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Wound Healing Activity: A Comprehensive Review

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ABSTRACT

This review provides a comprehensive evaluation of the mechanisms involved in skin wound healing, highlighting the complex interplay of biological processes and factors that govern effective tissue repair. The discourse begins by underscoring the critical physiological functions of the skin—the body's largest organ—and the clinical significance of extensive dermal injuries. It elaborates on the orchestrated cascade of cellular and molecular events involved in wound healing, encompassing a dynamic network of immune cells, growth factors, cytokines, and signaling pathways, all functioning synergistically to restore tissue integrity and close dermal lesions.Wounds are broadly categorized into acute and chronic types. Acute wounds typically follow a predictable healing trajectory, whereas chronic wounds exhibit impaired healing, often due to persistent inflammation, microbial colonization, or underlying pathologies. Furthermore, wounds can be classified based on their physical characteristics into open wounds (e.g., incised, lacerated, abrasions, avulsions, puncture, penetrating, and gunshot injuries) and closed wounds (e.g., contusions, crush injuries, and hematomas). The physiological process of wound healing is delineated into four temporally overlapping yet distinct phases: hemostasis, inflammation, proliferation, and remodeling. These phases are tightly regulated and sequentially executed, and deviations in their order or duration can significantly impair the healing response. Several local and systemic factors are known to hinder wound repair. These include tissue hypoxia, microbial infection, advanced age, hormonal imbalances, diabetes mellitus, venous insufficiency, tobacco use, and obesity. Each of these variables can disrupt the cellular and molecular dynamics necessary for efficient tissue regeneration. Finally, the review touches upon current therapeutic interventions aimed at enhancing wound healing outcomes. These include both conventional topical agents and herbal formulations, with specific attention given to their bioactive constituents and mechanisms of action in modulating the wound healing cascade.

Keyword: - Wound Healing, Acute Wounds, Chronic Wounds, Tissue Repair, Extracellular Matrix (ECM), Fibroblasts.

Introduction

Skin

The skin, as the largest organ in the human body, plays a critical role in several physiological functions, including hydration maintenance, protection against toxins and pathogens, initiation of vitamin D synthesis, excretion, and thermoregulation. Consequently, severe skin damage can be life-threatening. Cutaneous wound healing is a complex biological process characterized by coordinated cellular and molecular events involving various cell types, growth factors, and cytokines that collectively work to restore tissue integrity. While acute wounds can follow a trajectory leading to full regeneration (restitutio ad integrum), the challenges posed by chronic wounds are primarily associated with inadequate therapeutic interventions and suboptimal management strategies, which hinder effective healing. Therefore, considerable research efforts are directed toward developing advanced wound care therapies aimed at minimizing treatment costs, enhancing patient comfort, and improving scar resolution. Wound care approaches are broadly categorized into conventional and regenerative treatments. Conventional therapies typically result in scar formation, often with compromised functional and aesthetic outcomes. [1,2]

Wounds

Globally, it is estimated that approximately six million individuals are affected by chronic wounds. [3–7] A wound is defined as a physical disruption of tissue integrity due to mechanical, chemical, or thermal insults. [8–11] Effective wound management is essential to re-establish the anatomical and functional integrity of the skin. The acute wound healing process is a complex cascade of tightly regulated cellular and biochemical events, modulated by endocrine and paracrine factors. [12–14] This process can be divided into three or four temporally overlapping but distinct stages: the hemostasis

phase, the inflammatory phase, the proliferative phase (characterized by granulation tissue formation and collagen synthesis), and the remodeling phase, which determines the mechanical strength and appearance of the healed tissue. [15–19]

Classification of Wounds

Acute Wounds

Acute wounds represent a significant public health concern, affecting an estimated 11 million individuals annually in the United States and resulting in approximately 300,000 hospital admissions. [20,21] The healing of acute wounds is a highly regulated process involving platelets, keratinocytes, immune cells, microvascular endothelial cells, and fibroblasts, all contributing to a predictable restoration of tissue architecture. [22,23] The repair process progresses through four overlapping stages: coagulation, inflammation, proliferation, and tissue remodeling or scar formation.

