



## Short Review

## Studies on wound healing potential of topical herbal formulations- do we need to strengthen study protocol?

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## ABSTRACT

Healing of wound is a normal biological process that occurs naturally as long as it is not obstructed by infection. Many monoherbal and polyherbal formulations have been reported to hasten/accelerate wound healing activity in freshly prepared incisional and excisional experimental wound models. In the present review, an attempt has been made to throw light on importance of microbial infection in the process of wound healing and antimicrobial activity of herbal formulations. Different herbal formulations have been reported to hasten/accelerate the process of wound healing by enhancing epithelialization, neovascularization, formation of granulation tissue, collagen synthesis, wound contraction, tensile strength, etc. As these studies have been conducted in freshly prepared non-infected wounds, it is difficult to ascertain the wound healing potential of these formulations in absence of microbial colonization/infection and results are not justifiable because the healing is limited to non-infected wounds. It would be more appropriate to ascertain the wound healing potential and not hastening/accelerating the wound healing property of newer herbal formulations on wound healing in experimental animals in presence of colonization/infection. Hence, it is recommended to strengthen these study protocols further using suitable controls to find out the antimicrobial activities of herbal formulations and their effect on wounds colonized/infected with pathogenic microbes in significant numbers to achieve more meaningful and concrete conclusions.

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Wound is a physical injury to any of the tissues in the body that results in a break in the continuity of soft parts of body structures. A process of healing of wound is a normal biological response to the injury that occurs naturally, as long as the local care is adequate. The normal phases of wound healing i.e. reaction, regeneration, and remodeling take place without any difficulty, if wound is debrided properly of non-viable tissue and repaired it in a physiological manner [1]. In absence of infection, trauma and ischemia, which are the most important obstacles in the healing process (especially the infection), healing of wound proceeds without any problem in an orderly scheme. However, proliferation and multiplication of pathogenic microbes in wounds in significant number can cause disturbances in this orderly wound healing scheme and affects each of the processes of healing. Thus, wound infection is one of the

major obstacles for poor wound healing and is the most common reason for impaired wound healing as the persistence of bacteria in wound results in prolonged elevation of proinflammatory cytokines such as interleukin-1 and tumour necrosis factor - alpha that in turn cause increased levels of matrix metalloproteinases, a decreased level of tissue inhibitors to the metalloproteinases and decreased production of growth factors and thereby impair the process of wound healing [2].

*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Streptococcus pyogenes*, *Klebsiella* spp., *Proteus* spp. and other pathogenic microbes are the most common pathogens associated with wound infections. Significant reduction in the number of microbes using appropriate topical agent is very important in regularizing the process of healing and satisfactory healing of wound is possible only when the infection is brought under control. Thus, reduction in the number of microbes in wounds accelerates the process of healing [2–6].

In a recent past, many medicinal plants (herbal formulations- monoherbal as well as polyherbal formulations) have been

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reported to hasten/accelerate wound healing activity and found useful in the treatment of wound models (freshly prepared incisional and excisional wounds) in experimental animals and in vitro studies [7–17]. In a study carried out by Nayak et al. (2006) in excisional and incisional wounds in rats, aqueous extracts of *Allamanda cathartica* and *Laurus nobilis* have been found to enhance the rate of wound contraction, epithelialization and formation of granulation tissue. *A. cathartica* was found to be more effective than *L. nobilis* in their study [7]. An alcoholic extract of *Kaempferia galangal* has also been reported to enhance epithelialization and wound contraction rate [8]. *Cecropia peltata* Leaf extract has also been shown to cause significant decrease in wound areas [9]. Similarly, ethanolic extract of *Lawsonia inermis* Linn. and aqueous extract of the roots of *Radix paeoniae* have been reported to cause increase in rate of wound contraction, epithelialization and granulation tissue [10,11]. However, ethanolic leaf extracts of *Lycopodium serratum* was found to enhance collagenation, epithelialization and also increase in the rate of wound contraction [12]. The topical application of the methanolic extract of *Jasminum grandiflorum* L (Oleaceae) leaves to full thickness excision cutaneous wounds in rats has been found to improve the rate of wound healing by accelerating the rate of collagen synthesis, by causing significant increase in tissue growth and by improving the anti-oxidant status [13]. In a recent study, the ethanolic extract of *Bambusa vulgaris* leaves has been reported to promote wound healing in freshly created wounds in rats by enhancing epithelialization, granulation tissue, collagen synthesis, contraction rate and tensile strength. It has also been reported to improve anti-oxidants level significantly [14].

