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A review on physiological stages of wound healing

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Abstract

A wound is defined as a disruption in the normal anatomical structure and physiological function of body tissues caused by physical, biological, thermal, or chemical injury. Wound healing restores tissue integrity through four overlapping phases: hemostasis, inflammation, proliferation, and remodeling. It is regulated by cells, cytokines, growth factors, and extracellular matrix proteins. Adequate nutrition, oxygenation, blood flow, and immune function are required for normal repair. Infection, diabetes, malnutrition, vascular insufficiency, and aging can disrupt healing and cause chronic wounds.

Keywords: Wound Healing; Inflammation; Tissue Injury; Hemostasis.

1. Introduction

Wound Healing is a complex and coordinated physiological process through which damaged tissues are repaired following injury. The process involves interactions among inflammatory cells, extracellular matrix proteins, cytokines, enzymes, vascular components, and growth factors that collectively restore tissue integrity and function [1].

The skin serves as the largest organ of the body and acts as a protective barrier against microbial invasion, dehydration, ultraviolet radiation, and environmental injury. Once tissue integrity is disrupted, several physiological mechanisms are activated to restore normal tissue architecture and maintain homeostasis [2].

Wound healing occurs through four overlapping but coordinated phases: hemostasis, inflammation, proliferation, and remodeling. These phases involve cellular migration, proliferation, angiogenesis, extracellular matrix deposition, and tissue remodeling [3]. Several pathological conditions such as diabetes mellitus, vascular insufficiency, infection, hypoxia, obesity, and malnutrition may impair wound healing and result in chronic wound formation [4].

The physiology of wound healing has become an important area of study in Physiology because impaired wound repair contributes significantly to morbidity, prolonged hospitalization, reduced quality of life, and increased healthcare costs worldwide [5].

1.1. Overview of the Healing Process

Normal wound healing aims to restore barrier function and tissue strength, though healed tissue never fully regains pre-injury strength. The process begins immediately after injury and may take years to complete [6]. The stages of wound healing after tissue injury include:

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(A) Hemostasis (1st stage): Following tissue injury, blood vessels constrict, the coagulation cascade initiates, and activated platelets form a clot to limit bleeding.(B) Inflammation (2nd stage): Chemoattractant (e.g., chemokines and cytokines) released from platelets and other cells/tissues recruit neutrophils and macrophages to the local wound environment to clear bacteria and debris. These recruited leukocytes, in turn, secrete chemoattractants that result in the recruitment of keratinocytes and fibroblasts. (C) Proliferation (3rd stage): Proliferation and differentiation of fibroblast cell populations proliferate and differentiate, resulting in collagen synthesis and deposition. In parallel, granulation tissue is formed as the wound microenvironment begins to undergo neovascularization. (D) Remodeling (4th stage): The wound's fibrotic extracellular matrix remodels over months to years into mature scar tissue [7].

1.2. Types of Wounds

- Open Wounds: Open wounds involve visible breaks in the skin or mucous membrane, exposing underlying tissues to the external environment. Examples include abrasions, puncture wounds, lacerations, and avulsions [5].
- Closed Wounds: Closed wounds occur without visible disruption of the skin surface and include hematomas, contusions, and crush injuries [1].
- Acute Wounds: Acute wounds are defined as sudden disruptions of tissue integrity caused by trauma, surgery, or burns, which proceed through orderly phases of hemostasis, inflammation, proliferation, and remodeling to achieve closure within weeks [6,8].
- Acute wounds progress through the normal stages of healing within an expected timeframe and usually heal without major complications [3].
- Chronic Wounds: Chronic wounds fail to progress through normal healing processes because of persistent inflammation, infection, poor circulation, or metabolic diseases [4].

Chronic wounds impose a substantial psychological and cognitive burden beyond their clinical morbidity. [9] reviewed evidence showing that individuals with chronic wounds experience elevated rates of anxiety, depression, and cognitive impairment, mediated by persistent pain, malodor, exudate, and restricted mobility. These factors contribute to social isolation, reduced autonomy, and diminished quality of life across physical, emotional, and social domains.

