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WOUND HEALING PERSPECTIVES OF PROMISING HERBAL RESOURCES: A REVIEW

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ABSTRACT: A wound is described as a break in a tissue's cellular and anatomic continuity. A wound is a cellular, anatomical, and functional disturbance of living tissue induced by physical, chemical, electrical, or microbiological threats to the tissue. Wound healing is a multi-step process involving injured tissue regeneration or restoration. The typical wound-healing response is a coordinated series of processes that starts with an injury. Wound healing is a series of interconnected cellular and biochemical activities that result in restoring structural and functional integrity and re-establishing strength in wounded tissues. This study includes a review of plants with wound-healing activities found *via* ethnobotanical and folklore medicinal surveys. This article discusses the wound-healing capabilities of plants, as well as their botanical names, common names, families, parts utilized, and references, all of which might assist researchers to design novel wound-healing formulations for human use.

INTRODUCTION: The worldwide medicinal market is dominated by medicinal plant materials and herbal treatments developed from them. Throughout history, herbal treatments and medications have played an important role in treating ailments. Despite the abundance of literature on their curative powers, there are no standard processes for quality control of plant materials in terms of identification (phytochemical, pharmacological, and therapeutic activity). Medicinal plant standardization ensures uniformity and therapeutic efficacy.

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Herbal products are assessed for their identification (characterization), quality, and the quality of the extracts present. This information is essential to assess their medicinal effectiveness, i.e., to understand their pharmacological activity to prove authenticity. Ulcers, wound healing, skin infections, inflammation, scabies, leprosy, and venereal disease are the disorders that herbal medicines can treat and cure.

Disinfection, debridement, and creating a moist environment that encourages the establishment of an adequate natural healing climate are all examples of herbal medicines used in wound therapy or care. Many plants are used in folklore cultures to cure cuts, wounds, and burns [1]. A wound is a cellular, anatomical, and functional disturbance of living tissue induced by physical, chemical, electrical, or microbiological threats to the tissue.

Wound healing is a multi-step process involving injured tissue regeneration or restoration. The typical wound healing response is a coordinated series of processes that starts with an injury. When platelets come into touch with exposed collagen, a healing cascade begins, resulting in platelet accumulation and the release of coagulating factors, which leads to the development of a fibrin clot at the injury site.

The fibrin clot acts as a temporary matrix, setting the tone for the actions that come with healing. Inflammatory cells and platelets provide vital signals known as cytokines or growth factors to the damage site. The connective tissue fibroblast is in charge of collagen deposition, which is required to repair tissue injury. Collagen gives normal tissues their strength, integrity, and structure. When tissues are injured following an injury, collagen is necessary to repair the defect and restore anatomical structure and function. If wound healing does not proceed progressively, it might lead to chronic wound expansion. According to patents and papers, various herbal compositions assist expedite wound healing and are beneficial in wound therapy. The wound healing activity of medicinal plants has been proven, and they have been shown to be beneficial in treating wounds [2].

Structure and Function of the Skin: The skin acts as a life-protective barrier between the body and the outside world, protecting it from physical harm, infections, and fluid loss. It also contains immune-neuroendocrine activities that help maintain body homeostasis. The epidermis and dermis are the two layers that make up its structure. Keratinocytes, melanocytes, dendritic cells, Langerhans cells, and other immune cells, sensory axons, and the epidermal-dermal basement membrane are all found in the epidermis. The skin appendages, mast cells, fibroblasts, antigen-presenting dermal cells, and resident and circulating immune cells are all found in the dermis. The extracellular matrix complex, which supports intercellular connections, cellular mobility, and controls cytokine and growth factor actions, is also found in the dermis.

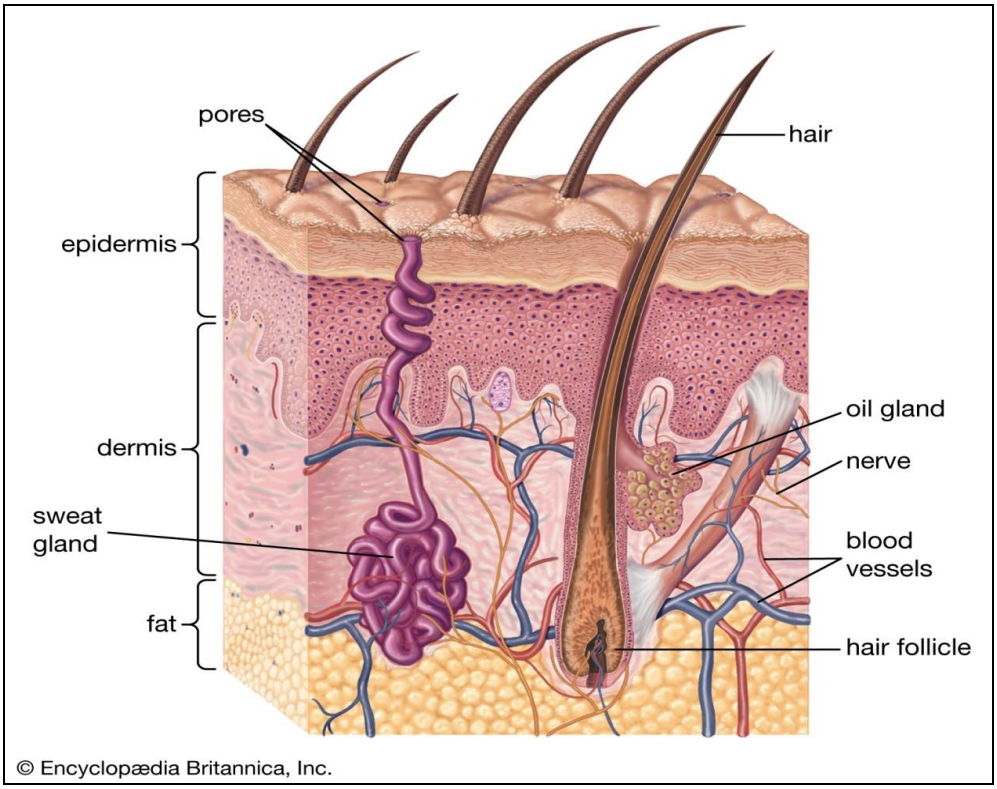

FIG. 1: ANATOMY OF HUMAN SKIN

A dense network of sensory and autonomic fibers establish tight connections with keratinocytes and send pain, temperature, pressure, vibration, and itch feelings to the skin. Parallel arterial-venous thermoregulatory shunt circulation is regulated by tonic adrenergic sympathetic vasoconstrictor and vasodilator neurons, which give rise to a subepidermal capillary network that supplies

oxygen and nutrients to the epidermis while also removing CO_2 and waste products. Lymph capillaries travel horizontally under the epidermis, then precollector vessels deeper in the dermis and lymph collecting vessels in the subcutaneous fat layer, which comprise the skin's lymphatic veins. The skin's local draining lymph nodes are linked to lymph vessels, and lymph vessels exiting these lymph nodes converge on the regional sentry lymph nodes before reaching the thoracic duct [3].

Wounds: Wounds are often categorized based on the underlying reason of wound formation.

Acute Wounds: Tissue damage/injury occurs in acute wounds, which usually follows an orderly and time-reparative phase that restores anatomical and functional integrity in a long-term manner. Cuts or surgical incisions are the most common causes of acute wounds.

Closed Wounds: In closed wounds, blood exits the circulatory system but remains inside the body. Bruises become visible as a result of this.

Open Wounds: Blood seeps from the body *via* an open wound, causing visible bleeding. The open wound may be further split into types based on the cause of the wound.

Incised Wounds: This is a wound with no tissue loss and just little tissue injury. Sharp items, such as a scalpel or knife, are the primary cause.

Tear or Laceration Wounds: This is a non-surgical injury that occurs in the presence of other forms of trauma and leads in tissue loss and damage.

Puncture Wounds: These are produced by an instrument puncturing the skin, such as a nail or a needle. Because dirt may enter deep into the incision, infection is a regular occurrence.

Abrasive or Superficial Wounds: Abrasion is caused by sliding slide on a rough surface. Abrasion is scraped off the top layer of the skin, the epidermis, at this period, exposing nerve endings and leading in a painful injury.

Penetration wounds: An instrument like a knife going in and out of the skin is the most common cause of penetration wounds.

Gunshot Wounds: They're usually caused by a bullet or other object that pierces or penetrates the body.

Chronic Wounds: Chronic wounds haven't yet gone through to the normal healing phases and have therefore reached a level of pathologic inflammation. They will take a long time to mend [4].

The Healing Process: Skin integrity must be repaired as soon as possible after an injury to sustain its functions.

The wound healing process involves peripheral blood mononuclear cells, resident skin cells, extracellular matrix, cytokines, chemokines, growth factors, and regulatory molecules.

The inflammatory, proliferative, and remodelling phases are three consecutive and overlapping processes in the complex skin healing process. The inflammatory phase involves cutaneous neurogenic inflammation and hemostasis, which begin within seconds after damage and persist for around an hr.