Chronic Wounds

Unlike acute wounds, chronic wounds fail to proceed through the normal healing phases within a predictable timeframe, often requiring more than 12 weeks for resolution. These wounds are characterized by persistent infection, sustained inflammation, delayed epithelialization, and the presence of antibiotic-resistant microbial populations. [24,25]

Open Wounds

Open wounds involve a breach in the skin that exposes underlying tissues. These wounds are classified based on their etiology:

- **Incised wounds**: Clean cuts typically resulting from surgical procedures.
- **Lacerations**: Irregular tears in the skin caused by sharp or blunt trauma.
- **Abrasions**: Superficial injuries caused by friction against a rough surface.
- **Avulsions**: Traumatic injuries involving the forcible separation of tissue, as seen in amputations.
- **Punctures**: Deep, narrow wounds resulting from sharp objects such as nails or splinters.
- **Contusions**: Blunt-force trauma resulting in underlying tissue damage without skin rupture.
- **Penetrating wounds**: Injuries where an object enters the body through the skin.
- **Gunshot wounds**: Traumatic injuries caused by bullets or similar projectiles. [26]

Closed Wounds

In closed wounds, the skin remains intact, but underlying tissues are damaged. These include:

- **Hematomas**: Localized collections of blood beneath the skin due to vascular injury.
- **Crush injuries**: Result from prolonged or intense compressive force applied to tissues. [27]

Physiology of Wound Healing

Wound healing is a dynamic and highly orchestrated biological process aimed at restoring the structural and functional integrity of damaged skin. This process involves the interaction of various cellular populations and molecular mediators across four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. [27,28] The correct initiation, sequence, timing, and duration of each phase are essential for successful healing. Disruption in any phase may lead to impaired healing or chronic wound formation. [29] These phases are interdependent and continuous, with each stage influencing the progression and efficacy of the next. In acute wounds, this process typically proceeds without complications; however, chronic wounds often experience a prolonged inflammatory phase, delaying progression to later stages. [30–32]