1.3. Causes of Wounds

[10] reported that injuries constitute a significant cause of morbidity among patients presenting to Nigerian tertiary hospitals. In their retrospective study conducted at the National Orthopaedic Hospital, Enugu, road traffic accidents were identified as the leading cause of injuries, accounting for the majority of trauma cases managed during the study period. The authors further observed that young adults within the economically productive age group were the most commonly affected population. These injuries frequently resulted in tissue damage and wounds that required effective physiological healing processes for restoration of tissue integrity and function.

Asides road accidents, other causes of wounds include: burns from fire, chemical exposure, radiation exposure (x-ray, UV rays), pathological causes (e.g. diabetic ulcers, cancer-related ulcers,), insect bites, surgical incisions [10].

1.4. History of Wound Care

Wound care has evolved from empirical practices in ancient civilizations to a science grounded in physiology and microbiology. [11] traces early wound management to ancient Egypt, where papyrus records such as the Edwin Smith Papyrus (~1600 BCE) documented wound assessment, irrigation, and suturing techniques. Hippocrates (~400 BCE) introduced principles of wound cleansing, positioning, and the importance of inflammation as part of healing, while Galen (2nd century CE) emphasized debridement and the use of wine and honey as antiseptics. The Middle Ages saw stagnation in wound care due to limited anatomical knowledge, but the Renaissance revived surgical techniques, with Ambroise Paré rejecting cauterization with boiling oil and advocating for gentler wound dressings in the 16th century. The 19th century marked a turning point with Joseph Lister's introduction of antisepsis using carbolic acid, which dramatically reduced postoperative infection and mortality. Modern wound care has since shifted toward understanding cellular and molecular mechanisms, moist wound healing, and advanced therapies such as growth factors, bioengineered skin, and negative pressure wound therapy [11].

1.5. Importance of Wound Healing

Wound healing is essential for restoring tissue integrity, maintaining physiological function, and preserving homeostasis. Effective wound healing prevents excessive blood loss, microbial invasion, and tissue destruction [12]. Knowledge of wound healing physiology is important in trauma care, surgery, burn management, and treatment of chronic ulcers. Advances in regenerative medicine and tissue engineering also depend on understanding wound repair

mechanisms [13].Impaired wound healing contributes significantly to prolonged hospitalization, emotional distress, disability, and increased healthcare expenditure worldwide [5].

1.6. Physiology of Wound Healing

Wound healing is a coordinated physiological process involving vascular, cellular, biochemical, and molecular mechanisms aimed at restoring tissue integrity after injury. The process occurs in four overlapping phases: hemostasis, inflammation, proliferation, and remodeling [1].

1.6.1. Hemostasis Phase

Hemostasis is the immediate response to vascular injury and the first phase of wound healing. Its purpose is to stop bleeding, prevent blood loss, and create a provisional matrix that initiates repair [14]. It occurs within seconds to minutes and involves coordinated vascular, platelet, and coagulation events.

1.6.2. Steps to normal Hemostasis

- Vascular spasm: Injury triggers reflex vasoconstriction of the damaged vessel to reduce blood flow.
- Platelet plug formation: Exposed subendothelial collagen binds von Willebrand factor. Platelets adhere via glycoprotein receptors, become activated (activated platelets release mediators such as thromboxane A2 and adenosine diphosphate that promote platelet aggregation and clot stabilization), and aggregate to form a temporary platelet plug.
- Coagulation cascade: Tissue factor initiates the extrinsic pathway, leading to thrombin generation. Thrombin converts fibrinogen to fibrin, which cross-links to stabilize the platelet plug into a definitive clot.
- Clot retraction and repair initiation: The fibrin clot contracts and releases platelet-derived growth factors, chemokines, and cytokines that recruit inflammatory cells and fibroblasts to the wound bed [14].

1.7. Inflammatory Phase

The inflammatory phase begins shortly after hemostasis and involves migration of inflammatory cells into the wound site to eliminate pathogens and remove damaged tissue. Neutrophils are the first inflammatory cells to arrive, and their primary functions include phagocytosis of bacteria and clearance of cellular debris. Macrophages subsequently dominate the wound environment and regulate the transition to repair by secreting cytokines and growth factors [12].