The rapid recruitment of neutrophils to the damaged tissue during the first 24 hrs was followed by a reduction in the following week.

Inflammatory monocytes-macrophages infiltrate the wound on the second day after injury and continue to grow, reaching a peak during the proliferative phase before beginning to fall over the next two weeks, becoming the main mononuclear cell in the tissue healing process. Circulating lymphocytes move to the skin early after injury, reaching a peak by day 4 and remaining there for another two weeks before fading away.

The last phase, which begins the second week following damage, involves modifying the tissue created during the proliferation phase and forming a scar to restore skin integrity. This last step might take months to complete.

This review summarizes current knowledge on the essential role of resident and peripheral immune cells and the microenvironment and their interactions in wound healing [5].

The different phases (inflammatory, proliferative, and remodeling phases) of wound healing are described.

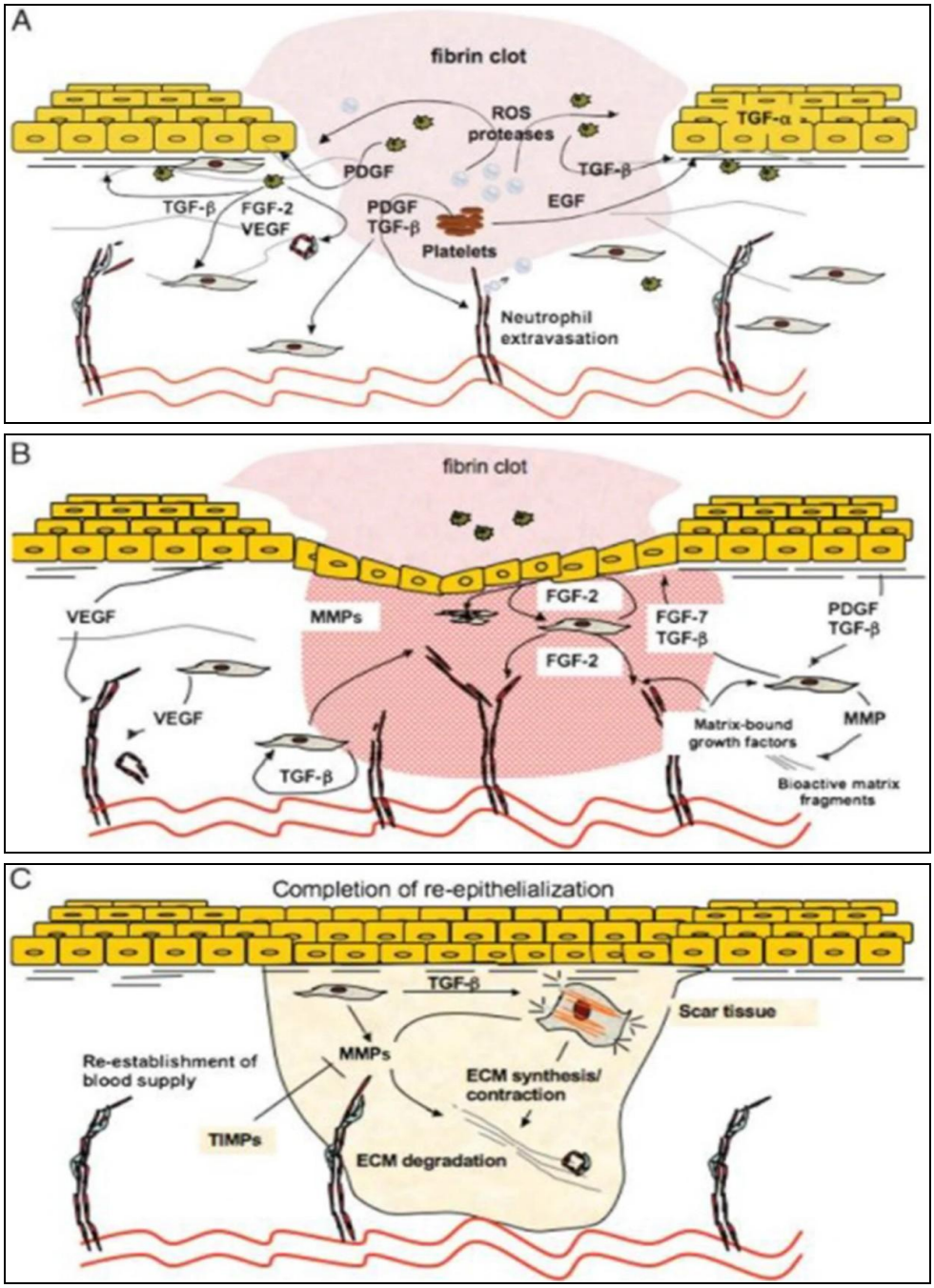

FIG. 2: THE DIFFERENT PHASES (A) INFLAMMATORY PHASE, (B) PROLIFERATIVE PHASE, AND (C) REMODELING PHASE OF WOUND HEALING ARE DESCRIBED

The Inflammatory Phase:

Cutaneous Neurogenic Inflammation: When a skin injury occurs, the peripheral nervous system is one of the first to react. TPRV1 and TPRA1 are transient receptor potential channels found in primary sensory neuron terminals as well as other cells that operate as nociceptive receptors, such as keratinocytes, mast cells, dendritic cells, and endothelial cells. When sensory neurons are stimulated, action potentials are generated that travel orthodromically to the spinal cord, causing pain. The axon reflex is initiated by action potentials moving antidromically in other axonal branches of sensory nerve terminals, causing substance P and calcitonin gene-related peptide to be released from sensory nerve endings. These neuropeptides have three targets: (a) CGRP acts on microvascular smooth muscle fibres in blood vessels, promoting vasodilation and increased blood flow; (b) SP causes vascular permeability, edoema, and recruitment of inflammatory leukocytes; and (c) SP stimulates mast cell

degranulation, promoting increased microvascular permeability of the blood vessels encircling the wound (redness and warmth); and (d) SP stimulates mast cell de (swelling). Furthermore, the release of histamine from mast cells causes the release of substance P and CGRP from sensory nerve terminals, forming a bidirectional relationship between cutaneous neurogenic inflammation and sensory nerve endings. During the many stages of skin wound healing, the peripheral nervous system maintains regulatory relationships with mast cells, monocyte-macrophages, Langerhans cells, and lymphocytes, as well as microvascular and other local skin cells [6].

Platelets Hemostasis: Blood platelets are the second most numerous cells after erythrocytes, with 160,000-400,000/μl. An average healthy adult makes 1011 platelets daily, which circulate for around 10 days. Platelets maintain many of the nucleated cell's RNA metabolic functions. They have a lot of noncoding RNAs, such as microRNAs and long noncoding RNAs, and they use posttranscriptional processes to keep their 4000 protein proteome intact. Platelets' longevity in the blood is determined by the gradual breakdown of the antiapoptotic protein Bcl- once released into the bloodstream and eliminated from circulation in the liver and spleen at the end of their lives. Platelets do not interact with the endothelium surface under normal physiological circumstances.

Due to their tiny size, platelets are forced to travel slightly toward the wall, where the glycocalyx barrier prevents them from making contact with the endothelium surface. Vascular damage exposes basement membrane proteins and extracellular matrix macromolecules. Platelet membrane surface receptors connect to collagen, causing platelets to activate and produce thrombin, which initiates the coagulation cascade. Platelet integrins connect to fibrinogen to produce fibrin, which binds to the interstitial collagen and traps neutrophils, erythrocytes, and other blood components to create a clot. Fibrin monomers produce fibrin protofibrils, which are stabilized by intermolecular connections thanks to the activity of Factor XIIIa. *In-vitro* studies show that fibroblasts and endothelial cells use integrins to connect to native collagen type I fibres, and that fibroblasts and endothelial cells use this extracellular provisional matrix to migrate and promote proto myofibroblast-mediated contraction of the provisional extracellular matrix. Metalloproteinases produced from fibroblasts and macrophages further modify this first extracellular matrix, generating a new temporary extracellular matrix to enable neutrophil and monocyte migration. Apart from hemostasis, degranulation of alpha granules from platelets produces TGF, which functions as a chemoattractant for recruiting different immune cells such as neutrophils and macrophages. Platelet cell surface receptors play a role in cell-cell interaction and microbial recognition, as well as the release of growth factors like PDGF, TGF-1, FGF, and VEGF, which interact with endothelial cells, neutrophils, monocytes, dendritic cells, B-cells and T-cells, and natural killer cells, promoting neutrophil activation, pathogen detection, trapping, and modulation of innate and adaptive immune responses [7].

The Role of Peripheral Blood Mononuclear Cells during the Inflammatory Phase:

Neutrophils: Neutrophils make about 50-70 percent of all leukocytes in healthy persons. Neutrophils circulate in the circulation as dormant cells that last 8-12 hrs in the blood and 1-2 days in the tissues. They are cleansed from circulation in the liver, spleen, and bone marrow as they near the end of their lives. At the onset of the inflammatory phase at sites of acute inflammation or infection, neutrophils follow platelets as the first effector cells.

