DOI: 10.55735/hjprs.v2i3.96

THE HEALER
Journal of Physiotherapy & Rehabilitation Sciences

Review Article

Medicinal Plants: An Insight into Wound Healing

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ABSTRACT

Medicinal plants have been used for centuries to treat trauma, infection, sickness, and injury as these are affordable, easy to access and have fewer side effects than commercial pharmaceuticals. Recent research has shown that several medicinal plants can treat wounds using *in vivo* and *in vitro* pre-clinical models of wound recovery. Furthermore, the mechanisms by which these medicinal plants enhance wound therapy have also been revealed. Medicinal herbs have been shown in research to have the ability to have an antioxidant effect, to promote angiogenesis, to activate NF-B, to favor specific pro-inflammatory cytokines, to boost the appearance of iNOS and α-1 type-1 collagen, and to favor certain pro-inflammatory cytokines. All these effects can be brought about by medicinal herbs. Considering this, throughout this evaluation, an effort was made to provide a glimpse into freshly discovered medicinal plants that have wound recovery mechanisms and may be effective in the treatment and the invention of new wound-healing pharmaceuticals. Herbal medicines involve disinfection, debridement, and creating a healing environment. The purpose of the study was to review and gather the evidence related to the use of medicinal plants in wound healing. The use of herbal remedies is found to be both affordable and effective, mainly when used in conjunction with wound healing, bacterial activity and reducing oxidative stress in animals. During this evaluation, the cellular processes of recently discovered medicinal plants with a capacity for wound healing were brought to light. These mechanisms can potentially be helpful in therapeutic practice and the advancement of innovative medications for treating wounds. Several factors can delay the wound-healing

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Keywords: Herbal Ointments; Medicinal Plants; Wound Healing

Citation: Ullah F, Kashif M, Jamil M, Ullah H, Farooq U, Nazar MW. Medicinal plants: An insight into wound healing. The Healer Journal of Physiotherapy and Rehabilitation Sciences, 2022; 2(3):254-264.

