries, as it has been estimated that 70% of all medical doctors in France and German regularly prescribe herbal medicine (Murray and Pizzorno, 2000). With the US Food & Drug Administration (FDA) relaxing guidelines for the sale of herbal supplement, the US market is booming with herbal products (Brevoort, 1998; Gottlieb, 2000). Americans paid an estimated US$ 21.2 billion for services provided by alternative medicine practitioners (Eisenberg, *et al.,* 1998).

India is sitting on a gold mine of well-recorded and well-practiced knowledge of traditional herbal medicine (Sharma *et al.,* 2008). In India around 20,000 medicinal plant species have been recorded (Dev, 1997), but more than 500 traditional communities use about 800 plant species for curing different diseases (Kamboj, 2000). The annual turnover of the Indian herbal medicinal industry is about Rs. 2,300 crore as against the pharmaceutical industry's turnover of Rs. 14,500 crores with a growth rate of 15 percent (Krishnan, 1998).

Application of herbal drugs in wound healing

Herbal drugs have been used to evaluate their wound healing efficacy in different animal models ranging from laboratory animal to large animals. Even cellular models

have proved quite effective for the evaluation of wound healing efficacy of herbal drugs (Graham, 2004). However among animal models rabbits have proved most useful. Rabbits are significantly larger than the more commonly used laboratory animals such as mice and rats, but remain easy to handle and inexpensive (Ramos *et al.,* 2008) Different wound models ranging from partial thickness to full thickness wounds or incisional wounds to excisional wounds have been used (Asif *et al.,* 2007). The efficacy of drugs has been evaluated from different parameters including gross, histopathological, bacteriological and even biochemical evaluation of different enzymes (Kalirajan *et al.,* 2012; Gupta *et al.,* 2007).

Herbal drugs have been used for wound healing in either crude form or in the form of different extracts. Kirtiker and Basu (1935) used poultices of plant *Vernonia cinera* and roots of *Eriolsena quinquelocularis* for treating wounds and sores. They found positive effect in healing of the wounds. Deshpande and Pathak (1966) used fresh juice of *Jasmina auricularum* and found 20% hastening in wound healing and 35% increase in tensile strength between 6-9 days after local treatment of wounds. Herbal drugs have been found equally effective in suppurative conditions of wounds also. A herbal skin gel "Charmil" caused faster wound healing in the treatment of experimentally induced supparative wounds in calves. The healing effect of the gel is attributed to its antimicrobial, fly repellant and larvicidal effect (Pradhan, 1995). Volatile oil obtained from *Allium sativum*, *Curcuma longa* and alcoholic extract of fresh roots of *Moringa pterygosperma* inhibit the growth of both Gram positive and Gram negative organisms (Chopra *et al.,* 1958). Aqueous extract of *Helianthus annus* plant has been found to have healing effect. Aseptic wounds of albino rats became dry and scab was formed after 36 hours of wounding when treated with 5% aqueous extract of the plant. The contraction was complete by 15th day (Deshpande *et al.,* 1965). Powder, alcoholic and choloroform extract ointment of *Adhatoda vasica* treated wounds showed an early fibroblastic proliferation, less inflammatory changes and early epithelialization of newly formed connective tissue as compared to controls. Histo-chemical observations

