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A SYSTEMATIC REVIEW ON WOUND HEALING

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Abstract
The body's initial line of defence, the skin protects the inside organs from heat, chemical, and mechanical harm. It has a highly developed immune system that protects the body from harmful illnesses. The body's natural response to tissue damage is wound healing. But wound healing is a complicated process that involves a wide range of cell types, cytokines, mediators, and the vascular system interacting with one another. It is a complex, strictly controlled process that is essential to retaining all other skin functions in addition to the skin's barrier function. Numerous factors, both modifiable and non-modifiable, can impact this process. In order to successfully restore the damaged tissue, wound healing is a dynamic process supported by a variety of cellular processes, including as homeostasis, inflammation, proliferation, and remodelling. These activities must be properly integrated with one another. When there is damage to the skin, bacteria can swiftly infiltrate the tissues behind the skin, leading to life-threatening infections and chronic wounds. Natural phytomedicines with significant pharmacological qualities have been used extensively and successfully to treat wounds and prevent infections. Phytotherapy has been used for millennia to effectively cure skin wounds and delay the formation of infections. This study focuses on cutaneous wound healing and highlights the classical wound healing phases because wound healing occurs in many regions of the human body. Changes in any one of these stages may encourage the development of chronic wounds and hinder their healing. Numerous plants have been shown to aid in wound healing through a variety of processes.
Keyword: Wound healing, herbal drug, wound infection, classification of wounds.

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Introduction

A wound is characterised as a break in the cellular, anatomical, and functional continuity of a living tissue. It might result from an injury to the tissue that is physical, chemical, thermal, microbiological, or immunological. Burn injuries are brought on by fire, heat, radiation, chemicals, electricity, or sunlight. Tears, cuts, or punctures in the skin are referred to as open wounds, and contusions caused by blunt force trauma are called closed wounds. Put another way, a wound is a rupture in the skin's epithelial integrity. It can also be caused by an abrasion, contusion, hematoma, or disturbance of the structure and function of the normal tissue beneath it [1]. Wound infections are most common in developing countries because of poor hygienic conditions. Some important organisms causing wound infection are *S. aureus, S. pyogenes, E. coli, P. aeroginosa, S. pneumoniae* and *K. Pneumonia* [2,3]. Acute wounds frequently heal according to the anticipated or predictable rate of healing in four weeks, fully and without complications [4]. Acute and chronic wounds have a devastating effect on economies and healthcare systems worldwide [5, 6]. The annual cost of treating injuries in the US is over $50 billion [7]. Medicare is a health insurance programme, and its participants annual costs for wound care range from 28.1 to 96.8 billion dollars. The most expensive wounds are surgical wounds and diabetic ulcers, at 38.3 and 18.7 billion dollars, respectively [8]. By 2024, the global market for wound therapy is expected to reach a value of approximately USD 15–22 billion [9].

Classification of Wounds

Many factors can be used to categorise wounds. When it comes to wound healing and damage care, time is crucial. As a result, depending on how long it takes for a wound to

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heal, it can be clinically classified as acute or chronic wounds [10].

Acute wounds

Acute wounds are defined as those that heal spontaneously, follow a prompt, organised healing pathway, and ultimately result in both functional and anatomical restoration. Acute wounds can arise from surgery or from trauma-related tissue loss. The healing process typically takes from 5 to 10 days or within 30 days [10, 11]. These might be full-thickness skin damage where the subcutaneous layer is affected, or they can be superficial injuries affecting only the epidermis and superficial dermis. Abrasions, lacerations, heat wounds, and surgical incisions are a few types of acute wounds [12].

Chronic wounds

Chronic wounds fail to show signs of healing within 4 weeks and do not follow the sequential stages of healing, frequently "stalling" in one phase [13]. Numerous factors that prolong one or more phases of hemostasis, inflammation, proliferation, or remodelling impair and disrupt the healing process. These elements include of exudation, necrosis, tissue hypoxia, infection, and elevated inflammatory cytokine levels. Numerous conditions, such as naturopathy, hypertension, burns, venous and arterial insufficiency, and vasculitis, can produce chronic wounds[10]. Chronic wounds can lead to major consequences and are more difficult to manage due to their unusual healing progress, poor healing period, and persistence. Leg ulcers, pressure ulcers, severe burns, and diabetic ulcers are examples of persistent wounds [14].