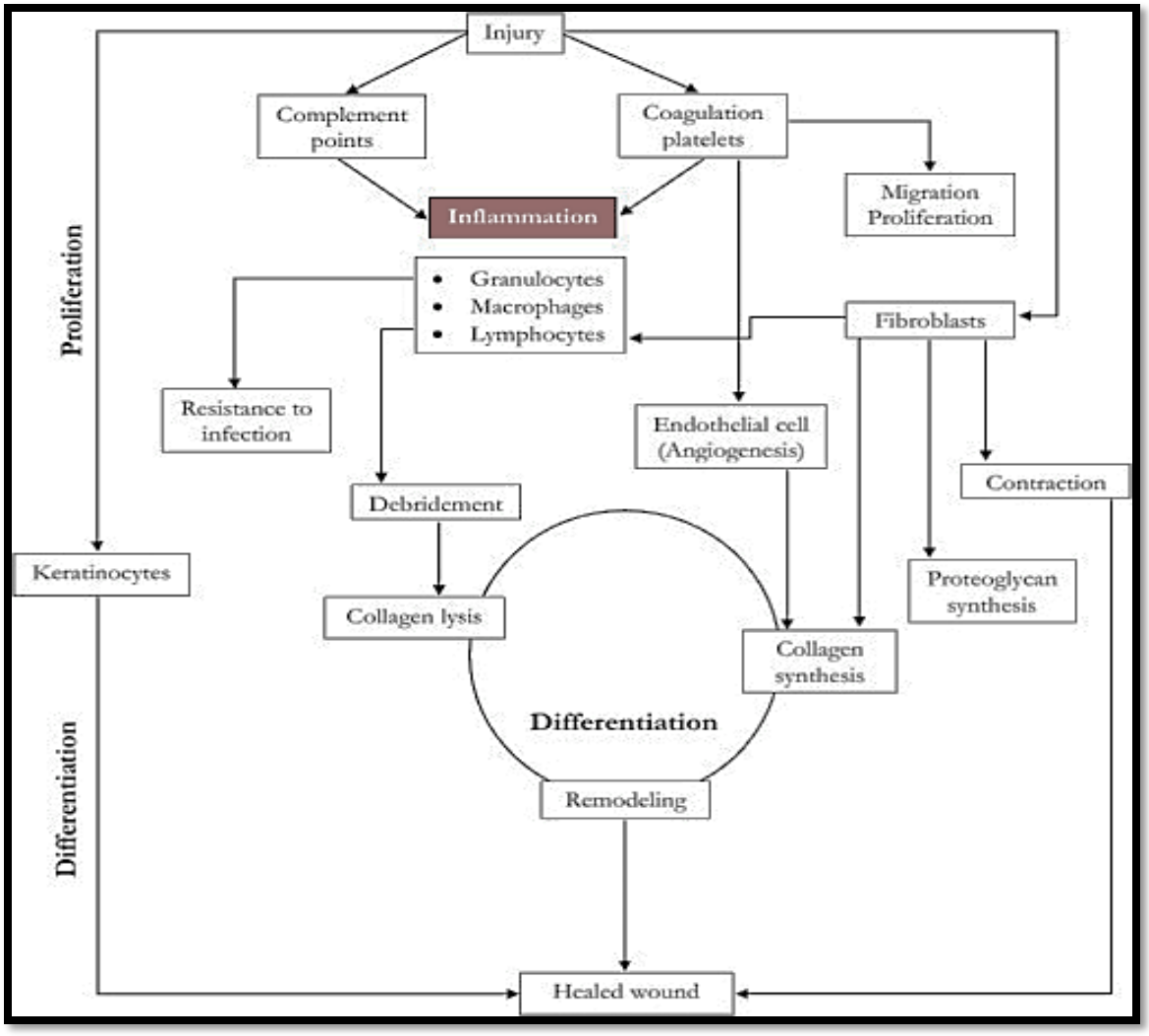
DOI: 10.55735/hjprs.v2i3.96

such as anemia, diabetes, nutritional deficiency, hematoma, local infections, etc. In the treatment of wounds, many medicinal plants and other herbal immunomodulators are considered useful. Through different pathways, these herbal ointments promote healing and regeneration of the lost tissues without producing side effects.

INTRODUCTION

A wound is characterized as a disorder in tissue's anatomical and cellular endurance, which can occur with or without microbial infection.[1] The epithelial cells of the skin can be damaged in various ways, including physically, chemically, thermally, immunologically, and microbiologically.[1] This can lead to a disruption in the functional continuity of live tissue in wounds. Wounds that are not treated properly can lead to discomfort, soreness, contamination, and occasionally even the failure of organs.[1] The process of wound healing (Figure I) is comprised of several distinct phases, the most notable of which are the inflammatory phase, the proliferative phase, and the remodeling phase.[2]