Growth factors and chemokines generated by active platelets in a blood clot and N-formyl peptides released by germs and injured cells trigger their recruitment. The amount of neutrophils in the wound rises during the early inflammatory phase and decreases after 4 days. The presence of DAMPs released during cell damage and necrosis, as well as PAMPs from bacteria and fungi, creates a gradient that is sensed by the numerous neutrophil pattern recognition receptors (PRRs): transmembrane Toll-like receptors, C-type lectins, cytosolic NOD-like receptors, and RIG-like receptors, activating the innate immune response. Neutrophil adhesion receptors (selectins/selectin ligands and integrins) attach neutrophils to the endothelium, triggering the leukocyte recruitment cascade, which includes rolling, adhesion, crawling, and migration to the inflamed tissue **Fig.**

3. To keep neutrophil recruitment going, neutrophils produce additional neutrophil-chemoattractant mediators after they've arrived at the site.

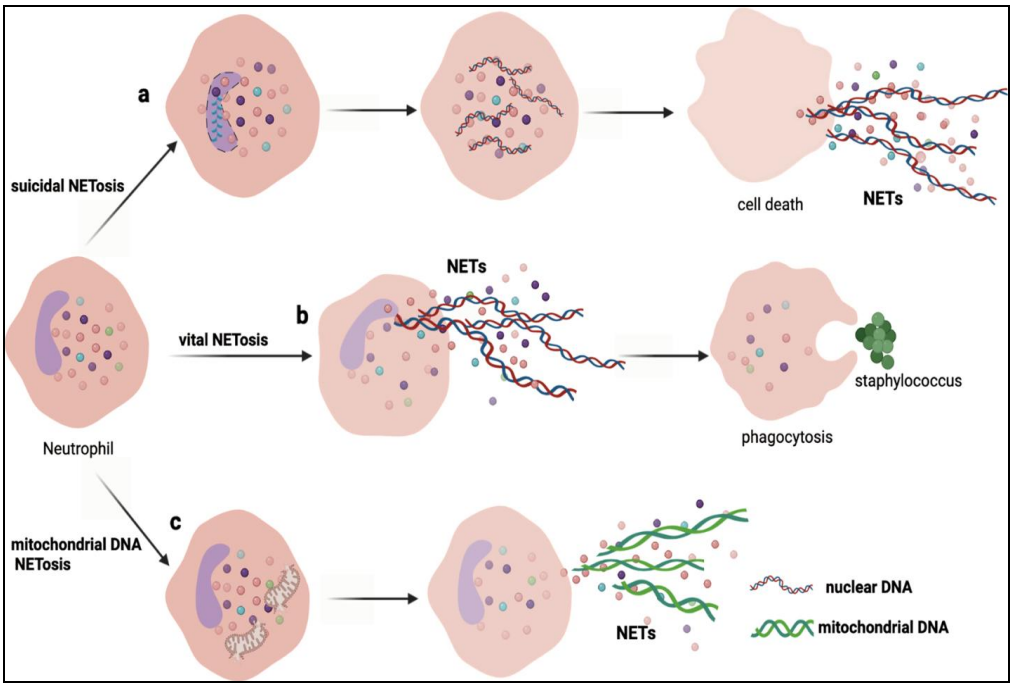

FIG. 3: ROLE OF NEUTROPHILS IN WOUND HEALING

Neutrophils are the most numerous immune cells in the wound, with a concentration of more than 5 $\times 10^6$ in the first 24 hrs and continue to rise on day 2. Neutrophils grab Fc-receptors of opsonized pathogens in the inflamed tissue, allowing for phagocytosis, while reactive oxygen species and antibacterial proteins found in neutrophil granules are discharged into the phagosome to kill the pathogen. In addition to internal killing mechanisms, neutrophils expel neutrophil extracellular traps (NETs), which are made up of DNA, histones, antimicrobial proteins, and lytic enzymes linked to them, either on their own or in response to pro-inflammatory chemicals and platelets. NETs immobilize and kill bacteria via these processes. Furthermore, neutrophils participate in cellular crosstalk through cell-cell contact, where various cytokines, chemokines, and angiogenic factors activate resident hematopoietic cells, macrophages, dendritic cells, B cells, T cells, and natural killer cells, modulating innate and adaptive immune responses [8].

Monocytes: Human monocytes circulate due to a monocyte-dendritic progenitor (hMDP) in the bone marrow that gives rise to monocytes and a dendritic cell precursor (hCDP). These cells are discharged into the bloodstream and develop into macrophages or dendritic cells in the peripheral organs. CD14++CD16 classical monocytes (inflammatory) capable of transmigrating and entering tissues, CD14++CD16+ intermediate monocytes with increased proangiogenic and antigen processing and presentation activities, and CD14+CD16++ non-classical monocytes that patrol the vessels with endothelial and tissue monitoring capabilities have all been identified in the blood. These three monocytes' size, shape, and transcriptional patterns are all different. A progressive shift from monocyte progenitors to non-classical monocytes was observed in a recent investigation of *in-vivo* leukocyte dynamics employing deuterium labeling. Monocyte precursors develop into classical monocytes in the bone marrow, where they stay for a postmitotic maturation period of 38 hrs before being discharged into the bloodstream, where they have a limited lifetime of one day, according to this research.

However, most of these cells die or leave the bloodstream, and just a tiny percentage grows into intermediate monocytes with a four-day lifetime. Finally, most of these cells transform into non-classical monocytes with a 7-day lifetime before dying or leaving circulation. Monocyte emigration happens constitutively in the steady state, when

they might continue as monocytes, gain antigen-presenting skills, or develop into macrophages. The monocyte-macrophage population in skin tissue is formed by circulating monocytes [9].

Monocyte-Macrophages: Tissue-resident macrophages detect the presence of DAMPs and PAMPs after an injury, causing patrolling monocytes to move into the wound. Monocytes produce cytokines and chemokines once inside the wound to attract neutrophils. The release of neutrophil granule contents encourages the recruitment of inflammatory monocytes, which grow into macrophages and eventually become the wound's dominant monocyte-macrophage population.

These cells have a high degree of flexibility, allowing them to differentiate into various monocyte-macrophage phenotypes or transdifferentiate into other cell types in response to the wound's surroundings. For example, macrophages use their pattern recognition receptors (PRRs) to detect PAMPs and DAMPs, and the production of interferon-gamma (IFN) and tumour necrosis factor-alpha (TNF-α) by innate or adaptive immune cells causes macrophages to adopt an inflammatory phenotype (M1), which produces pro-inflammatory cytokines as well as reactive oxygen and nitrogen species, which are required to kill and control microbial pathogens **Fig. 4**.

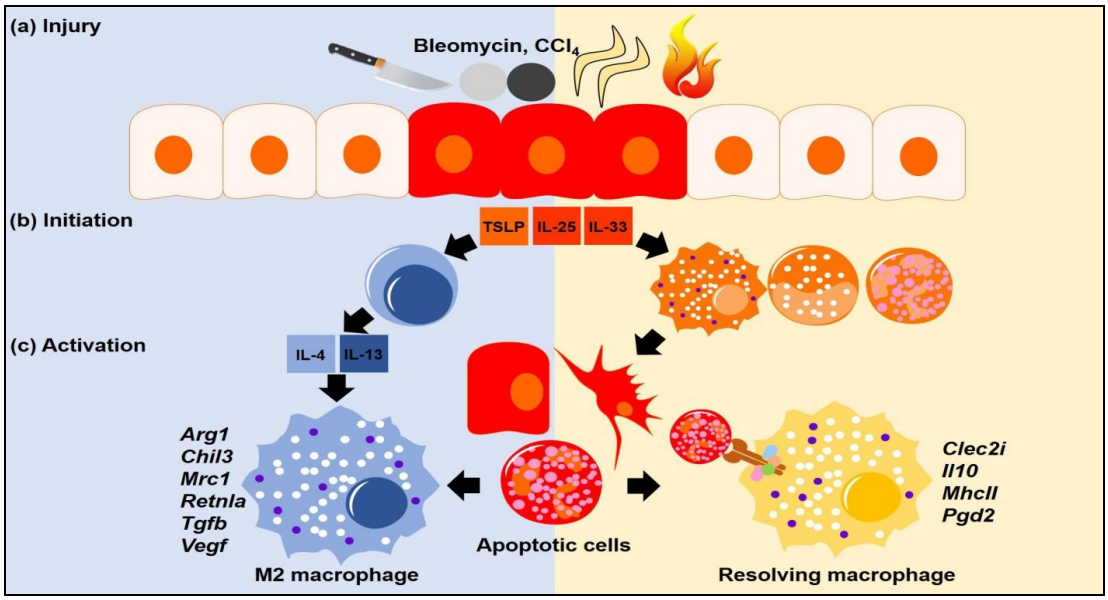

FIG. 4: ROLE OF MACROPHAGES IN WOUND HEALING

Macrophages work with neutrophils to clear germs, dead cells, apoptotic neutrophils, tissue debris, and other foreign items from the body. This myelomonocytic interaction is crucial for wound healing. During the onset, development, and resolution of the inflammatory phase, neutrophils and monocyte-macrophages work together as partners in time and space. The fact that neutrophils and monocyte-macrophages share a common progenitor explains why they have similar functions such as phagocytosis, intracellular killing mechanisms, NET formation, similar transcriptional profiles, and cell surface receptors, as well as their role in modulating innate and adaptive immune responses. Once the wound is clean, neutrophils and macrophages work together to bring the inflammatory phase to a close.