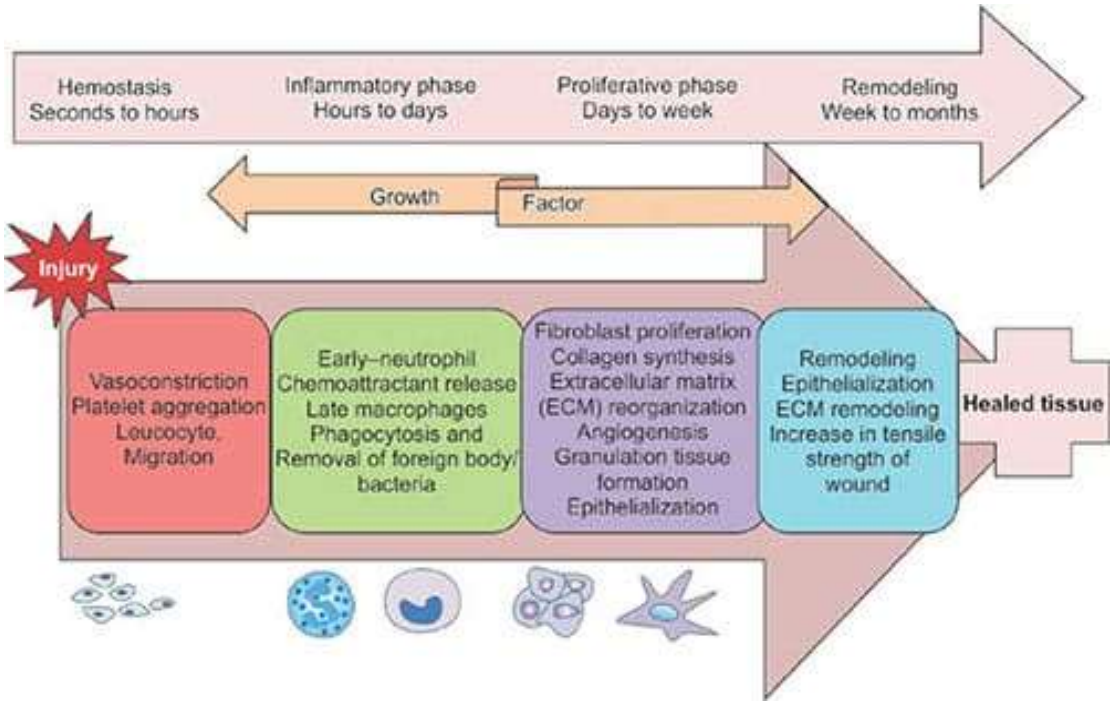

Figure no.1Distinct and overlapping phases of wound healing[33]

Hemostasis Phase

Hemostasis is the initial physiological response to vascular injury and occurs immediately following trauma. It involves a tightly regulated sequence of events designed to arrest bleeding and initiate tissue repair. The process is generally divided into three phases: vasoconstriction, primary hemostasis, and secondary hemostasis. Platelets and fibrinogen are key components in this phase. Under normal physiological conditions, endothelial cells form a non-thrombogenic barrier that prevents platelet activation. However, upon injury, this barrier is compromised, allowing circulating platelets to adhere to exposed extracellular matrix proteins and become activated. [34–37]

Fibrinogen, synthesized by hepatocytes and released into circulation, plays a critical role by being converted into fibrin fibers during clot formation. In addition to fibrin, other glycoproteins such as fibronectin, vitronectin, and thrombospondin contribute to the formation of a stable and insoluble clot (eschar), which not only physically seals the wound but also serves as a provisional matrix that supports cellular infiltration, prevents microbial invasion, and concentrates cytokines and growth factors at the injury site. [38–40].To prevent pathological thrombosis, anticoagulant mechanisms are activated once a sufficient clot is established. These include prostacyclin-mediated inhibition of platelet aggregation, antithrombin III inhibition of thrombin, and degradation of clotting factors V and VIII by activated protein C. [41] Concomitantly, platelet-derived growth factor (PDGF) promotes the proliferation of vascular smooth muscle and endothelial cells, thereby initiating vascular repair. Given the limited proliferative capacity of mature endothelial cells, endothelial progenitor cells are also recruited to aid in revascularization. [42–43]

Inflammation Phase

The inflammatory phase begins within the first 24 hours of injury and may persist for up to 48 hours. It is characterized by a rapid infiltration of leukocytes to the wound site, leading to classical signs of inflammation such as erythema and edema. Tissue-resident immune cells, including mast cells, Langerhans cells, and γδ T-cells, are activated early, releasing cytokines and chemokines that orchestrate the recruitment of additional immune cells. [44]. Key chemoattractants such as transforming growth factor-beta (TGF-β), complement proteins (C3a, C5a), bacterial peptides (e.g., formylmethionyl peptides), and platelet-derived products contribute to neutrophil recruitment within 24 to 36 hours of injury. [45] Neutrophils undergo margination and adhere to the vascular endothelium before transmigrating to the wound site. [46–47] They initiate phagocytosis of microbial and necrotic debris and produce reactive oxygen species (ROS), nitric oxide (NO), and proteolytic enzymes. [48–49]. Neutrophils also deploy neutrophil extracellular traps (NETs)—networks of decondensed chromatin associated with antimicrobial proteins—to immobilize or kill pathogens extracellularly. [50–51] In addition to microbial clearance, neutrophils secrete pro-inflammatory cytokines that sustain the inflammatory response and recruit macrophages, T-cells, and additional neutrophils to the site. [48]

Proliferation Phase

Following the resolution of hemostasis and initial immune response, the wound healing process enters the proliferative phase, focused on tissue regeneration and extracellular matrix (ECM) deposition. [52]

Fibroplasia:

Fibroblasts begin migrating to the wound site around day 3 post-injury, stimulated by cytokines secreted by lymphocytes and macrophages. [53] These fibroblasts synthesize and deposit ECM proteins, including type I and III procollagen, fibronectin, and hyaluronic acid. This ECM serves as a scaffold for further cellular migration and tissue organization. By day 7, fibroblasts differentiate into myofibroblasts, which contribute to wound contraction. [54]