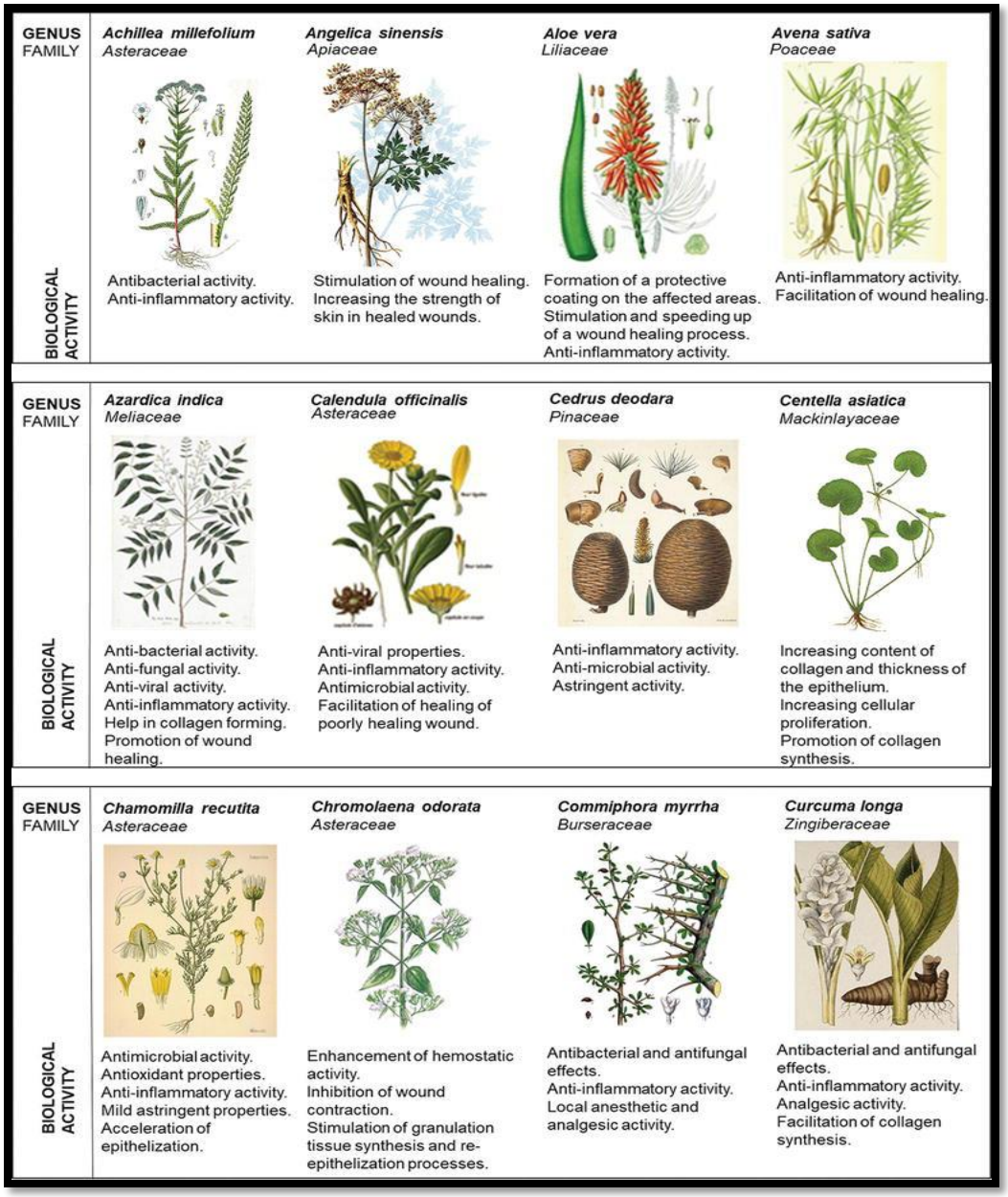
Figure I: Process of Wound Healing



DOI: 10.55735/hjprs.v2i3.96

Herbal therapy has been an integral component of human medical practice for ages. Many of the chemical components extracted from herbs are beneficial in curing a broad range of disorders. More than eighty percent of individuals in every region of the world use herbal treatments, as indicated by statistics provided by the World Health Organization (WHO), and various plants utilized for wound therapy are presented in Figure II.[4]