This stage begins one or two days after the neutrophils enter the inflammatory tissue. Apoptotic neutrophils reveal phosphatidylserine on their surface, marking them for efferocytosis, and neutrophils release microparticles carrying proresolving proteins annexin A1 and proresolving lipid mediators. Neutrophil microparticles transport their molecules to macrophages, which improves the manufacture of pro-resolving mediators such as lipoxins, resolvins, protectins, and maresins, which are then released into the wound tissue. Inflammatory macrophages increase the production of miR-21 by efferocytosis apoptotic neutrophils, boosting the anti-inflammatory phenotype of the postefferocytotic macrophage. This alternate differentiation pathway produces anti-inflammatory M2 populations that are diverse. M2a macrophages

have an anti-inflammatory phenotype, produce IL-10, limit the production of IL-1 and TNF-, and help the inflammatory phase to resolve. M2b and M2c macrophages play a key role in ending the inflammatory phase by minimising the damage produced by extended M1 macrophage activation and promoting inflammation resolution. The proper progression of the tissue repair and remodelling stages of wound healing requires a well-ordered and well-controlled inflammatory phase [10].

Lymphocytes: The skin's immune system preserves and protects the body's integrity. The innate immune system, which includes neutrophils and monocyte-macrophages, responds to infections and poisons in a non-specific way. To combat particular intracellular and extracellular infections, innate cells interact with T and B cells of the adaptive immune system, which keep specific memory for a long period [11].

Innate Lymphocytes: When compared to T-cells, B-cells, and natural killer (NK) cells, innate lymphoid cells (ILCs) are divided into three subgroups with distinct cell lineage markers. Group 1 is made up of NK cells that produce interferon-gamma (INF) and tumour necrosis factor (TNF-), as well as having cytolytic abilities. ILC2 cells are found in healthy skin and increase in number when the skin is inflamed. ILC2 responses increase re-epithelialization and wound closure when IL-33 is stimulated. Invariant NKT cells (iNKT) promote skin wound healing by increasing INF-α production early in the healing process, stimulating macrophages and fibroblasts to secrete VEGF and TGF, increasing collagen deposition, producing myofibroblast differentiation and angiogenesis, and inhibiting neutrophil inflammatory response [12].

CD8+ T-Cells: DAMPs and PAMPs generated by injured cells and pathogens are recognized by a system of pattern recognition receptors in the skin, which includes transmembrane Toll-like receptors, C-type lectin receptors and cytoplasmic proteins, retinoic acid-inducible gene-I-like receptors, and NOD-like receptors (NLRs). PRRs start the immune response by releasing pro-inflammatory cytokines and antimicrobial peptides and attracting neutrophils and macrophages. Recent research has looked at the involvement of Toll-like receptors in acute skin wounds. DAMPs and PAMP antigens are transported into cells by endocytosis and processed by professional and nonprofessional skin resident dendritic cells shortly after an acute lesion (DC). The antigen is then presented to naive CD8+ T cells by professional DC, which moves to cutaneous local draining lymph nodes (LN). Naive T cells differentiate into CD8+ skin-homing effector memory T cells and CD8+ central memory T cells once their corresponding antigen is identified in the lymph node.

Migrating cells expressing cutaneous lymphocyte antigen (CLA) and CCR4 move to the skin wound to release pro-inflammatory, immune-regulatory, and microbicidal mediators, aiding pathogen clearance. Once antigen sources are removed, the bulk of cells die from apoptosis, leaving just a tiny population of antigen-specific T lymphocytes expressing CCR8 in the skin.

These cells, also known as CD8+ non-circulating tissue-resident memory T-cells, are the most common T-cells in human skin under resting circumstances, with an estimated 2 x 1010, or double the number of T cells in whole blood. Only 10% of these cells circulate in the blood, with 90% remaining in the skin. The lymph node homing receptors CCR7 and CD62L are expressed in secondary lymphoid organs, which proliferate and differentiate into lymph node homing lymphocytes that migrate to other peripheral lymph nodes, providing systemic immunological memory, and migrate to the inflamed site during local skin inflammation. Local DC delivers the antigen to skin CD8+ cells, which multiply and recruit from the blood to mediate pathogen clearance after reexposure to the pathogen. Later, CD8+ cells move to the epidermis, occupying the space formerly inhabited by delta gamma T cells, and serve as the first line of defence against reinfection [13].

CD4+ T-Cells: Skin immunosuppressive CD4+Foxp3+ regulatory T cells regulate skin homeostasis and peripheral tolerance to commensals and self-antigens, suppressing the aberrant consequences of self-reactive immune cells' responses. Circulating cells that express the cutaneous lymphocyte antigen (CLA) and the skin-homing receptor CCR6 move and collect in the skin's hair follicle niche. Increase the expression of

epidermal growth factor receptor (EGFR), which promotes wound re-epithelialization and wound closure, reduces the amount of inflammatory macrophages, and controls tissue inflammation by restricting IFN production. After the pathogen has been cleared from the skin, they need IL-7 to stay in the skin and display CD45RO, a sign for past antigen exposure, as well as the memory markers CD27 and BCL-2; data that classify them as regulatory resident memory T cells (Treg Trm) in the skin. Only 5% of recirculating CD4+ T-cells in adult healthy human skin express the transcription factor Foxp3, but 20% of tissue-resident CD4+ T-cells do. Dendritic cells process and communicate their cognate antigen to resident Treg Trm in the event of antigen reexposure, enabling them to react quickly. Th1, Th2, Th17, Th22, and Th9 CD4+ helper T cells provide host defence by producing cytokines that increase the production of INF-α, defensins, and antimicrobial peptides and creating a protective inflammatory response to protect skin against intracellular and extracellular infections [14].

B-Cells: B cells are part of the immune system's humoral branch. They develop into antibody-producing plasma cells, present antigens to T cells, and control local immune responses by releasing growth factors and pro- and anti-inflammatory cytokines. The wound healing process was shown to be delayed in a model of splenectomized injured mice, and the injection of external B cells that generated antibodies against the damaged tissue to these animals restored the normal wound healing process. The generation of cytokines by B cells that aided wound healing has also been documented. A recent study found that B cells are present in the wound bed 4 days after damage and remain up to day 17 following injury. A 5 mm biopsy was taken in the dorsal skin of mice, and topical injection of mature B cells at the time of injury sped up wound healing by 2-3 days [15].

The Proliferative Phase (Wound Damage Repair): Fibroplasia, which includes fibroblast proliferation and differentiation into myofibroblasts, extracellular matrix deposition, and wound contraction, (b) re-epithelialization and epithelial-mesenchymal interaction between keratinocytes and fibroblasts, (c) angiogenesis, which includes endothelial cell proliferation and new vessel formation, and (d) peripheral nerve repair, which includes collateral re-innervation and nerve regeneration, are all examples of the proliferation. The proliferative phase of skin wound recovery is orchestrated by macrophages, the most common inflammatory cells.

Fibroplasia: Fibroblasts are a nebulous, diverse collection of cells with a wide range of functions in various dermal layers. Platelets, macrophages, fibroblasts, endothelial cells, and keratinocytes release tissue soluble extracellular signals such as interleukin-1 (IL-1), tumour necrosis factor alpha (TNF-α), transforming growth factor beta-1 (TGF-1), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and fibroblast growth factor-2 (FGF-2). These cytokines and growth factors cause fibroblasts to proliferate and regulate the synthesis of metalloproteinases and metalloproteinase inhibitors **Fig. 5**.

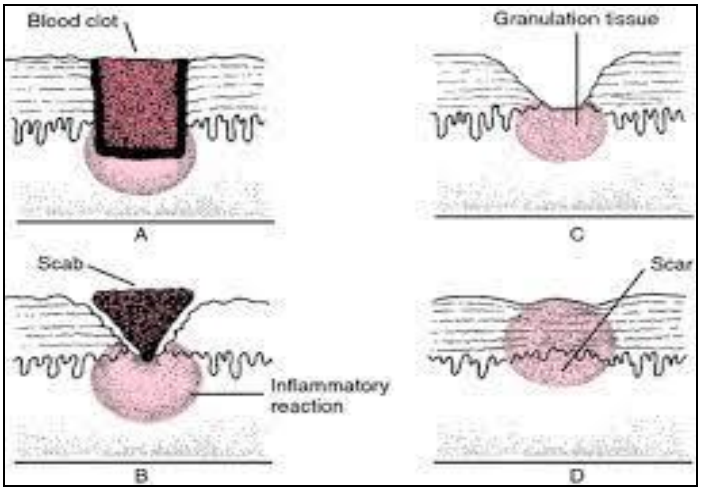

FIG. 5: FIBROPLASIA PHASE

Mature fibroblasts move into granulation tissue, start collagen synthesis, replace the fibrin temporary matrix, and develop into myofibroblasts, increasing collagen deposition and wound contraction. Fibroblasts also detect the magnitude and direction of mechanical stress and convert this information into gene expression and growth factor synthesis, which are manifested as adaptive responses that change the phenotypic of the fibroblast. Vimentin, for example, is an intermediate filament that drives TGF-–Slug signalling, which causes the epithelial–mesenchymal transition, regulates fibroblast proliferation, and boosts collagen deposition, which activates keratinocyte mesenchymal differentiation and re-epithelialization [16].