Wound Healing Process

Life will always involve wounds. Physical, chemical, or microbiological factors can cause wounds. Numerous cell types, cytokine mediators, and the extracellular matrix interact intricately during wound healing. Normal wound healing occurs in four stages: hemostasis, inflammation, proliferation, and remodelling. Although the wound healing process is ongoing, each step of the process is different and overlaps with the subsequent phase, because sufficient blood and nutrition must be delivered to the location of tissue injury in order for wounds to heal successfully [15].

The initial phase of wound healing is called hemostasis. In hemostasis, clotting factors come into play and create a platelet knot that limits blood loss from the wounds [16]. The coagulation cascade is instantly activated to stop blood loss and other bodily fluid loss so that tissue healing can start. Important processes include blood vessel constriction, platelet clumping, degranulation, fibrin clot formation, and neutrophil infiltration take place during this phase. Additionally, platelets release a number of growth factors to speed up the healing of wounds [17]. Now, an inflammatory response begins to counteract any potential fungal and bacterial infections that may have invaded the site. Pro-inflammatory cells such neutrophils, monocytes, basophils, mast cells, and macrophages are also more prevalent during this period [18]. The following stage, known as the proliferation phase, is marked by an increase in the number of endothelium, keratinocyte, and fibroblast cells all of which are involved in the activities involved in wound repair. Additionally, these cells migrate to the wound bed where they set off a series of events that activate fibroblasts, keratinocytes, form blood vessels, secrete collagen, and release other components of the extracellular matrix (ECM), ultimately resulting in wound closure and the re-epithelialization of lost tissue. Different cytokines released during the healing process are responsible for coordinating and controlling these activities [18, 19]. The last stage of the wound healing process, remodelling, is marked by the deactivation of active fibroblasts and keratinocytes as well as the inhibition of the inflammatory response through the activation of apoptotic pathways. At this stage, the healing process is accelerated and the quality of the healed wound is improved by collagen remodelling, vascular maturation, and higher tensile strength of the healed tissue [18, 20].

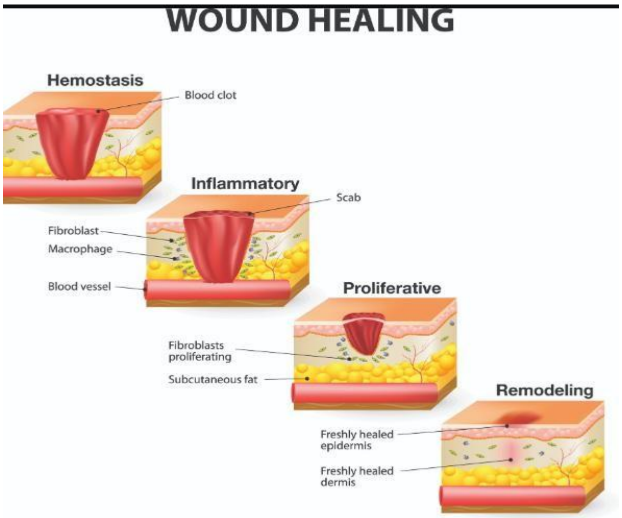

Figure:1 Phases of the wound healing process. Adapted from http://www.shieldhealthcare.com/community/popular/2015/12/18/how-wounds-heal-the-4-main-phases-of-wound-healing/

Wound Infection

Microorganisms, such as bacteria and fungus, can cause infection in the wounded areas and impair the host's immune system. Common bacterial contributors of delayed wound healing include *Pseudomonas aeruginosa, Streptococcus pyogenes, Staphylococcus aureus*, and some species of Clostridium. Hypoxia, ischemia, and immunological weaknesses (e.g., virus and chemotherapy) are additional variables associated with wound infection [21]. Although bacteria on the surface of a wound will multiply in healthy persons, this does not result in any clinical signs or activate the host immune response. The high microbial load on the wound site has been shown to be the reason of the delay in wound healing, which is attributed to the production of bacterial biofilms [22]. Unfortunately, a number of local and systemic reactions are set off when the wound pathogen colonises and invades the host's living tissues. Soft tissue damage can subsequently result from purulent drainage and clinical cellulitis [23]. When compared to acute wounds, chronic wounds are more likely to become infected. This is brought on by decreased phagocytosis and reduced leukocyte movement in the presence of a high microbial bioburden [24]. Around 75% of burn wounds are more likely to get contaminated because of the microorganisms that are already present in the hair follicles, sebaceous glands viz. Pseudomonas aeruginosa, and Staphylococcus aureus [25]. Ignored wound care can also eventually result in bacteremia and septicemia, which can be lethal [26].