Figure II: Traditionally Used Medicinal Plants for Wound Healing



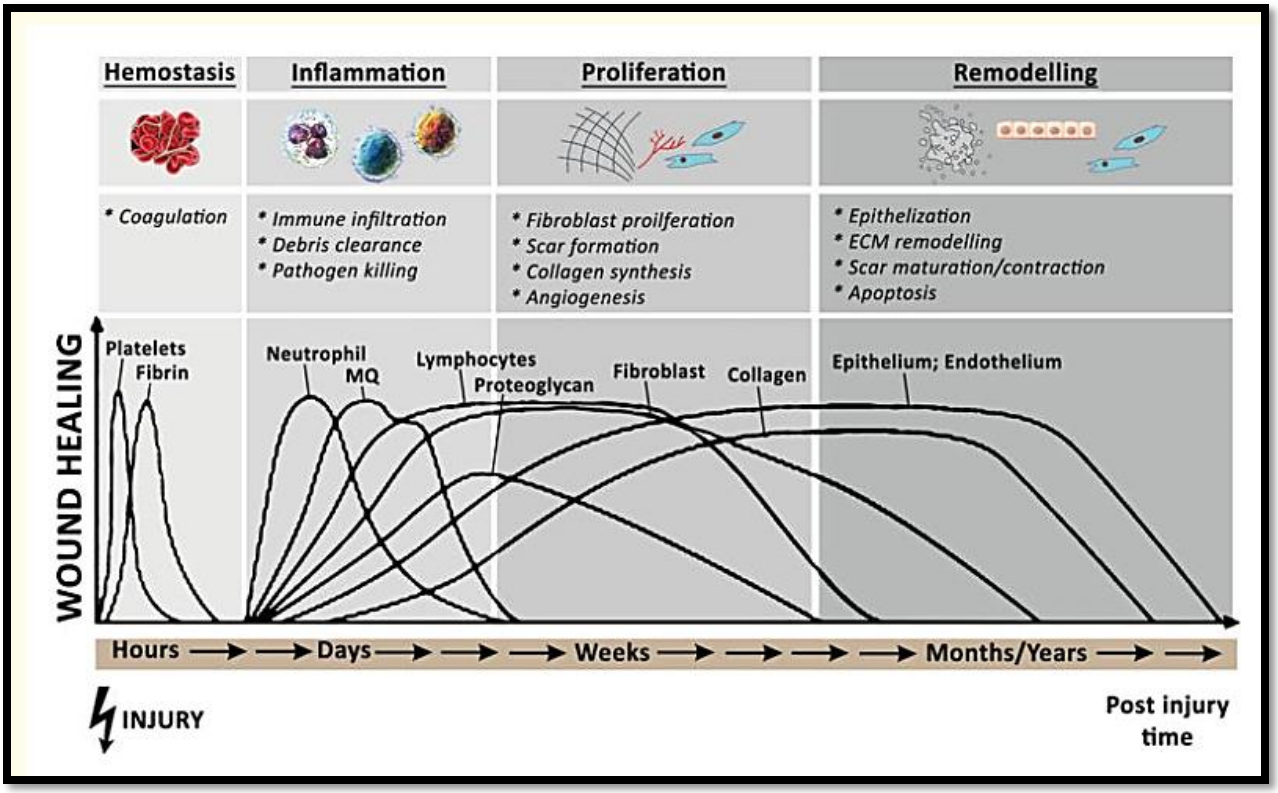
DOI: 10.55735/hjprs.v2i3.96

Currently, a great deal of investigative effort has been put into determining the biochemical mechanisms that underlie plant extracts' capacity to hasten wound healing. Angiogenesis,[6,7] stimulation of NF-B (nuclear factor B cells),[8] encouraging pro-inflammatory cytokines,[9] an increase of iNOS,[10] and α-1 type-1 collagen[11] are among the mechanisms that have been.[9] As a consequence, this examination intended to gather and provide evidence that has just now been published by investigators concerning the molecular processes of wound healing by plants.

Healing Of Wounds

The healing process for wounds consists of 4 stages: homeostasis, inflammatory, proliferative, and remodeling stage (Figure III).

Figure III: Stages of the wound healing process



It is possible for an inflammatory phase to begin practically immediately after the damage and to continue for anywhere from 48 hours to, in the most exceptional of cases if two weeks. The hemostatic features of this phase immediately bring an end to the blood flow by narrowing the blood vessels and causing the platelets in the blood to clump together. Following this point, vasodilation and phagocytosis occur at the wound site; eventually, these two processes produce inflammation.[12] After this phase, the proliferative phase typically lasts for two to three weeks. During this period, the production of collagen fibers and the development of new blood vessels both continue in parallel. When the boundaries of the injury are brought closer together to diminish its size, epithelial tissues are generated over the location of the incision.[13]

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Depending on how extensive the renovation is, the process could take anywhere from three weeks to two years. At this stage of the procedure,vitamin C-dependent hydroxylation was used to create cross-links between collagen fibers that increased the tissue's tensile strength.[13]

Evidence On Wound-Healing Plants

A study was performed to investigate the antioxidant and lipid peroxidation effects of *Garlic* in albino male Wister rats (160-180gm) weight. The animals were randomly put into four groups, with six animals in each group. In group 1 rats were treated with (saline control), group 2 used (NDEA 200mg/kg + CCL4 3ml/kg body weight), and group 3 (NDEA 200mg/kg + 1ml of *Garlic* extract 250mg/kg body weight), group 4 (Aqueous garlic extract 250mg/kg body weight).

The aqueous extract of garlic used in groups 3 and 4 significantly increase results in the levels of antioxidant, β-carotene, ascorbic acid, α-tocopherol, GSH, GPx, SOD, and CAT were engorged as equated to the group 2.[14] In an experiment reported by Sidik et al. (2006), the usage of garlic aqueous extract in combination with honey as a topical applicant for wound dressing significantly accelerated healing. The combination not only maintained the wound sterility till complete healing in all animals but also its healing action was more effective than honey alone.[15]