1.7.1. Steps in Inflammatory Phase

- Vascular permeability increases and neutrophils are the first inflammatory cells recruited to the wound site, where they cause phagocytosis of bacteria and removal of cellular debris.
- Neutrophils remain for 2–5 days and release cytokines such as TNF-α, IL-1β, and IL-6 to amplify the inflammatory response before undergoing apoptosis.
- Monocytes enter the wound approximately 3 days after injury and differentiate into macrophages, which subsequently dominate the wound environment.
- Early macrophages adopt a pro-inflammatory phenotype to sustain microbial clearance, then shift to an anti-inflammatory phenotype that secretes TGF-β, VEGF, and IL-10 to resolve inflammation and promote tissue repair.
- Macrophages clear apoptotic neutrophils and this clearance triggers the release of pro-resolving mediators that signal the transition to the proliferative phase. The inflammatory phase typically lasts several days and resolves by day 5–7 in acute wounds [15].

1.8. Proliferation Phase

The proliferative phase follows resolution of inflammation and is characterized by formation of granulation tissue, angiogenesis, and re-epithelialization. Fibroblasts migrate into the wound and synthesize collagen and extracellular matrix to form the structural basis of new tissue. Endothelial cells proliferate to create new blood vessels, restoring perfusion to the healing area. Keratinocytes migrate across the wound surface to restore the epithelial barrier through re-epithelialization. Myofibroblasts contribute to wound contraction, reducing the size of the defect. This phase typically lasts several weeks in acute wounds [2].

1.9. Remodelling/Maturation Phase

The remodeling or maturation phase begins weeks after injury and can last months to years as the wound gains strength. Collagen type III deposited during the proliferative phase is gradually replaced by collagen type I, which increases the

tensile strength of the scar. Excess fibroblasts, myofibroblasts, and endothelial cells undergo apoptosis, leading to regression of granulation tissue and blood vessels. The extracellular matrix is reorganized and cross-linked, resulting in a mature scar that is less cellular and less vascular than normal skin [16].

1.10. Factors Affecting Wound Healing.

[17] categorize factors influencing repair as local and systemic.

1.10.1. Local factors:

- Oxygenation: Hypoxia impairs fibroblast proliferation, collagen synthesis, angiogenesis, and bacterial killing, delaying repair.
- Infection: Microbial replication prolongs inflammation, elevates pro-inflammatory cytokines and MMPs, and degrades growth factors, resulting in chronic non-healing wounds.
- Foreign body: Presence of foreign material sustains inflammation and prevents normal progression of repair.
- Venous sufficiency: Inadequate venous return contributes to ischemia and impaired tissue oxygenation in chronic wounds.

1.10.2. Systemic factors:

- Age and gender: Aging causes delayed T-cell infiltration, reduced macrophage function, and slower re-epithelialization, collagen synthesis, and angiogenesis.
- Sex hormones: Estrogen deficiency in aged females and hormonal changes in aged males influence the rate of acute wound healing.
- Psychological stress: Stress suppresses inflammatory and immune function through neuroendocrine pathways, impairing wound closure.
- Ischemia: Reduced blood flow limits oxygen and nutrient delivery, creating a hypoxic wound environment that delays healing.
- Diseases: Diabetes, keloids, fibrosis, hereditary healing disorders, jaundice, and uremia disrupt cellular activity and matrix remodeling.
- Obesity: Chronic inflammation and altered metabolism in fat tissue disrupt macrophage and fibroblast function, reduce new blood vessel formation, and slow tissue repair.
- Medications: Glucocorticoid steroids, NSAIDs, and chemotherapy inhibit inflammation and fibroblast activity.
- Alcoholism and smoking: Reduce tissue perfusion, decrease oxygen delivery, and impair immune function, slowing closure.
- Immunocompromised conditions: Cancer, radiation therapy, and AIDS weaken immune response and delay repair.
- Nutrition: Deficiencies in protein, vitamins, and trace elements limit collagen formation and immune competence.

2. Cellular and biomedical mechanisms involved in wound healing

2.1. Cells Involved in Wound Healing.

Wound healing is a highly coordinated physiological process involving interactions among inflammatory cells, connective tissue cells, vascular cells, extracellular matrix proteins, cytokines, chemokines, and growth factors. Cellular activities during wound healing are tightly regulated to ensure tissue repair, restoration of barrier function, and maintenance of homeostasis [1].