Method for Assessment of Wound Healing

Over many years, models of experimental wound healing have been created in an effort to better understand the tissue repair process and evaluate novel treatment approaches. These models typically fall into two categories: in vitro and animal (also known as in vivo or preclinical) models, each of which has benefits and drawbacks [27]. For many of these investigations, in vitro models like cell culture, scratch models, and skin explant cultures are crucial because significant first findings inform the planning of follow-up studies. In vivo models entail inflicting wounds on lab animals and tracking the healing process. It is also possible to include biological, chemical, or physical changes to the wound environment [27, 28]. Because they provide a realistic picture of the wound environment, encompassing different cell types, environmental signals, and paracrine interactions, in vivo models continue to be the most predictive models for researching wound healing [29]. A number of factors should be taken into account when selecting a model, including the lesion's accurate reproducibility, the capacity for multiple investigations, the ability to obtain multiple biopsy samples, compatibility with animal facilities, handling ease, and the amount of time needed to obtain meaningful results [30]. A model that accurately captures some features of human physiology without requiring real subjects for testing is ideal [31]. Since small animals typically recuperate more quickly than humans do, experiments with them typically last for days rather than the weeks or months that human research typically last [32]. Methods used for assessing wound healing in animal models include both noninvasive and invasive. Noninvasive methods include wound healing rate, imaging and biophysical approaches. Invasive methods include histopathological, immunological and biochemical analysis [33]. Mice and rats are the species most frequently employed. Despite the known distinctions between the physiology and structure of rat and human skin, studies on wound healing that take these distinctions into account can yield important translational data [34]. Rats are simple to keep, handle, and house, and a large range of specialised reagents are available for use in research [35, 36].

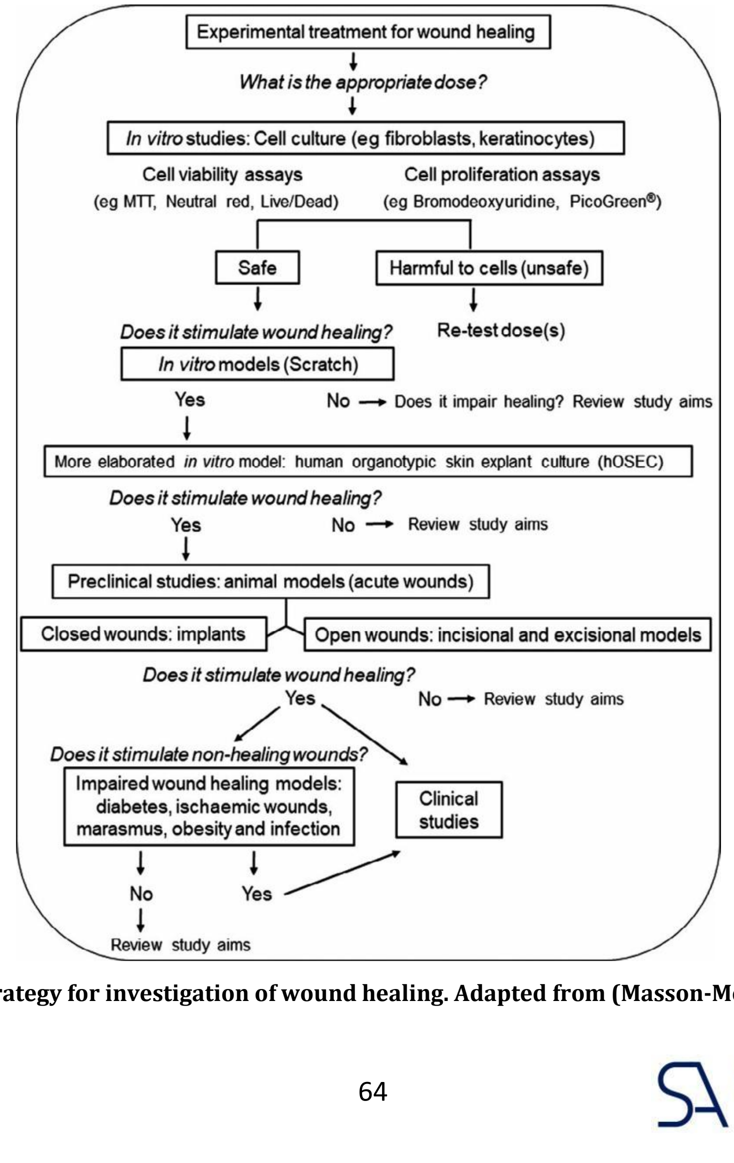

Figure No.01: Strategy for investigation of wound healing. Adapted from (Masson-Meyers et al. 2018)