revealed more collagen, elastin and mucopolysaccharide in treated wounds than control wounds, while insignificant changes were seen in extent of formation of reticulin fibers (Bhargava *et al.,* 1986). Zama *et al.,* (1991) reported that the rate of healing was highest in wounds treated with alcoholic extracts of *Adhatoda vesica.* Similarly powder, alcoholic or chloroform extract ointment of *Annona squamosa* showed early and better wound healing effect. Among these alcoholic extract ointment was found the best. The percent healing and tensile strength, collagen and elastin contents gradually increased from 3rd to 30th day and was higher in wounds treated with ointment of alcoholic extract of *A. squamosa.* Maximum concentration of hexosamine was found on day 3rd in all treated wounds upto day 30th. Zinc contents showed significant and gradual increase from day 3rd to 30th day in powder and alcoholic extract ointment treated wounds *(*Bhargava *et al.,* 1988). Aqueous extract of *Triticum vulgare* is effective in promoting the tissue repair process by supporting wound repair process through epidermal regeneration. Extract aids cutaneous wound healing due to its mitogenic effect on fibroblasts, and endothelial cells and by promoting epidermal cell proliferation in damaged epidermal areas (Mastroianni *et al.,* 1998). Wound healing activities of the aqueous and methanol extracts of the roots of *Berberis lyceum* has been shown in rats using incision, excision and dead wound space models in rats. Application of both extracts yields increased epithelilization, wound contraction, skin breaking strength, tissue granulation, dry weight and hydroxyproline content and collagen formation. The methanol extract is more effective than the aqueous extract (Asif *et al*., 2007). *Bergenia celiata* rhizome possesses promising therapeutic potential and could be considered as potential source for drug development by pharmaceutical companies as its methanolic and aqueous extracts have been found to have antioxidant activity (Venkatdhari *et al.,* 2010). The antimicrobial activity of methanolic and aqueous extracts of the medicinal plant *Cocculus hirsutus bestows it* potential wound healing activity. The methanolic extract of the plant was found to be more

effective against *V. cholera*and *S.aureus* and in the mean time the aqueous extract was found to be more effective against *V.cholera* and *K. pneumoniae*. Both methanolic and aqueous extracts of this plant have no fungicidal activity against any fungal pathogen (Kalirajan *et al.,* 2012).

On clinical, pathological, histochemical and microbiological studies healing was found best with *M. chamomilla* lotion, followed by *M. chamomilla* ointment and *P. bistorta* ointment, *Nigella sativa* lotion, and *P. bistorta* ointment, with *S. fragalis* lotion the least (Ahmed *et al.,* 1995). *Aloe vera* influences the healing process by enhancing collagen turnover in wound tissue. It increases biosynthesis of collagen and activity of collagenase (collagen degradation). It also increases levels of lysyl oxidase which indicates increased crosslinking of newly synthesized collagen (Chithra *et al.,* 1988). Asiaticoside isolated from *Centella asiatica* when applied topically as 0.2% solution causes 56% increase in hydroxyproline, 57% increase in tensile strength and increases collagen contents and better epithelialization . Topical application of 0.4 % solution of asiaticoside has been also found effective in streptozotocin-diabetic rats(where healing was delayed) where it increased hydroxyproline content, tensile strength, collagen content and epithelialization. Its oral administration @ 1mg/kg dose in guinea pig punch wounds was also found active. It promotes angiogenesis in chick chorioallontois membrane model at 40 µg concentration, thus it has been concluded that it exhibits significant wound healing activity in normal as well as delayed wound healing models (Shukla *et al.,* 1999).

Methanol extract of *Leucas avandulaefolia* both in the form of ointment as well as injection in both excisional and incisional rat wound models showed significant wound contracting ability, reduction in closure time, increase in tensile strength and regeneration of tissues at the wound site (Kakali-Saha *et al.,* 1997). *Rhodiola imbricate* rhizome ethanol, rich in polyphenols improves rate of wound contraction and decreases time taken for epithelization .The extract also increases cellular proliferation

and collagen synthesis at the wound site, which could be evidenced by increase in DNA, protein, hydroxyproline and hexasamine contents (Gupta *et al.,* 2007). Ethanolic extract of *Morinda citrifolia* leaves has been found to have wound-healing activity in rats, using excision and dead space wound models. Ethanolic extract of Morinda *citrifolia* when given orally @ 150 mg kg^{-1} day^{-1} by mixing in drinking water exhibited 71% reduction in the wound area when compared to 57% in controls. Enhanced wound contraction, decreased epithelialization time, increased hydroxyproline content and histological characteristics suggest that this leaf extract has therapeutic benefits in wound healing (Nayak *et al.,* 2009).