Re-epithelialization: Re-epithelialization begins 16-24 hrs after damage and lasts until the wound remodelling phase. Keratinocytes differentiate and move between the fibrin clot and the rich collagen dermis shortly after damage, whereas suprabasal keratinocytes behind the leading edge proliferate to fill the gap. Close to the leading edge, suprabasal keratinocytes change form and move on top of basal keratinocytes to become leading cells. Cells dedifferentiate into epithelial cells that are firmly connected to the basal membrane during the last phases of re-epithelialization **Fig. 6**.

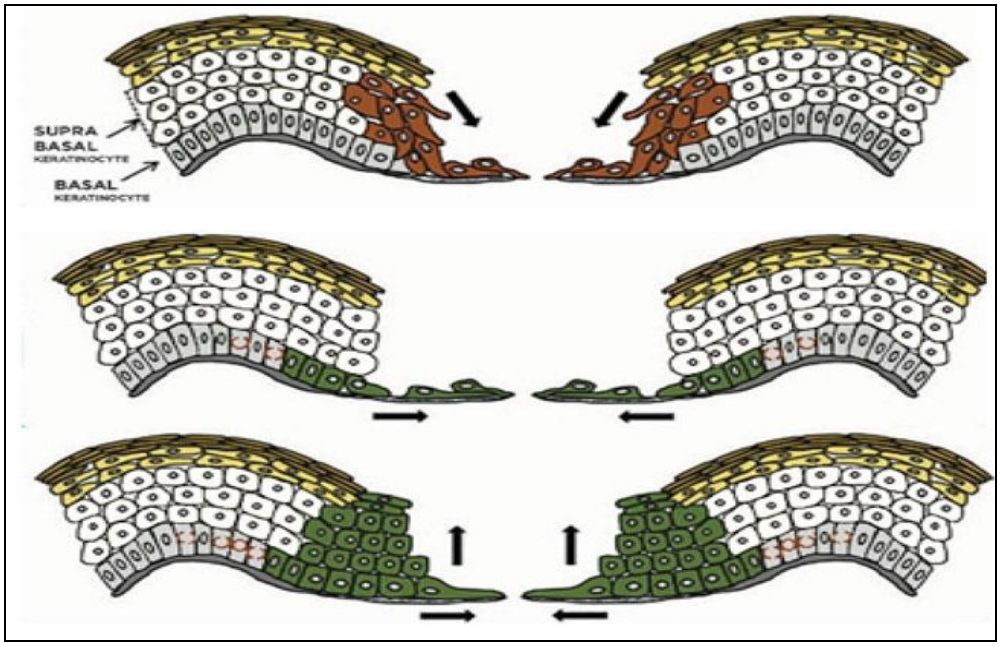

FIG. 6: RE-EPITHELIALIZATION PHASE

Growth factors and cytokines generated by different cell types induce keratinocytes to migrate across the provisional matrix created in the clot to cover the wound, while keratinocytes at the wound borders begin to proliferate and follow the moving front. In the re-epithelialization process, the extracellular matrix plays a crucial function. Simultaneously, an active paracrine interaction between keratinocytes, fibroblasts, neutrophils, monocytes-macrophages, and endothelial cells increases the amount of cytokines, growth factors, and other biomolecules to promote the epithelial-mesenchymal interaction between keratinocytes and fibroblasts, in which keratinocytes stimulate fibroblasts to release growth factors, which in turn stimulates Finally, fibroblasts become myofibroblasts, which increase collagen deposition and initiate wound contraction [17].

Angiogenesis: The anti-inflammatory phenotype (M2) of macrophages develops as the dominant cellular population during the proliferative phase, regulating interactions with endothelial cells, fibroblasts, keratinocytes, extracellular matrix (ECM), and peripheral nerves.

The injured tissues become hypoxic as a result of the reduced blood supply and the faster metabolism of cells striving to heal the damage, which is a primary stimulant for angiogenesis. In macrophages, fibroblasts, vascular endothelial cells, and keratinocytes, hypoxia-inducible factor-1 (HIF1) is produced in response to hypoxia. Neovascularization is triggered by the production of pro-angiogenic molecules such as VEGF, VEGFA, FGF2, PDGF, and TGF-1, as well as a metabolic flips in endothelial cells **Fig. 7**.

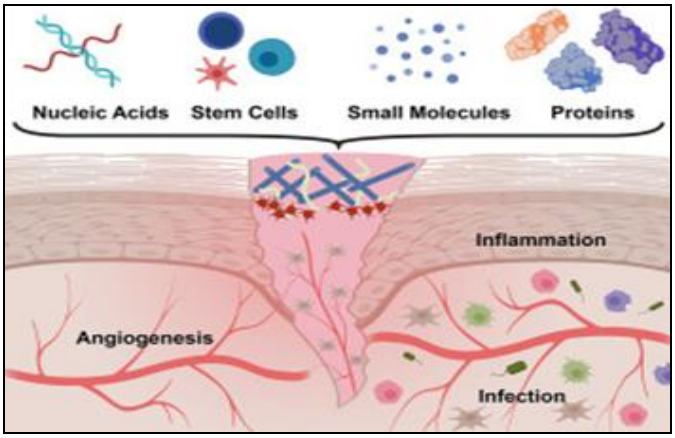

FIG. 7: ANGIOGENESIS PHASE

Angiogenesis is Driven by Three Kinds of Endothelial Cells: highly migratory tip cells that direct the new forming bud, proliferative stalk cells that extend the new vessel, and quiescent falanx cells that line the blood vessel. The increasing abundance of VEGF and macrophages guides the differentiation of endothelial cells into each subtype. The structures of immature endothelial cells anastomose with those of other established blood arteries, a fusion aided by macrophages. Endothelial cells release PDGF, which recruits pericytes and expresses receptor (PDGF-R) and covers the nascent vessels with these mural cells, establishing new stable blood vessels. Finally, fibroblasts produce and deposit new extracellular matrix, which provides support for cells and new blood vessels, resulting in the formation of granulation tissue [18].

Peripheral Nerve Repair: Nerves that have been severed have an impact on the skin's homeostatic function after an injury. After severe peripheral nerve damage, two mechanisms are involved in the recovery of neurological functions: collateral reinnervation and nerve regeneration. Skin denervation encourages collateral sprouting of nociceptive skin afferents from nearby intact axons to reinnervate the skin. The peripheral nervous system (PNS) may restore nerve function in adults by regrowing the terminals of myelinated two nerve stumps and reconnecting the severed nerve after an injury.

Inflammatory cytokines, transcription factors, complement, and arachidonic acid metabolites all play a role in this process, as do monocyte-macrophages, Schwann cells (SC), fibroblasts, inflammatory cytokines, transcription factors, complement, and arachidonic acid metabolites. SC have a lot of plasticities, so when they become injured, they throw away their myelin sheath and dedifferentiate into a progenitor-like cell to stimulate axonal regeneration. SC leave the nerve stumps and interact with the fibroblasts that have gathered around the damage site. Ephrin-B, which is found in fibroblasts, binds to the EphB2 receptors on SC, promoting their directional migration. Simultaneously, SC dedifferentiation causes the release of monocyte chemoattractant protein-1 (MCP-1), interleukin-1 (IL-1), and pancreatitis-associated protein III (PAP-III), which attracts circulating monocytes/macrophages to the injury site, where these cells release additional factors, increasing monocyte/macrophage recruitment even more. Macrophages respond to hypoxia by producing vascular endothelial growth factor (VEGF) and hypoxic growth factor (HIF), both of which aid angiogenesis. The SC cords then employ the newly aligned vasculature as a scaffold to drive axon growth over the bridge between the two nerve stump ends [19].

Fibroplasia: After an acute skin injury, plasma fibrinogen, fibronectin, proteoglycan, and platelets come into contact with extracellular matrix (ECM) collagen, generating a fibrin-rich early provisional matrix cross-linked with fibronectin (EPM). Resting fibroblasts in the area get stimulated and begin making collagen, transforming the EPM into a late collagen-rich ECM over time.