Li *et al.* in 2007 reviewed the pathophysiology of critical wounds and described the several stages of healing a wound. Hemostasis, inflammation, tissue proliferation, and remodeling are all stages of wound healing. Tissue reverts to its normal form and function due to retrieval. However, any interruption to these phases would prolong the time needed for the lesion to heal and if the wound becomes contaminated and infected could prove lethal to the animal.[12] Sathiya and Muthuchelian (2008) did a study at India's Madurai Kamaraj University to determine the antibacterial properties of *Prosopis juliflora* Ethanolic Leaf Extract. Tannins, acids, glycosides, flavonoids, and alkaloids were extracted as active ingredients in the phytochemical study of the leaves. In vitro, antibacterial experiments, the ethanolic leaf extracts inhibited therapeutically significant bacterial strains. Bacterial strains were constrained by extracts at intensities of 50, 100, 200 and 300 mg/ml solvent. When compared to common antibiotics like streptomycin and penicillin, the results demonstrated that *Prosopis juliflora* extract had a sufficient inhibitory effect against all the bacteria tested.[16] Yesmin *et al.* (2008) designed a study at the Khulna university campus (Bangladesh) to check the antioxidant and antimicrobial pursuits of *Calotropis procera Linn*.

They investigate the antioxidant pursuit of it against free radicals and used the scavenging activity of the stable 1,1-diphenyl-2-picryl hydrazine (DPPH) free radical to estimate the methanolic extract's antioxidant effect. The plant extract contains IC50 in methanol extract with a concentration of 110.25 µg/ml, and it exhibits a strong antioxidant effect. Aqueous plant extract showed effective results against both gram-positive and negative micro-organisms. The zone of inhibitions produced by methanolic and aqueous extracts of *Calotropis procera* against a small number of sensitive strains was quantified and contrasted with those of normal antibiotic Gentamycin.[17]

Singh *et al.* (2011) explored the antibacterial effect of various parts of the *Prosopis juliflora* using the disc diffusion method against different strains of pathogens like *E. coli, Staphylococcus aureus, Bacillus cereus, Pseudomonas putsida, Klebsiella, Salmonella, Acinetobacter, and Alcaligen*. Various parts of the plant, such as the leaf, pod, and flower

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extract, were used against microbes, and this exhibited a strong antibacterial effect, and the MIC value calculated ranged between 25µg/ml-100µg/ml. The leaf extract has more antibacterial activity than the other plant parts. The leaf extract has more antibacterial activity than the other plant parts. An antibiotic sensitivity test was performed against microorganisms via the zone of inhabitation method. The results show that the alkaloid extract of *Prosopis juliflora* inhibits the growth of Acinetobacter and Alcaligen more than the antibiotics.[18] A study was done by Prasad et al. (2011) to find the antioxidant properties of *Prosopis juliflora* against staphylococcus aureus.

The experiment was performed in the Department of Zoology, S.V. University, Tirupati, India. Four groups, each consisting of ten rats, were taken in the experimental design. Group 1 acted as the control group. Bacterial suspensions were given to the group at a dose rate of 0.1 ml intraperitoneal. An aqueous extract of 5% *Prosopis juliflora* was given to groups 3 and 4 for 15 days and after the investigation, a necropsy was performed. The results demonstrated that the activity levels of superoxide dismutase, glutathione peroxidase, and other free radicals were significantly reduced in the livers of *staphylococcus aureus* intoxicated rats compared to controls.[19]

Londhe *et al.* (2011) studied that allicin which is an active ingredient in *Allium sativum* (garlic) is formed sufficiently when raw garlic is ground and the enzyme alliinase is allowed to work on the stable precursor allin. *Allium sativum* is widely acknowledged as an antidiabetic, antibacterial, and perhaps anticancer agent because a lot of scientific literature is available that supports these properties. Hepatoprotective, antioxidant, and anthelmintic properties are also found in *Allium sativum*. Garlic's anticoagulant, anti-inflammatory, immunomodulatory, and wound-healing characteristics are yet another pharmacological impact that researchers ought to investigate.[20] Following an accident, a wound is an anatomical and functional abnormality of the skin. In reaction to an injury, the body goes through a complicated process of tissue remodeling or repair called wound healing. Historically, plants and plant-derived components have been widely utilized to treat and manage many types of wounds. To provide an inexpensive, practical, stable, and successful delivery system for the treatment of wounds, many types of biopolymers are now being explored.[21] A study was conducted by Mauti et al. (2015) to determine how well cinnamon, garlic, and turmeric worked against microbes.