Different cells participate at different stages of healing, although many function simultaneously throughout the repair process. The major cells involved in wound healing include platelets, neutrophils, macrophages, fibroblasts, keratinocytes, endothelial cells, mast cells, and lymphocytes.

- **Platelets:** Platelets are the first cells activated immediately after tissue injury. Their primary role is to initiate hemostasis and prevent excessive blood loss through clot formation. Platelets adhere to exposed collagen fibers at the site of vascular injury and aggregate to form a temporary platelet plug [5].

Beyond hemostasis, platelets play important regulatory roles during wound healing by releasing several bioactive substances and growth factors such as platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), epidermal growth factor (EGF), and vascular endothelial growth factor (VEGF). These mediators stimulate

inflammatory cell recruitment, fibroblast proliferation, angiogenesis, extracellular matrix deposition, and tissue regeneration [18].

Platelets also release chemokines and cytokines that attract neutrophils and macrophages into the wound area, thereby initiating the inflammatory phase of healing.

- Neutrophils: Neutrophils are the earliest inflammatory cells recruited to the wound site, usually appearing within hours after injury. Their primary function is to provide antimicrobial defense through phagocytosis of microorganisms and removal of necrotic tissue debris [12].

Neutrophils produce reactive oxygen species, proteolytic enzymes, and antimicrobial peptides that destroy invading pathogens and reduce microbial contamination. They also release inflammatory mediators that amplify the inflammatory response and facilitate recruitment of additional immune cells.

Although neutrophils are essential for wound sterilization, excessive neutrophil activity may prolong inflammation and contribute to tissue damage and chronic wound formation.

- Macrophages: Macrophages are considered one of the most important regulatory cells in wound healing because they coordinate the transition from inflammation to tissue repair. Macrophages differentiate from circulating monocytes that migrate into the wound site during the inflammatory phase [19].

Macrophages perform several physiological functions during wound healing. These include: phagocytosis of microorganisms and dead cells, regulation of inflammation, stimulation of fibroblast, promotion of angiogenesis, and activation of extracellular matrix synthesis.

Macrophages release numerous cytokines and growth factors such as TGF-β, VEGF, fibroblast growth factor (FGF), and tumor necrosis factor-alpha (TNF-α), which regulate tissue regeneration and remodeling.

Two major macrophage phenotypes are recognized during wound healing:

- M1 macrophages, which promote inflammation and microbial destruction,
- and M2 macrophages, which support tissue repair and remodeling.
- Failure of macrophage transition from the inflammatory phenotype to the reparative phenotype contributes significantly to impaired wound healing and chronic ulcers[1].

- Fibroblasts: Fibroblasts are connective tissue cells responsible for synthesis of collagen and extracellular matrix proteins necessary for tissue strength and structural support. Fibroblasts migrate into the wound site during the proliferative phase under the influence of growth factors such as PDGF and TGF-β.

Fibroblasts synthesize collagen, fibronectin, proteoglycans, elastin, and glycosaminoglycans. These extracellular matrix components provide mechanical stability and support tissue repair. Fibroblasts also contribute to wound contraction through differentiation into myofibroblasts. Myofibroblasts contain contractile proteins that pull wound edges together and reduce wound size.

Excessive fibroblast activity may lead to pathological scar formation such as hypertrophic scars and keloids [18].

- Keratinocytes: Keratinocytes are the major epithelial cells of the epidermis and are primarily responsible for epithelialization during wound healing. Following injury, keratinocytes at the wound margins become activated and migrate across the wound surface to restore epidermal continuity [5].

Keratinocyte migration is stimulated by growth factors such as EGF and KGF. During migration, keratinocytes undergo cytoskeletal reorganization and detach from neighboring cells to move across provisional extracellular matrix proteins.

Keratinocytes also produce cytokines, chemokines, and antimicrobial peptides that contribute to immune defense and regulation of inflammation.

Successful epithelialization is essential for restoration of skin barrier function and prevention of microbial invasion.