Myofibroblasts are formed when activated fibroblasts deposit collagen and develop into myofibroblasts (MFs). TGF-1 regulates the expression of alpha-smooth muscle actin and muscle myosin, which create intracellular stress fibres connected to the fibronexus, a cellular-ECM structure that connects intracellular actin filaments to extracellular fibronectin fibrils through transmembrane integrins. Through fibronexus complexes, MFs link intracellular stress fibers to extracellular collagen. Furthermore, stress fiber contraction locally condenses the ECM, leaving a gap that is filled with freshly generated collagen. Other local MFs repeat the process, causing wound contraction by modifying tiny regions of the ECM. Collagen builds up in the wound site over time, resulting in a nearly avascular and acellular scar made up of 80-90 percent Type I collagen fibres and the remainder of Type III collagen fibres [20].

Re-epithelialization: The endothelial mesen-chymal transition begins when basal keratinocytes near the wound edge lose their desmosome link to each other and the hemidesmosome bind to the basal membrane after damage. The cytoskeleton is subsequently remodelled, losing its cuboidal structure and taking on a flattened morphology with lamellipodia, which express K6 and K16, allowing them to migrate into the temporary matrix to bridge the gap. The keratinocytes that stay

behind the edge begin to multiply at the same time [21].

Angiogenesis: Angiogenesis in wound healing is assumed to be a two-phase process: the proliferation of new blood vessels and the pruning and modification of existing blood vessels. Following injury, hypoxic circumstances induce the creation of hypoxia inducible factor-1 (HIF-1) in vascular endothelial cells, fibroblasts, keratinocytes, and macrophages, followed by the release of angiogenic factors VGEF, FGF, PDGF, and TGF-1 by these cells, resulting in neovascularization. Pericyte loss and capillary sprouting follow vascular basement membrane degradation, with three different EC subsets involved: (1) highly migratory tip cells that guide the new sprout, with VEGF as a major chemoattractant for these cells, (2) highly proliferative stalk cells that elongate the sprout, and (3) quiescent phalanx cells that form the blood vessel lining. Lumen creation inside the sprout gives rise to the fledgling vessel, which creates a new basal membrane after being covered by pericytes and endothelial cells, similar to how a mature vessel is covered by a basement membrane and mural cells. The contraction of the chosen blood vessels initiates the regression and remodelling process. Endothelial cells adhere to the same cells on the opposite side of the vessel wall, occluding the lumen and stopping blood flow. The EC of the retreating branch disintegrate and die as a result of apoptosis, leaving a modified vascular network in their wake [22].

Peripheral Nerve Regeneration: After an injury, the peripheral nerve is transectioned, and the stumps are retracted. The bridge between the stumps, which is weakly vascularized, becomes hypoxic. When macrophages detect hypoxia, they produce VEGF, which promotes angiogenesis along the original tubes of the basement membrane bridge. Meanwhile, Wallerian degeneration causes the distal stump to degenerate; Schwann cells detach from the degenerating axons, release their myelin, and dedifferentiate into a progenitor-like condition. These dedifferentiated SC recruits more macrophages, and collectively they clear myelin and axon debris. The vascularization of the bridge between the two stumps is aided by macrophages, which prepares the area for axonal regeneration. Dedifferentiated Schwann cells travel along the newly created vasculature at the same time, generating Büngner bands and directing the re-growing axons to their original goal. When axons re-innervate, their original targets, Schwann cells, re-differentiate and re-myelinate axons, bringing the inflammatory response to a halt [23].

The Remodeling Phase (Restoring Skin Integrity): The granulation tissue undergoes a slow declining process throughout the last phase of wound healing. The skeletal muscle's epidermis, dermal vasculature, nerves, and myofibers are modified to become a functioning tissue. The granulation tissue's vascular components of fibroblasts and myofibroblasts are reduced, and PBMC cells die or exit the wound. Similarly, the quantities of structural and hydration-related proteoglycans and glycosaminoglycans are reduced. Collagen metalloproteinases secreted by fibroblasts and macrophages destroy collagen Type III in granulation tissue, replacing it with collagen Type I, which is then rearranged into paralleled fibrils, resulting in a low cellularity scar.

Common Complications of Normal Skin Acute Wound Healing Process: Fibrosis and chronic skin wounds are two typical problems linked with changes in the normal skin acute wound healing process. These changes have an impact on millions of individuals throughout the globe, posing a significant health risk and increasing healthcare costs for patients and nations alike. In the next paragraph, several difficult issues will be briefly discussed. Excessive extracellular matrix formation is a hallmark of fibrosis. Fibrosis is manifested in the human skin as hypertrophic scars and keloids.

After surgery, trauma, or burns, hypertrophic scars occur, producing deformity and contractures throughout the joints. Keloids are characterized by extensive scarring that spreads beyond the initial injury, resulting in deformity, pruritus, and hyperesthesia. Tissue remodelling, scar formation, peripheral blood mononuclear cells, resident skin cells, extracellular matrix components, and signalling pathways are all choreographed in a highly controlled process to restore tissue homeostasis during normal skin wound healing. Skin fibrosis, on the other hand, is characterized by a deregulation of this process, which includes: (1)

pathologically sustained inflammation caused by the presence of inflammatory macrophages and altered communication between macrophages, fibroblasts, epithelial and endothelial cells; (2) increased fibrosis caused by the constant presence of activated myofibroblasts and collagen hyperproduction; and (3) altered signalling pathways of fibroblast growth factor (FGF), hepatocyte The primary players in fibrosis include macrophages, myofibroblasts, matrix, mechanics, and miscommunication, according to a recent study. Chronic non-healing wounds, also known as venous and arterial leg ulcers, pressure sores, and diabetic foot ulcers, are the second consequence. The most significant pathophysiological problems of diabetic foot ulcers will be briefly discussed. Diabetic foot ulcers are a major and costly consequence of diabetes that often leads to amputation due to peripheral vascular dysfunction and neuropathy in the lower extremities. Because these cells are unable to limit intracellular glucose transport in the presence of hyperglycemia, diabetes hyperglycemia impairs glucose metabolic balance in endothelial cells, neurons, Schwann cells, and peripheral blood mononuclear cells (PBMC).

The flow of glycolysis is disrupted when there is an overabundance of glucose. Reactive oxygen species, peroxynitrite, and hazardous advanced glycation end products are produced due to intermediates being redirected onto collateral pathways (AGES). Vascular abnormalities and pro-inflammatory gene expression are caused by elevated PKC activity. These toxic changes affect the arteries, nerves, and PBMCs, resulting in vascular disease, neuropathy, and immunological changes. Changes caused by hyperglycemia may also be seen in the epidermis, keratinocytes, and fibroblasts. As a result, diabetic foot ulcers have a chronic inflammatory state and a changed molecular environment, which includes growth factors, cytokines, and proteases, and inflammatory cells have a defective phenotype [24].

Factors Affecting Wound Healing:

Oxygenation: Oxygen is required for practically all wound healing processes and is required for cell metabolism, specifically the creation of energy through ATP. It protects wounds from infection, promotes angiogenesis, boosts keratinocyte differentiation, migration, and re-epithelialization, improves fibroblast proliferation and collagen production, and aids wound contraction. Due to absorption by metabolically active cells, the early wound's microenvironment is extremely hypoxic and deprived of oxygen. Reduced vascular flow is caused by a variety of systemic illnesses, such as increasing age and diabetes, which sets the scene for insufficient tissue oxygenation. In the sense of recovery, this combination of insufficient perfusion results in a hypoxic wound. Chronic wounds are particularly hypoxic; tissue oxygen concentrations of 5 to 20 mm Hg were measured transcutaneously in chronic wounds compared to control tissue values of 30 to 50 mm Hg [25].

Infections: Microorganisms normally confined to the skin's surface get access to the underlying tissues when the skin is damaged. The condition of infection and reproduction status of the microorganisms is determined by whether the wound has inflammation, colonization, local invasion/critical colonization, and/or spreading invasive infection. Contamination refers to the presence of non-replicating bacteria on a wound, while colonization refers to replicating germs on the wound that do not cause tissue damage. Local infection/critical colonization are an intermediate stage that includes microorganism multiplication and the onset of local tissue responses. Invasive infection is defined as the presence of reproducing organisms inside a wound that causes harm to the host. Inflammation is a normal element of the healing process and is required for the removal of infectious microorganisms.

Because microbial clearance is inadequate, inflammation may persist for long, even if decontamination is effective. Pro-inflammatory cytokines, including interleukin-1 (IL-1) and TNF-α will contribute to bacteria and endotoxins, extending the inflammatory process. If this continues, the wound will become chronic and will not heal. Furthermore, chronic inflammation causes an increase in matrix metalloproteases (MMPs), a protease family that may destroy the ECM. In addition to the increased protease content, there is a reduction in the levels of naturally occurring protease inhibitors. The fast degradation of growth factors in chronic wounds may be caused by this alteration in protease equilibrium [26].

Age: The senior population (those aged 60 and over) is expanding faster than any other age group (a significant risk factor for delayed wound healing is the World Health Organization and elevated age). Several human and animal investigations have looked at age-related alterations and delays in wound healing at the cellular and molecular levels. It is well known that aging causes a temporary halt in wound healing in healthy older persons, but not a true impairment in terms of healing consistency [27].