Angiogenesis:

Revascularization of the injured site is critical for providing nutrients and oxygen. Angiogenesis is driven by endothelial cell proliferation and migration, facilitated by growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and TGF-β, as well as cues from the ECM. [55–56]

Maturation and Remodeling Phase

The final stage of wound healing involves remodeling of the ECM and restoration of tissue integrity. During this phase, type III collagen initially deposited by fibroblasts is replaced by the stronger, more organized type I collagen. This transformation strengthens the tissue, allowing it to regain up to 80% of its original tensile strength by three months post-injury, although full restoration is rarely achieved. [57]. Myofibroblasts, characterized by the expression of alpha-smooth muscle actin, are responsible for wound contraction, reducing wound size and limiting the volume of granulation tissue required for closure. [58] However, contraction can become problematic in areas where mobility is limited, necessitating the use of skin grafts or flaps to prevent contractures.Simultaneously, keratinocytes from the wound margins migrate to re-epithelialize the wound bed, restoring the epidermal barrier. Variations in migration rates facilitate both stratification and full epithelial thickness restoration. [59] The resulting scar tissue, initially hypervascularized and collagen-rich, appears red, raised, and firm, typically remodeling over 6–9 months to become flatter, paler, and less vascularized. [60]

Factors Contributing to Delayed Wound Healing

Wound healing may be impeded by a range of local and systemic factors:

Local Factors

- **Oxygenation:**
  Adequate oxygen supply is essential for angiogenesis, collagen synthesis, epithelialization, and overall wound contraction. Hypoxia, commonly associated with ischemic conditions, disrupts these processes and contributes to the development of chronic or ulcerated wounds. [61]

- **Infection:**
  Infection prolongs the inflammatory phase and increases the production of pro-inflammatory cytokines such as interleukin-1 (IL-1) and tumor necrosis factor-alpha (TNF-α). Elevated levels of matrix metalloproteinases (MMPs) degrade ECM components, while their natural inhibitors are reduced, further impairing tissue repair. [62]

Systemic Factors

- **Age:**
  Aging leads to epidermal thinning and systemic metabolic changes. The inflammatory response in elderly individuals is compromised, with reduced leukocyte chemotaxis, impaired macrophage phagocytosis, and diminished cytokine/growth factor secretion. Consequently, fibroblast activity, angiogenesis, re-epithelialization, and collagen remodeling are significantly delayed. [63–65]

- **Sex Hormones:**

  Estrogens exhibit anti-inflammatory properties by reducing leukocyte infiltration and cytokine production. They also promote endothelial and keratinocyte proliferation, thus enhancing re-epithelialization and angiogenesis. Conversely, androgens such as testosterone and 5α-dihydrotestosterone exert pro-inflammatory effects, prolonging inflammation and impairing healing. [66–67]

- **Diabetes Mellitus:**

  Hyperglycemia impairs neutrophil function, cytokine signaling, collagen synthesis, and angiogenesis. Maintaining blood glucose levels close to normal significantly improves healing outcomes. Patients with HbA1c levels below 7.1% exhibit faster wound closure rates. [68]

- **Venous Insufficiency:**

  Chronic edema due to venous hypertension results in capillary leakage of fibrinogen into the dermis, forming fibrin cuffs that impede oxygen and nutrient diffusion. This induces tissue hypoxia, suppresses fibroblast and epithelial cell activity, and promotes anaerobic infections. [68]

- **Smoking:**
  Cigarette smoke contains over 4,000 harmful chemicals. Nicotine induces vasoconstriction and platelet aggregation; carbon monoxide binds to hemoglobin, reducing oxygen delivery; and hydrogen cyanide interferes with oxidative metabolism. These effects collectively impair oxygenation and delay wound repair. [69]