In addition to these monoherbal formulations, some polyherbal formulations have also been reported to potentiate wound healing activities. In a study by Pushpangandan et al. (2008), a polyherbal formulation containing *Urtica solicifolia curcas*, *Clerodendrum infortunatum* and *Centella asiatica* has been reported to cause wound contraction [15]. In another study, a polyherbal formulation containing *Comphora officinarum*, *Shorea robusta*, *Apis mellifera*, *Acacia catechu*, *Sesamum indicum* and *Azardica indica* has been reported to enhance wound contraction, epithelialization and increase tensile strength of incisional wounds in rats [16]. Similarly, in a recent study by Talekar et al. (2017) use of a polyherbal formulation containing extracts of leaves of *Vitex nigundo*, bark of *Emblia officinalis* Gaertn and whole plant of *Tridox procumbens in vitro* as well as on excisional wound models in experimental animals has been found to accelerate wound healing by causing proliferation and mobilization of fibroblasts and keratinocytes, increase in neovascularisation, re-epithelialization of epidermis and sub-epidermal cells, decrease in oxidative stress, and by regeneration of skin and wound contraction [17].

Earlier studies indicate that these mono- and poly-herbal formulations have potential to hasten/accelerate wound healing in freshly prepared wounds and their role as accelerating agent in the process of wound healing is beyond doubt. But it is obvious from the study protocol of these earlier reports that these studies have been conducted in freshly prepared non-infected incisional or excisional wounds which are not showing any sign of infection/colonization with microbes (microbe-free environment). Rather experimental wounds in animals were closely observed for sign of infection and the wound showing signs of infections were separated and excluded from the studies and replaced with newer one [12]. Also, no efforts have been made to throw light on antimicrobial activity of these herbal preparations in any of the studies reported above [7–17].

Although the effect of large number of medicinal plants on various aspects of wound healing is very fruitful, it is difficult to ascertain or reach the final conclusion regarding their potential as wound healing agent (and not as accelerating agent) of different herbal formulations on wound healing based on the reports of

studies in a microbe-free environment in absence of microbial colonization/infection of wounds [18,19]. As it has been proved beyond doubt that the wound healing occurs naturally unless it is obstructed by infection, trauma and ischemia, especially infection is the most important and leading cause for non-healing of wounds, and it is a scientifically proved fact that the presence of microbes or their products can cause disturbances in the orderly scheme of wound healing process. The presence of microbes or their products can affect each of the processes of wound healing [2–6]. Thus, it is difficult to ascertain the wound healing potential of any new formulation in absence of infection, which is a leading cause of non-healing of wounds. In absence of persistent tissue level of bacteria, it is very difficult to confirm the efficacy. Healing of wound by using these monoherbal and polyherbal formulations in such situations is not justifiable because the healing in most of these studies is limited to the non-infected wounds, which could heal naturally without any medication.

Hence, our recommendations are to strengthen the wound healing study protocols by including *in vivo* study design and appropriate controls to study the type of infection (monomicrobial/polymicrobial), type of wound (acute/chronic), duration of treatment required, outcome variables, etc. So that it would be more appropriate to ascertain the effectiveness of newer herbal formulations on wound healing in experimental animals in presence of colonization/infection and also to study antimicrobial activity of these preparations to achieve more justifiable and meaningful results.

In a clinical situation where the chances of fresh wounds without colonization/infection are very rare and hence, we need to strengthen these study protocols further to find out the antimicrobial activities of these preparations and their effect on wounds colonized/infected with pathogenic microbes in significant numbers. The positive results of these additional parameters will help to achieve more meaningful and concrete conclusions.

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None.

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