The disc diffusion method was used to investigate the anti-microbial activity of species against *Escherichia coli* and *Bacillus subtilus* at various extract concentrations. Garlic demonstrated excellent microbiological activity against *Bacillus subtilis* and *Escherichia coli* zone ranging from 26 mm and 22 mm, respectively, according to results in selected species.[22] Timotius *et al.* (2012) carried out comparison research to assess the effects of 1% chloramphenicol and garlic juice on mouse wound healing. For this purpose, 5 groups were formed, and each group consists of 5 mice. A surgical incision was made on the dorsal region of the mice.

The wound was treated with 2.5% juice of garlic, 5% juice of garlic and 10% juice of garlic, distilled water and 1% chloramphenicol. This study showed a significant wound healing time with the juice of garlic as compared to distilled water and 1% chloramphenicol.[23] According to research by Aderounmua *et al.* (2013) mixing *Calotropis procera* (latex) and honey led to a significant decrease in the wound surface area in both groups of patients who received triamcinolone and those who received 50 percent latex in honey. On the fourteenth day

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of therapy, all treated groups had significantly less wound surface area than the control group. The surface area of the lesions had significantly decreased by the 21st day of treatment, except for the rabbits given honey alone. It displays how quickly the *Calotropis procera* may heal.[24] A study was evaluated by Tsala et al. (2014) to examine the antioxidant and wound-healing properties of the extract of *Calotropis procera*. The male albino-wistar rats weighing 150-180g were selected for experiments. Four groups were formed, and each group contained five rats. For Group 1: water; Group 2: Dexamethasone; Group 3: *Calotropis procera*; Group 4: Dexamethasone + *Calotropis procera* were used.

The study showed that it has excellent potential for dermal wound healing, improved collagen deposition, and reduced inflammatory response. It also significantly reduces the epithelization time to 17-18 days.[25] According to Farahpour *et al.* (2017) mice treated with *Allium sativum* (garlic) exhibited wound contraction, and different dosages of *Allium sativum* extract significantly boosted wound induction in this excised wound model. Mast cell dispersion increased generally seven days after wound induction, although this phenomenon was noticeably more pronounced in the Allium sativum-treated group.[26]

Khan *et al.* (2018) observed that a combination of *Allicin curcumin* gel (ACG) has better and more significant results in wound healing for normal and diabetic wounds. The study concluded that the gel of Allicin and Curcumin has excellent activity in the healing wound. It can be used as an alternative medicine for wound care. Various studies have shown that allicin and curcumin extracts have anti-inflammatory, antioxidant, and anti-microbial effects.[27] Alwadi *et al.* (2019) studied the topical application gels of 1% herbal plant extract of *Withania somnifera*, *Allium sativum*, and *Curcuma longum* has a rapid rate of wound healing and induced surgical incision in the rabbit. Garlic has an anti-inflammatory action due to allicin, flavonoid, and triacremonone, which speeds up the proliferative phase of wound healing, marked by re-epithelialization and the development of new blood vessels and fibroblasts.[28]

Ullah *et al.* (2022) studied that traditional treatments for a variety of illnesses have included aloe vera, with the plant's inner gel being the most extensively researched and used component. According to supporters, these plants are preferred because they are easily accessible, inexpensive, and have fewer negative side effects than pharmaceutical substances that are sold commercially.

The methods by which the function of the active ingredient, however, have not been sufficiently studied. The main objective of this review is to identify active substances and their functional processes in wound healing. It has been discovered that using A. vera gel for wound healing has a beneficial outcome, however, this has only been proven in the case of modest, straightforward lesions. It has been hypothesized that a combination of active ingredients, such as aloesin and aloin, rather than a single molecule acting alone, governs the actions of the plant. For the time being, the plant should only be combined with other well-known, backed-by-science medicines.[29]

The skin protects internal organs from the outside elements. Healthy skin is essential for normal physiology. Bacterial contamination, dampness, and dirt can all obstruct this process. Using antimicrobial treatments helps wounds heal more quickly. Aloe vera, honey, and turmeric are all used to treat and prevent disease. Tumor growth, cytokine release, oxidative stress, and metastasis are all prevented. The study results of past studies on aloe vera, turmeric, and honey are summarized by Jamil et al.[30] In a study

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conducted by Jamil *et al.*, the researchers examined the effectiveness of acacia honey and aloe vera gel on rabbit wounds. To carry out this study, a total of 30 mature male rabbits in good health were divided into three groups (A, B, and C). All the rabbits were given an injection of atropine sulphate through the subcutaneous (s/c) route half an hour before their surgeries at a dose of 0.035 mg/kg of body weight. When it came time to put the animals to sleep, a mixture of ketamine (35 mg/kg) and xylazine (5 mg/kg) was administered intravenously. The rabbits in groups A and B were given aloe vera gel twice a day, while the rabbits in group C were given pyodine and the rabbits in group A were given acacia honey twice a day.