Obesity

Obesity affects approximately one-third of the adult population in the United States and represents a significant public health concern. [70] This condition is associated with numerous physiological impairments that can negatively impact wound healing. The increased adipose mass in obese individuals places

a greater demand on the cardiovascular system to supply oxygenated blood to peripheral tissues. When cardiac output is insufficient to meet this demand, tissue ischemia may occur, leading to cellular hypoxia, necrosis, and delayed wound repair. [71]. Additionally, the accumulation of excess adipose tissue restricts diaphragmatic movement and limits thoracic expansion, often resulting in a state of chronic hypoventilation. This respiratory compromise decreases vital lung capacity and arterial oxygenation. [72] As a consequence, tissue oxygenation around the wound site is impaired, which inhibits the function of fibroblasts and disrupts oxygen-dependent cellular processes such as collagen synthesis and angiogenesis—both critical to effective wound healing. [72,73]

Treatment:

- **Synthetic Treatment** –

Tabel no.1 Synthetic cream

S.No	Types of Cream	Active substance
1	Silver sulphadiazine cream	Silver nitrate,sulfonamide sodium sulphadiazine
2	Phenytoin cream	100mg Phenytoin sodium,lactose monohydrate,confectioner sugar,talc, magnesium stearate
3	Dexpanthenol	20.0%Dexpanthenol 20.0%Argania spinosa kernel oil,20.0%,polyglyceryl-3-polyricinoleate,30.0%Emolient,50.0%Emulsifier and surfactants,5.0%Antioxidant,5.0%Preservatives by weight of total composition.
4	Framycetin cream	Emulsifiers,waxymaterial,cosolvent,acids,preservatives,buffering agent antioxidants chelating agent
5	Cetuximab	Chimeric monoclonal lgG1 antibody produce in a mammalian cell line by recombinant DNA technology

- **Herbal treatment**

Tabel no.2

Medicinal plants and their components for wound healing applications

S. no.	**Medicinal plants**	**Part used**	**Metabolites**	**Uses**	**Reference**
1.	Turmeric (Curcuma longa)	Rhizomes	Curcumin, vitamin A, proteins	Chronic wound healing	[75]
2.	Liquorice (Glycyrrhiza glabra)	Roots	Glycyrrhizin, glycyrrhetinic	Acute/chronic wound healing	[76]
3.	Centella (Centella asiatica)	Leaves	Asiatic acid, asiaticoside madecassoside, madecassic acid	Incision wound healing	[77,78]
4.	Carbonal (Mimosa tenuiflora)	Stem	Mimosine (an alkaloid), sitosterol, amino acids, linoleic acid, tannins, polyphenols, and oleic acid	Chronic wound healing	[79]
5.	Honey (Apis mellifera)	Secretion from hive	5-Hydroxyimidacloprid, 4,5-dihydroxyimidacloprid, desnitroimidacloprid, 6-chloronicotinic acid, olefin	Acute wound healing	[80]
6.	Theaceae (Camellia pubipetala)	Leaves	Flavonoids, theanine and caffeine	Excision wound healing	[81]
7.	Forest Champa (Spermadictyon suaveolens)	Roots	Triterpenes, sesquiterpenes, alkaloids	Chronic wound healing	[82]
8.	Neem (Azadirachta indica)	All portions	Azadirachtin, azadirone, nimbin, nimbidin, nimbinin	Open wound healing	[83]