Plant based Medicines on Wound Healing

Natural items, such as medicinal herbs, are abundant in the world. Because they have the potential to provide a wide range of therapeutic advantages for all of humanity, medicinal plants are currently receiving more attention than ever before. These plants' medical significance stems from their bioactive phytochemical components, which have specific physiological effects on humans. The most significant bioactive phytochemical components are tannins, terpenoids, alkaloids, flavonoids, essential oils, saponins, phenolic compounds, and many more. These organic substances serve as the basis for contemporary medications [37]. Studies on numerous medicinal plants in the field of wound healing have been tried and are still going on. The findings of these studies have demonstrated that certain plants have demonstrated encouraging wound healing activities via various pathways [38]. Despite the field of contemporary medicine having made amazing advancements, medicinal plants still play a vital part in wound treatment strategy due to its capacity for wound healing [39].

Table below presents a summary of plants reported to be effective in wound management with their mechanism of action.

Table No. 1: Review of plants with wound healing property

S/No	Medicinal plant	Type of Assay	Experimental model	Mechanism of action	Reference no.
1	*Curcuma longa*	*In vivo*	Albino rats	Anti-bacterial, anti-fungal, and anti-inflammatory activities. Increased collagen secretion, fibroblasts migration and angiogenesis.	40
2	*Glycyrrhiza glabra*	*In vivo*	Male Sprague- Dawley rats	Enhanced fibroblast proliferation, angiogenesis, collagen secretion and tensile strength of the wounds.	41
3	*Bacopa monnieri*	*In vivo*	Albino rats	Enhanced re-epithelialization and collagen secretion.	42
4	*Azadirachta indica*	*In vitro/In vivo*	Diabetic rats/ Wistar rats	Antimicrobial, cell proliferative and anti- inflammatory activity.	43
5	*Aloe vera*	*In vivo*	Sprague Dawley rats	Increased collagen formation and neovascularization.	44
6	*Acalypha indica*	*In vivo*	Albino rats	Activated TNF-alpha and increase cell proliferation.	45
7	*Chromolaena odorata (L.) (Siam weed)*	*In vitro/In vivo*	Fibroblast, keratinocytes and endothelial cells, adult male Sprague-Dawley rats	Hemostasis, vasoconstriction, anti-inflammatory, antimicrobial, and Antioxidant	46
8	*Calotropis gigantea*	*In vivo*	Rats	Increased hydroxyproline and breaking strength of incision wounds.	47
9	*Cassia fistula*	*In vitro/In vivo*	Male Wistar albino rats	Anti-bacterial, faster re- epithelialization and increase collagen secretion.	48
10	*Gymnema sylvestre*	*In vitro/In vivo*	Diabetic rat	Enhanced re-epithelialization, fibroblast proliferation and antioxidant activity.	49
11	*Gmelina arborea*	*In vivo*	Wistar albino rats	Anti-inflammatoryand antioxidant activity.	50
12	*Salvia officinalis*	*In vivo*	Wistar rats, Swiss albino rats	Anti-inflammatory, anti- nociceptive, increased blood vessels formation and inhibited ROS production	51
13	*Malva sylvestris*	*In vivo*	Wistar rats and BALB/c albino mice and Diabetic rats.	Increased collagen synthesis, reduce fibrosis, increased re-epithelialization time and anti-inflammatory	52

Conclusion

A skin damage triggers a series of phases that are all part of the well-coordinated and synchronised process of wound healing. Changes in any one of these stages may encourage the development of chronic wounds and hinder their healing. In order to effectively manage wounds, modifiable risk factors must be identified and optimised. The present review elucidates that medicinal plants that have outstanding wound-healing properties are introduced by nature. Recent decades have yielded scientific information that has expanded our understanding of the molecular mechanisms underlying the effects of herbal medicines on wound healing. Plants can heal wounds and be used to treat skin wounds because of their natural active ingredients, mostly as a result of their antioxidant, antibacterial, and anti-inflammatory properties.

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No conflict of interest.

Ethics Approval and Consent to Participate
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Author Contribution
All authors are contributed equally.

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