The efficacy of various treatments was evaluated based on several criteria, including the length of time it took for the wound to heal, the degree to which it contracted, the length of time it took for the epithelization process to complete, the wound's tensile strength, its histology to prevent infections to the greatest extent possible, wounds were properly bandaged with sterile cloths. In comparison to a group, wound contraction was observed to be much greater on day 10 and was fully achieved on day 20 in both groups (A and B) (Control group). The time allotted for euthanasia in groups A and B was reduced more quickly than it was in group C. (the control group).

The length of time needed to heal was significantly less than that of the group, and this difference was statistically significant. The disparity between group A and group B stood out significantly. On day 15, the wound index values for group A decreased, whereas the values for group B increased (1.78). On day 20, there was no discernible difference between the two test groups and the control group.[31] To heal cutaneous wounds effectively, using herbal treatments and items derived from plants is beneficial in this research (Habibullah *et al.*, 2021). *Camellia sinesis, aloe vera*, and *Curcuma longa* are three plants that are frequently utilized in the treatment of wounds. The continued employment of traditional methods and the continued popularity of these methods demonstrates that traditional approaches have a lot to offer. Natural products and the derivatives of those products can contain undiscovered mixes, reagents, and adjunct compounds, some of which may have potential medicinal use.[32] Jamil et al. (2020) elaborated that the wound-healing process begins automatically as soon as the skin reacts to a wound. By preventing bacterial contamination, moisture, and dirt from getting into the wound, this process can be aided in several different ways.

A variety of antiseptic dressings are available for this purpose, and when applied topically, they promote the wound-healing process. They speed up wound healing and stop any microorganisms from contaminating the wound. One of these is aloe vera, which has powerful wound-healing abilities. Since at least 5000 years ago, both conventional and alternative types of medicine have used herbs extensively. Herbal treatments for wounds include debridement, cleaning, and the creation of an environment that will promote the healing process naturally. The main goal of this study is to synthesize the research done by prior experts and provide a solid rationale for using herbal treatments like aloe vera because they are affordable, accessible, and safe.[33]

Inflammatory cytokine production, tumor growth, myocardial infarction, oxidation, platelet aggregation, and metastasis are all inhibited by turmeric. The skin protects the body and preserving skin integrity is essential for healthy body operation. Skin breaks that expose internal organs are considered wounds and are potentially fatal. The skin's initial reaction to a wound naturally triggers the start

DOI: 10.55735/hjprs.v2i3.96

of wound healing. When worn topically, antiseptic dressings stop wound contamination and speed up wound healing. This study sought to synthesize earlier researchers' findings about the safety, accessibility, and affordability of natural remedies like turmeric.[34] The purpose of the study was to review and gather the evidence related to the use of medicinal plants in wound healing. There is, however, a need for scientific evaluation, standardization and safety assessment of these herbal ointments.

CONCLUSION

The use of herbal remedies is found to be both affordable and effective, mainly when used in conjunction with wound healing, bacterial activity and reducing oxidative stress in animals. During this evaluation, the cellular processes of recently discovered medicinal plants with a capacity for wound healing were brought to light. These mechanisms can potentially be helpful in therapeutic practice and the advancement of innovative medications for treating wounds. Several factors can delay the wound-healing process such as anemia, diabetes, nutritional deficiency, hematoma, local infections, etc. In the treatment of wounds, many medicinal plants and other herbal immunomodulators are considered useful. Through different pathways, these herbal ointments promote healing and regeneration of the lost tissues without producing side effects.

DECLARATIONS

Consent to participate: Written consent had been taken from patients. All methods were performed following the relevant guidelines and regulations.

Availability of data and materials: Data will be available on request. The corresponding author will submit all dataset files.

Competing interests: None

Funding: No funding source is involved.

Authors' contributions: All authors read and approved the final manuscript.

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