9.	Sesame (Sesamum indicum L.)	Seeds	Metronidazole, E and C vitamins, sesamolinol, sesamol, sesaminol, sesamolin	Acute/chronic wound healing	[84]
10.	Trumpet tree (Cecropia peltata)	Leaves	Flavanoids, terpenes phenols, alkaloids, sterols, waxes, fats, tannins, gums, resin acids	Closed wound healing	[85]
11.	Kencur (Kaempferia galanga)	Rhizomes	Amino acids, protein, carbohydrate, alkaloids, steroids, cholesterol, cardiac glycosides,	Incision wound healing	[86]
12.	Druce (Prosopis cineraria)	Leaves	Patulitrin, diketones, spicigerin, β-sitosterol, stigmasterol, hentriacontane, octasanol, and prosogerin A, B, C, and D	Closed wound healing	[79]
13.	Maidenhair (Ginkgo biloba)	Leaves and seeds	Flavonoids, lactones, and ginkgolic acid	Closed wound healing	[87]
14.	Indian mulberry (Morinda citrifolia)	Leaves and fruit	Anthraquinones, steroid, phenol, tannin, and terpenoids	Closed wound healing	[88]
15.	Club Moss (Lycopodium serratum)	Spores and whole fern	Alkaloids, steroids, tannins	Acute/chronic wound healing	[89]
16.	Madagascar periwinkle (Catharanthus roseus)	Leaves	Monoterpenoids alkaloids, vinblastine, Vincristine	Acute/chronic wound healing	[90]
17.	Asthma Weed (Euphorbia hirta)	Leaves	Saponins, tannins, flavonoids, alkaloids, glycosides	Chronic wound healing	[91]
18.	Red sandalwood (Pterocarpus santalinus)	Bark wood	Santalin A and B, savinin, calocedrin, pterolinus K and L, and pterostilbenes	Acute/chronic wound healing	[92]
19.	Lawsonia alba (Lawsonia inermis)	Leaves and roots	Coumarins, naphthoquinone, flavonoids, sterols, triterpene, and xanthones	Chronic wound healing	[93]
20.	Jandi or Ghaf (Prosopis cineraria)	Leaves and pods	Patulitrin, diketones, spicigerin, β-sitosterol, stigmasterol, hentriacontane, octasanol, and prosogerin A, B, C, and D	Cutaneous wound healing	[94]
21.	Aloe (Aloe vera)	Leaves	Anthaquinone, C and E vitamins, amino acids	Open wound healing	[95,96]
22.	Bay (Sphagneticola trilobata)	Leaves	Flavonoids, terpenoids, alkaloid, and saponin	Incision wound healing	[97,98]
23.	Adusa (Adhatoda vasica)	Leaves	Flavonoids, tannins	Excision wound healing	[99]
24.	Humble plant (Mimosa pudica)	Whole plant	Mimosine (an alkaloid), sitosterol, amino acids, linoleic acid, tannins, polyphenols, and oleic acid	Excision wound healing	[79]
25.	Papaya (Caricapapaya)	Latex, fruit	Papain	Diabetic, burn, soft tissue wounds	[100]
26.	Jungle flame (Ixora coccinea)	Root,Leaves	Sesquiterpenes, Triterpenes, geranyl acetate, ursolicacid	Cutaneous, excision	[101]

27.	Betle Piper (Piper betle L.)	Leaves	Phenolic complex, betal-phenol, chavicol	Excision wound healing	[102]
28.	common wireweed (Sida acuta)	Whole plant	Alkaloids, terpenes, and flavonoids	Excision, incision wound healing	[103]
29.	Drumstick tree (Moringa oleifera)	Leaves	Vitamins vicenin-2, beta-carotene, phenolics, amino acid,	Excision, incision wound healing	[104]
30.	Indian olive (Olea europaea)	Leaves, oil	Biophenolics, Oleuropein secoiridoid, Luteolin	Incision wound healing	[105]

Conclusion: -

Skin wound healing is a complex, essential biological process crucial for maintaining tissue integrity and systemic homeostasis. It involves a finely regulated sequence of cellular and molecular events orchestrated across four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. Successful healing requires timely progression through each phase; disruptions can lead to chronic, non-healing wounds. Acute wounds follow a predictable course, whereas chronic wounds are often hindered by persistent inflammation, infection, or impaired regeneration. Multiple local (e.g., oxygenation, infection) and systemic (e.g., diabetes, aging, obesity) factors significantly influence healing outcomes. Conventional therapies often result in scar formation, while regenerative approaches aim to restore normal structure and function. Both synthetic and herbal agents are explored for their therapeutic potential. A thorough understanding of wound biology is essential for designing effective treatments. Advancements in wound care must consider the multifactorial nature of impaired healing. Targeted strategies are especially vital in addressing chronic wound management

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