- Endothelial Cells: Endothelial cells are specialized vascular cells responsible for angiogenesis during wound healing. Angiogenesis refers to formation of new blood vessels from pre-existing vasculature and is essential for oxygen and nutrient delivery to healing tissues [13].Newly formed blood vessels improve oxygen delivery, enhance nutrient supply, facilitate waste removal, and support cellular metabolism during tissue repair. Impaired angiogenesis contributes significantly to chronic wound formation, especially in diabetic and ischemic wounds.

- Mast Cells: Mast cells are inflammatory cells that participate in early inflammatory responses during wound healing. They release histamine, serotonin, proteases, and inflammatory cytokines that increase vascular permeability and facilitate recruitment of inflammatory cells into the wound area [12].Histamine released by mast cells promotes vasodilation and enhances movement of plasma proteins and leukocytes into damaged tissues. Mast cells also influence fibroblast activity, angiogenesis, and extracellular matrix remodeling.

- Lymphocytes: Lymphocytes contribute mainly during the later stages of wound healing by regulating immune responses and tissue remodeling. T lymphocytes release cytokines that modulate macrophage activity, fibroblast proliferation, and collagen synthesis. B lymphocytes participate in humoral immune responses and antibody production against invading pathogens.

2.2. Growth Factors Involved in Wound Healing.

Growth factors are biologically active polypeptides that regulate cellular proliferation, migration, differentiation, angiogenesis, collagen synthesis, extracellular matrix deposition, and tissue remodeling during wound healing. These molecules function as signaling mediators that coordinate communication among inflammatory cells, fibroblasts, endothelial cells, keratinocytes, and other tissue cells [18].Growth factors are released by platelets, macrophages, fibroblasts, keratinocytes, endothelial cells, and inflammatory cells throughout different phases of wound healing.

- Platelet-Derived Growth Factor (PDGF): Platelet-derived growth factor is one of the earliest growth factors released following tissue injury. PDGF is secreted mainly by platelets and macrophages during the inflammatory phase of wound healing [1]. PDGF stimulates fibroblast proliferation, collagen synthesis, extracellular matrix deposition, and migration of inflammatory cells into the wound site. PDGF also promotes angiogenesis and granulation tissue formation, making it essential for tissue regeneration.

- Transforming Growth Factor-Beta (TGF-β): Transforming growth factor-beta is a multifunctional cytokine involved in regulation of inflammation, extracellular matrix synthesis, and scar formation. TGF-β is produced by platelets, macrophages, fibroblasts, and keratinocytes [20]. TGF-β stimulates fibroblast migration, collagen synthesis, wound contraction,
- and extracellular matrix production. The growth factor also suppresses excessive inflammatory responses and regulates tissue remodeling. Excessive TGF-β activity is associated with pathological scar formation such as hypertrophic scars and keloids.
- Vascular Endothelial Growth Factor (VEGF): VEGF is the principal growth factor responsible for angiogenesis during wound healing. VEGF stimulates endothelial cell proliferation, migration, and formation of new blood vessels within granulation tissue [20].New blood vessel formation increases oxygen and nutrient supply to healing tissues and enhances cellular metabolism necessary for tissue repair. Reduced VEGF activity contributes to impaired angiogenesis and chronic wound formation.
- Epidermal Growth Factor (EGF): Epidermal growth factor stimulates keratinocyte proliferation, migration, and epithelialization during wound healing [5].EGF accelerates restoration of epidermal integrity by promoting re-epithelialization and cellular differentiation. The growth factor also enhances fibroblast activity and granulation tissue formation.
- Fibroblast Growth Factor (FGF): Fibroblast growth factors regulate fibroblast proliferation, collagen synthesis, angiogenesis, and granulation tissue formation. FGFs are produced by macrophages, endothelial cells, and fibroblasts [19].FGF enhances wound contraction and tissue remodeling while supporting endothelial cell proliferation during angiogenesis.
- Insulin-Like Growth Factor (IGF): Insulin-like growth factor promotes protein synthesis, fibroblast proliferation, collagen production, and tissue regeneration [1].
- IGF also enhances keratinocyte migration and contributes to epithelialization during wound repair.

2.3. Keratinocyte Growth Factor (KGF)

Keratinocyte growth factor specifically stimulates keratinocyte proliferation and migration during epithelialization. KGF contributes significantly to restoration of epidermal continuity following tissue injury [5].