Stress: Human well-being and social conduct are both influenced by stress. Multiple illnesses, including cardiovascular disease, cancer, slowed wound healing, and diabetes, are linked to stress. Many studies have linked stress-induced neuroendocrine immune balance disruption to poor health. Stressors may exacerbate dangerous mental illnesses like depression and anxiety, which can change physiological systems and/or behavioral patterns, affecting health consequences. In addition to the direct effects of anxiety and depression on endocrine and immunological function, stressed persons are more prone to engage in dangerous behaviors such as inadequate food, irregular sleep cycles, less exercise, and a greater risk of using nicotine, alcohol, and other drugs [28].

Body Type: The healing of wounds may also be influenced by one's physical appearance. Due to a lack of adipose tissue blood flow, an obese patient's wound healing may be compromised. Furthermore, some obese people suffer from protein deficiency, which makes a recovery much more difficult. However, when a patient is underweight, the lack of oxygen and nutrient storage might obstruct wound healing [29].

Chronic diseases: Coronary heart disease, peripheral vascular disease, stroke, and diabetes mellitus are just some chronic disorders that might impede wound healing. Patients with chronic diseases should be constantly watched throughout their treatment to ensure that the best strategy is in place [30].

Vascular Insufficiency: The lower extremities may be affected by a variety of wounds or ulcers, including arterial, diabetic, pressure, and venous ulcers. A lack of blood flow often causes ulcers. To provide proper topical and supportive medicines, the practitioner must first determine the kind of ulcer [31].

Nutrition: For over a century, food has been recognized as an important factor in wound healing. The most obvious effect of malnutrition or particular nutritional deficits after trauma or surgery is that wound healing may be significantly slowed. Patients with chronic or non-healing wounds, as well as those with nutritional inadequacies, need special nutrients. The metabolism of energy, carbohydrates, proteins, lipids, vitamins, and minerals 32 influences healing.

Traditional use of Medicinal Plants in Wound Healing: Egyptians, African and Asian indigenous peoples, Romans, and Americans have employed medicinal herbs as first-line treatment for inflammation, burns, ulcers, and surgical wounds for over 5000 years. They include a variety of natural bioactive chemicals that aid in wound healing and tissue regeneration at the wound site. The following are some examples of medicinal plants and their wound-healing properties.

***Aloe barbadensis*:** Polysaccharides, glycosides, pyrocatechol, saponins, acemannan, anthraquinones, oleic acid, water-soluble polysaccharides, and phytol are among the numerous natural bioactive substances found in *Aloe barbadensis*. Alcohol and aqueous extracts of *A. barbadensis* leaves had less antibacterial activity than acetone extracts.

Gram-positive bacteria are more likely to infect *A. barbadensis* than gram-negative bacteria. Saponins, anthraquinone, and acemannan derivatives are antibacterial chemicals with a track record. Acemannan, a major mucopolysaccharide (mesoglycan) found in *A. barbadensis,* stimulates macrophage and T-cell function by inducing the transcription of pro-inflammatory mRNAs (including IL-1a, IL-1, IL-6, TNF-α, PGE_2, and NO). Endogenous mitogenic inhibitors and reactive oxygen species bind and absorb mesoglycan moieties, promoting phagocytosis. Glycans also stabilise secreted cytokines, growth factors, and other bioactives, extending their action. The use of topically administered acemannan, which acts via the cyclin D1 and AKT/mTOR signalling

pathways, has been shown to drastically shorten wound closure time [33].

***Arctium lappa*:** Burdock is a widespread perennial weed that is also known as burdock. In North America, Europe, and Asia, *Arctium lappa* is used to heal sore throats and skin conditions including boils, rashes, and acne. *In a clinical experiment, A. lappa was shown to have anti-bacterial, anti-oxidant, anti-diabetic, anti-inflammatory, anti-cancer, hepatoprotective, and antiviral properties*. *A. lappa* root extract has been demonstrated to improve dermal ECM metabolism, influence glycosaminoglycan turnover, and reduce apparent in vivo wrinkles in human skin. *A. lappa* has also been shown to influence the Wnt/β-catenin signalling pathway, which is considered to be a critical wound cure regulator, by controlling cell adhesion and gene expression in canine dermal fibroblasts. The pain and healing of human first and second-degree burns were shown to be managed more quickly in a pilot investigation of one medicinal medicine, *A. lappa*, burns and wounds (B&W) topical ointment [34].

***Azadirachta indica*:** It was used as an anti-ulcer, antifungal, antibacterial, antiviral, anticancer, and antioxidant wound dressing. In RAW 264.7 cell lines, Viji *et al.* investigated nitric oxide (NO) scavenging activity. In wells containing collagen integrated with 1000 μg/mL of neem extract, the NO content was determined to be 10 μg/mL. The biocomposite film exhibits anti-inflammatory and NO-scavenging properties. Using the neem-incorporated collagen film RAW 264.7 cell lines, the scientists conducted antioxidant activities and a biocompatibility test. Using the MTT test, the integrated collagen films of the neem extract (400 μg/mL) demonstrated an 80 percent improvement in DPPH scavenging and a more than 80 percent cell viability. The ability to electrospin four distinct plant extracts, including *A. indica*, *Indigofera aspalathoides*, *Myristica andamanica*, and *Memecylon edule* was investigated. The ability of human dermal fibroblasts (HDFs) to thrive on nanofibrous scaffolds was determined using a cell proliferation assay. The interaction between HDF and scaffolds was assessed using F-actin and collagen staining. The spread of HDF as a result of the tests was unavoidable. Edule's PCL integration was the lowest of all, and after 9 days, it was 31% greater than PCL nanofibers. *M. edule*-incorporated PCL showed higher cell density, and F-stain examination confirmed adequate cell-to-cell contact. The extracellular matrix (ECM) was secreted by the cells in *M. edule*-incorporated PCL, according to collagen staining. *M. edule* extract with nanofibers has also been used as a channel for stem cells to boost epidermal differentiation indicators discovered after isolating epidermal lines from human adipose-derived stem cells (ADSC) [35].

***Chamomilla recutita*:** The impact of electrospun polycaprolactone/polystyrene (PCL/PS) nano-fibrous membranes as chamomile-containing active wound dressings was investigated. Qualities of therapy specific phenolics and apigenin, flavonoids, patuletin, quercetin, luteolin, and their glucosides, make *Chamomilla* recutita (L.) Rauschert, a member of the Asteraceae family, present. Apigenin is the most uncommon flavonoid found in chamomile flowers, and it remarkably impacts wound healing. Nanofibers were shown to be effective against germs, Bacteria *S. aureus*, and *Candida albicans* (fungi), with inhibitory zones of 7.6 mm in diameter, in vitro studies revealed. In vitro cell adhesion and viability of mesenchymal stem cells on nanofibers were shown using the MTT test. According to the scientists, nanofibers containing 15% chamomile extract may heal up to 99.6% of wounds after 14 days of post-treatment, as shown using a rat wound model. The presence of re-epithelization and collagen in the dermis tissue, as well as the lack of necrosis, were seen on this wound evaluation [36].

***Centella asiatica*:** This herb, also known as Asian pennywort, was used to aid wound healing. Extracts from *Centella asiatica* aerial sections have been found to aid in healing chronic ulcers in terms of distance, depth, and size. In a punch wound, Asiaticoside, a compound derived from *C. asiatica*, has been found to induce epithelialization and collagen deposition. Isolated triterpenes from *C. asiatica* promote collagen remodelling and glycosaminoglycan production. Furthermore, oral treatment of madecassoside from *C. asiatica* has been found to stimulate collagen production and angiogenesis at the wound site [37].

***Curcuma longa*:** Curcumin, an active substance found in the *Curcuma longa* root and a member of

the ginger family, has been used as a cure and a culinary flavouring for many years. Ayurvedic medicine practitioners utilize curcumin to treat asthma, respiratory ailments, liver issues, diabetes, and skin injuries. Curcumin is a prominent stomach discomfort treatment in traditional Chinese medicine. Several ethnic groups have utilised curcumin for decades and is one of the most researched nutraceuticals. A pleiotropic molecule has been discovered to interact with important biological processes at the transcription, translation, and post-translation stages. The target pathways include apoptosis, pro-inflammatory cytokines, cyclooxygenase-2, NF-κB, STAT3, 5-LOX, prostaglandin E_2, C-reactive protein, phosphorylase kinase, cell adhesion molecules, triglycerides, transforming growth factor, creatinine, heme oxygenase-1, ET-1, ALT, and AST. Curcumin causes many of its therapeutic benefits via modifying the pericellular and extracellular matrix, according to experimental data from multiple *in vivo* studies and *in vitro* testing. Curcumin increases fibroblast proliferation, the creation of granulation tissue, and the deposition of collagen in the healing of cutaneous wounds, which is not unexpected [38].