Rheum emodi, in Kashmiree called Pambh challan is a household herb, believed to have many potential theraupetic characteristics including wound healing, However its evaluation as under cutaneous trial was conducted by Aakhoon (2001). He evaluated its wound healing efficacy in cow calves and credited it with anti-inflammatory, anti-bacterial and wound healing properties. Tang *et al.,* (2007) used emodin derived from Rhubarb topically and recorded increased content of hydroxyproline on day 7 post-wounding and more tensile strength on day 14 post-wounding in treated wounds. The mechanism attributed to the healing efficacy of *Rheum sp* include a complex mechanism involving stimulation of tissue regeneration and regulating Smads-mediated TGF-beta signaling pathway. Ethyl acetate extract of *R. emodi* has been reported having an immune-enhancing effect leading to anti-tumor, wound healing and antibacterial effects via Th-1 and Th-2 cytokine regulation in vivo and reported that the molecular mechanism involved is attributed to the increase in the release of NO, IL-12 and TNF-a and a decrease in the production of IL-10 as observed with RAW 264.7 cell lines (Kousar *et al.,* 2011).

Safety and health concerns

Safety is utmost important provision of herbal medicines and herbal products for health care, and a critical component of quality control. Over the past decade, interest

in drugs derived from higher plants has increased expressively. It is estimated that about 25% of all modern medicines are directly or indirectly derived from higher plants (Farnsworth and Morris, 1976; De Smet, 1997; Cragg *et al.,* 1997; Shu , 1998). Among consumers, there is a widespread misconception that "natural" always means "safe", and a common belief that remedies from natural origin are harmless and carry no risk. However, some medicinal plants are inherently toxic. Plants have hundreds of constituents and some are very toxic such as the most cytotoxic anti-cancer plant-derived drugs, digitalis, the pyrrolizidine alkaloids, ephedrine, phorbol esters, etc. However, the adverse effects of most herbal drugs are relatively less frequent when the drugs are used properly compared with synthetic drugs, but well-controlled clinical trials now confirm that they really exist (Bagheri *et al.,* 1998; Brinker, 1998; Brown, 1992; D'Arcy 1993; De Smet, 1995; Farnsworth, 1993; Drew & Myers, 1997). Most herbal products in the market today have not been subjected to drug approval process to demonstrate their safety and effectiveness. Some of them contain mercury, lead, arsenic (Kew *et al.,* 1993), corticosteroids and poisonous organic substances in harmful amount (De Smet, 1997). Sometimes patients use traditional and conventional medicines simultaneously. The interaction of these two types of drugs in vivo may be dangerous and have raised serious concern among the medical scientists about the safety of the patients (Chattopadhyay, 2003). It is essential to establish internationally recognized guidelines for assessing their quality. The World Health Assembly in resolutions WHA31.33 (1978), WHA40.30 (1987) and WHA42.43 (1989) has emphasized the need to ensure the quality of medicinal plant product by using modern control techniques and applying suitable standards (WHO, 1998). The WHO has published guidelines in order to define basic criteria for evaluating the quality, safety, and efficacy of herbal medicines aimed at assisting national regulatory authorities, scientific organizations and manufacturers in this particular area (Akerele, 1993). However, the situation will change very quickly because the increase in the world market for medicinal herbs has attracted most of the largest pharmaceutical

companies, including some multinationals, and some of them have recently acquired small companies specialized in phytotherapeutic agents (Blumenthal, 1999[a]; Blumenthal, 1999[b]; Grunwald, 1995).

CONCLUSION

Among the functions of body healing of wound is a priority function. Early healing of wound is a field of attraction for research workers. Different topical applications are used to manage wound healing. Among the different topical applicants many herbal drugs are nowadays under trial to evaluate their wound healing efficacy. The use of herbal drugs is on a flow due to their safer nature and less frequent adverse effects as compared to conventional drugs. Different wound models ranging from partial to full thickness or incisional to excisional wounds in different animal models or even in cellular models have been used to evaluate wound healing efficacy of herbal drugs. Efficacy of herbal drugs has been evaluated using different parameters (Histopathological, bacteriological, hemato-biochemical). So far, herbal drugs in crude form as well as in different extract forms have proven to be efficient wound healing agents with less adverse effects and toxicities.

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