2.4. Hepatocyte Growth Factor (HGF)

Hepatocyte growth factor stimulates proliferation and migration of epithelial and endothelial cells during wound healing. HGF also promotes angiogenesis and tissue regeneration while reducing fibrosis [13].

- Connective Tissue Growth Factor (CTGF): Connective tissue growth factor regulates extracellular matrix deposition, fibroblast proliferation, and collagen synthesis during tissue repair [20]. CTGF contributes to granulation tissue formation and scar maturation.

2.4.1. Tumor Necrosis Factor-Alpha (TNF-α):

Tumor necrosis factor-alpha is a pro-inflammatory cytokine produced mainly by macrophages and neutrophils during early wound healing. TNF-α regulates inflammatory cell recruitment, cytokine production, and immune responses at the wound site [13]. Although TNF-α is important for antimicrobial defense, excessive TNF-α activity may prolong inflammation and impair tissue repair.

2.4.2. Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF)

GM-CSF stimulates proliferation and activation of leukocytes involved in immune defense and tissue repair. The growth factor enhances macrophage function, keratinocyte activity, and wound epithelialization [18].

GM-CSF also contributes to granulation tissue formation and tissue remodeling.

3. Pathophysiology of impaired wound healing

Impaired wound healing occurs when normal repair processes are disrupted, delayed, or incomplete, leading to chronic wounds, prolonged inflammation, excessive scarring, or infection [5]. Normal healing requires coordinated hemostasis, inflammation, proliferation, and remodeling—disruption of any phase causes delayed or abnormal repair.

3.1. Causes of Impaired Wound Healing:

- Infection: Microbial invasion prolongs inflammation, damages tissue, and delays granulation and epithelialization [4].
- Poor Blood Supply/Hypoxia: Reduced oxygen impairs collagen synthesis, angiogenesis, fibroblast activity, and immune defense.
- Diabetes Mellitus: Hyperglycemia impairs leukocyte function, angiogenesis, collagen synthesis, and fibroblast activity, causing chronic ulcers and delayed closure [1].
- Malnutrition: Protein, vitamin, and mineral deficiencies impair collagen synthesis, immunity, and regeneration; vitamin C deficiency weakens collagen and wound strength.
- Aging: Reduced cellular proliferation, collagen deposition, angiogenesis, and immune response slow healing in the elderly [13].
- Excessive Inflammation: Prolonged release of proteolytic enzymes and ROS causes tissue destruction and chronic wound formation.

3.2. Chronic Wounds

Chronic wounds are wounds that fail to progress through the normal stages of healing within an expected period. Examples include: diabetic ulcers, pressure ulcers, venous ulcers, and arterial ulcers. Chronic wounds are characterized by: persistent inflammation, impaired angiogenesis, excessive protease activity, reduced collagen deposition, and delayed epithelialization [4].

Abnormal Scar Formation

Abnormal wound healing may result in excessive scar formation.

- **Hypertrophic Scars:** Hypertrophic scars occur because of excessive collagen deposition within the wound boundary.
- **Keloids:** Keloids are abnormal scars that extend beyond the original wound margins due to excessive fibroblast proliferation and collagen synthesis [20].

Traditional Wound Management/Treatment

Traditional wound management refers to indigenous and natural healing methods used before modern wound-care technologies. Still widely practiced in Africa and other developing regions, these approaches are affordable, accessible, and culturally accepted. They focus on cleansing wounds, preventing infection, reducing inflammation and pain, and stimulating tissue repair with locally available herbs and natural substances [21]. Many of these materials have antimicrobial, antioxidant, anti-inflammatory, and regenerative properties that support wound closure.

3.3. Wound Cleansing.

Wound cleansing is one of the oldest and most important wound-care practices. It involves washing the wound surface to remove dirt, microorganisms, blood clots, necrotic tissue, and foreign material that can delay healing [5].

In traditional settings, cleansing is often done with locally available materials such as clean or warm water, salt water, herbal decoctions, plant extracts, and lime preparations. These methods help reduce microbial contamination and create an environment that supports tissue repair.

3.4. Use of Lime in Wound Treatment

Lime (Citrus aurantifolia) is used traditionally in many African communities for washing wounds. Lime contains several bioactive compounds including vitamin C, citric acid, flavonoids, limonoids, and essential oils. These compounds have demonstrated antimicrobial, antioxidant, and anti-inflammatory activity in laboratory studies [22,23].