***Panax ginseng*:** It is one of the most widely used medicinal herbs in Japan, China, Eastern Siberia, and Korea. Recollection is also thought to boost immunity, improve physical agility, and decrease weariness. *Panax ginseng* is thus used to treat depression, anxiety, and chronic fatigue syndrome. *P. ginseng* has been proven to promote regulate blood lipids, vasodilation, reduce inflammation, and provide anti-cancer, anti-oxidant, anti-allergic, anti-bacterial, immunomodulatory properties, and anti-aging. *P. ginseng* has a variety of bioactive chemicals, the most effective of which is a saponin family (called ginsenosides and panaxosides). *P. ginseng* root preparations have been demonstrated to protect the skin from UVB irradiation and promote wound healing after laser burns and excisional wounds. *P. ginseng* extracts have been shown to improve keratinocyte migration and proliferation and boost collagen formation in human dermal fibroblasts *in vitro*. It has also been demonstrated that ginsenoside Rb2, isolated from *P. ginseng*, induces the development of epidermis in raft culture by increasing epidermal growth factor and receptor expression, fibronectin and receptor expression, and keratin and collagenase-I expression, all of which are important in wound healing [39].

***Sphagneticola trilobata*:** *Wedelia trilobata*, also known as *Sphagneticola trilobata*, is a plant that was formerly endemic to the tropical Americas but has since spread across the tropics as one of the most invasive species on the planet. Rheumatism, recurrent sores, and painful arthritic joints have all been treated with alcohol extracts from *W. trilobata* leaves. *W. trilobata* leaves contain luteolin, a flavonoid with neuroprotective, anti-cancer, anti-oxidant, and immunomodulatory properties. The leaves of *W. trilobata* are used by traditional healers to cure skin wounds. Luteolin suppresses the production of NF-κB-regulated pro-inflammatory cytokines, which are a common feature of skin infections and psoriasis. Balekar *et al.* separated ethanolic extracts from *W. trilobata* leaves and evaluated them in vitro in a research aiming to substantiate this traditional usage. Fibroblast viability, proliferation, and migration were shown to be aided by certain sub-fractions. *Staphylococcus aureus* and *S. epidermidis* were also shown to be susceptible to different sub-fractions [40].

Patents: Honey might be utilised in dressings, according to a patent filed by Roy *et al.* in 2010. The dressing is made out of an alginate fiber sheet that has been thoroughly saturated with honey. As a consequence, the dressing has porous surfaces, and when the exudate is absorbed and applied to the wound, the dressing becomes gel-like.

There are 11 claims in this invention that describe how honey is impregnated into the dressings. It may be used to heal both acute and chronic wounds. "Bioactive compounds from theacea plants for the healing of wounds and injuries," patented by Koganov *et al.* The invention is a bioactive topical preparation that contains bioactive components from theacea plants. Theacea plants' bioactive component has anti-inflammatory properties on the skin and the ability to normalise skin damage or tissue injury. Balkrishna *et al.* registered a "novel herbal formulation for wound healing therapy" in 2013. Their invention includes a new, synergistic herbal composition as a regenerative medicine that consists of a mixture of

therapeutically effective amounts of extracts obtained as a basis from *Glycyrrhiza glabara*, *C. longa*, *Tipha angustifolia*, *A. indica*, and *H. suaveolens*, as well as an optional basis consisting of Pig fatin *Sesamum indicum*.

A wound pad comprised of hydrophilic cotton fabric coated on one side with zwitter ionic low molecular weight chitosan and laced with organic-synthesized silver nanoparticles on top has been patented by Walia *et al.* Curcumin particles and tulsi extracts enhance their qualities using herbal medicinal principles and create a synergistic effect with all of the components working together to improve therapeutic outcomes.

"A regenerative medication, the herbal composition for wound healing treatment," Balkrishna *et al.* also patented. This herbal blend contains therapeutically appropriate extracts from G. glabara, C. longa, Tipha angustifolia, A. indica, and H. suaveolens, primarily used for wound healing and wound therapy. There are 27 claims in all and six drawing sheets that indicate testing on various wounds. As a regenerative medication, the innovation demonstrates innovative synergism and effective synthesis of herbs. This also includes a technique for making the herbal compound.

During this time, another scientist, Melikoglu *et al.*, patented "Herbal formulation for topical wound therapy" using novel herbal formulae that have shown to be effective for the topical treatment of skin wounds and oral mucosal wounds. To enhance analgesic, antibacterial, antifungal, and anti-inflammatory effects, a solution or gel containing polyhexamethylene biguanide as an anti-microbial agent and poloxamer as an emulsifier, as well as a product containing at least one herbal ingredient (Comfrey *Symphytum officinale* L. extract and/or *Commiphora molmol* tincture) with analgesic, antibacterial, antifungal As a protective agent, algaecide, bactericide/bacteriostatic, fungicide/ fungistatic, and microbicide/microbiostatic, poly hexamethylene biguanide (PHMB) was utilised. Kerri-Anne *et al.* patented a "Topical herbal formulation" that is very effective in the treatment of wounds and skin conditions. Gotu kola (*Centella asiatica*), yarrow (*Achillea millefolium*), figwot (*Scrophularia nodosa*), *Echinacea purpurea*, and *Plantago major*, are among the plants in this category. Both anti-inflammatory and anti-microbial capabilities are included in the composition. It was shown to be very useful as a synergistic healing agent in the treatment of wounds, scar prevention, and hair regeneration in the wound region. It was also proven to be effective in the treatment of typical human skin problems like as eczema and nappy rash.

"Buckwheat honey with bacitracin wound-healing dressing" was created and patented by Kenneth *et al.* In treating acute and chronic wounds and skin problems, as well as the regeneration of skin and/or dermal tissue in chronic wounds, the invention has been proven effective. The product is made up of buckwheat honey and bacitracin composition or formulation. The compound is gelled in one distinct manifestation. The mixture is administered directly to a wound or a patient's skin, or it is impregnated on gauze or other similar material and applied to an exuding or non-exuding acute or chronic wound or skin disease through a bandage or dressing.

"Herbal oil composition for topical use and medical uses thereof," patented by Upendra *et al.* The invention contains a topically applied herbal oil solution based on *Heterophragma roxburghii* bark extract that may be used to treat and heal a variety of skin irregularities and infections, all forms of wounds, and other medical issues related to a lack of blood flow in humans and animals. Diabetic gangrene, dry gangrene, wet gangrene, athlete's foot, burn wounds, diabetic foot ulcer, bedsore, untreated open wounds, snakebite wounds, and cellulite-formed gangrene are just a few of the medical disorders for which the topical herbal oil formulation is effective.

"Herbal preparation for expediting wounds and skin inflammations healing and its application" was patented by Tomulewicz *et al.* The invention relates to a pharmaceutical preparation that may treat wounds and skin inflammation. The herbal medicine is defined as emulsified or suspended organic medium extract of *Melittis melissophyllum* L. ethyl alcohol in the range of 10 percent to 40 percent by weight and 10 percent to 20 percent by weight. Vaseline album was utilized as an organic medium in an ointment from 40 percent w/w to 70 percent w/w, 2 percent w/w triethylamine, hydroxy cellulose, and filtered water, aqua purificata, from

30 percent w/w to 35 percent w/w. "Wakeri (*Wagatea spicata* Dalzell)" was patented by Omkar *et al.* for wound healing. Wakeri-fortified *Kampillakadi Tailam*/oil is used in the innovation. Wakeri fortification is made up of oil extract of Wakeri root bark powder, a Kampillakadi oil component. Oil extracts of Kutaj, Vavding, Trifala, Kapilla, Bala, Patolpatra, Lodhra, Nimsal, Charolya, Nagarmotha, Dhayatiphul, Khadirsal, Chandanadded, and Agaru with Sarjaras make up Kampillakadi oil. The invention also includes a tulle, an ointment, a liniment, a capsule, a wound healing spray, a cream, and a gel containing Wakeri-fortified Kampillakadi oil for topical application; the compositions include an ointment, a tulle, a capsule, a liniment, a wound healing spray, Wakeri Wight synonym of *Moullava spicata* with *Kampillakadi Tailam* is the subject of the innovation [41].

CONCLUSION: Wound healing has been a difficult clinical problem for wound management since ancient times. Multiple cell types, extracellular matrix, and soluble mediators, including growth factors and cytokines, all play a role in wound healing. Wound care has received a lot of attention in Ayurveda, focusing on innovative therapeutic procedures and the progress of acute and chronic wound therapy treatments (herbal). Researchers are testing new formulae, dressings, and medicinal plant compositions to establish a cost-effective, efficient, stable, and long-lasting wound management/treatment system.

Wound treatment is becoming more effective and patient-centric as nanotechnology, and innovative materials become available. Newer technologies, such as 3D printing, are also enabling the development of various medication delivery methods for wound management. Tissue engineering and regenerative medicine are two technologies that can potentially improve wound healing systems in the future. Improved quality control procedures for identifying, screening, and quantifying herbal components and well-designed preclinical and clinical trials will pave the way for new research avenues in wound care treatment.

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