3.5. Antimicrobial Effects of Lime

Crude extracts and oils from lime fruit show in vitro inhibition of bacteria commonly found in wounds, including Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Candida albicans. Citric acid and essential oils like d-limonene are thought to contribute to this activity. Reduced bacterial load may help prevent infection and support tissue repair

3.6. Antioxidant Effects of Lime

Lime is rich in vitamin C (which is important for collagen synthesis and stabilization during wound healing. Adequate collagen production improves tissue strength and wound closure) and flavonoids, which scavenge reactive oxygen species generated during inflammation. This antioxidant activity may help limit oxidative damage to healthy tissue during the healing process [23].

3.6.1. Honey Therapy.

Honey has been used traditionally for wound management for centuries because of its medicinal properties. Honey possesses antimicrobial, antioxidant, anti-inflammatory, moisturizing, and tissue-regenerative properties that support wound healing [24,25].

Honey exerts antimicrobial activity through: high osmotic pressure, acidic pH, hydrogen peroxide production, and phytochemical constituents. These mechanisms help reduce wound infection and microbial colonization.

Honey reduces: swelling, redness, pain, and inflammatory exudates.

Reduction of inflammation promotes faster tissue repair and minimizes tissue damage. Honey contains flavonoids and phenolic compounds that neutralize free radicals and reduce oxidative stress at the wound site.

Honey stimulates: fibroblast proliferation, angiogenesis, collagen deposition, granulation tissue formation, and epithelialization. These activities accelerate wound closure and tissue remodeling [25].

Traditionally, honey may be: applied directly onto wounds, mixed with herbal preparations, or used to soak wound dressings.

3.6.2. Bitter Leaf Therapy

Vernonia amygdalina is traditionally used in Africa for wound treatment due to its phytochemicals: flavonoids, tannins, alkaloids, saponins, terpenoids, and phenolic compounds. These confer antimicrobial, antioxidant, anti-inflammatory, and tissue-regenerative properties [26]. It inhibits wound microbes, reduces swelling and irritation, neutralizes free radicals, and promotes fibroblast proliferation, collagen synthesis, angiogenesis, and granulation tissue formation to

accelerate closure. Leaves are crushed into paste, squeezed for extract, or boiled as a decoction for wound washing, then applied directly to the wound.

3.7. Modern Treatment and Management of Wounds

Modern wound management involves scientific approaches aimed at promoting tissue repair, preventing infection, reducing complications, and restoring normal tissue function [5].Proper wound assessment involves evaluation of: wound size, depth, exudates, tissue appearance, and signs of infection. Assessment helps determine appropriate treatment methods.

Modern wound cleansing removes debris, microorganisms, and dead tissues without damaging healthy cells. Normal saline and sterile water are commonly used because they support cellular activities necessary for healing [1].Debridement is the removal of necrotic or infected tissue from wounds to promote healing and reduce microbial growth [3].

Types include: surgical debridement, mechanical debridement, autolytic debridement, enzymatic debridement, and biological debridement.

Modern dressings maintain a moist environment that promotes tissue repair and protects wounds from contamination.

Examples include: hydrocolloid dressings, hydrogel dressings, foam dressings, and alginate dressings.

Negative pressure wound therapy uses controlled suction to remove excess exudates, improve blood circulation, and stimulate granulation tissue formation [13]. Skin grafting involves transplantation of healthy skin tissue to cover large wounds or burns. It promotes rapid wound closure and reduces infection risk.

Growth factors such as PDGF and VEGF stimulate fibroblast proliferation, angiogenesis, and collagen synthesis.

Stem cell therapy promotes tissue regeneration and accelerates wound healing through cellular differentiation and secretion of growth factors [19].Adequate intake of: proteins, vitamin C, zinc, and iron is important for collagen synthesis, immune function, and tissue regeneration [12].

4. Conclusion

Effective wound healing relies on coordinated interactions among inflammatory cells, fibroblasts, endothelial cells, growth factors, matrix proteins, and vasculature. Understanding these mechanisms and the causes of impaired healing is essential for advancing wound care, regenerative medicine, and tissue engineering.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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