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REVIEW ARTICLE

Unravelling the Biology of Wound Repair: Molecular and Cellular Perspectives

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ABSTRACT
Any damage to tissue integrity brought on by physical, chemical, thermal, microbiological, or immunological forces is referred to as a wound. Hemostasis, inflammation, proliferation, and remodeling are all stages of the intricate, multi-phase wound healing process. These stages overlap and rely on cytokines, extracellular matrix, and cellular interactions. Wounds can be categorized according to their content (acute or chronic) or source (open wounds, such as puncture or incision wounds, and closed wounds, such as bruises). This paper describes the role of fibroblasts, platelets, neutrophils, macrophages, keratinocytes, and endothelial cells in biological wound healing processes. To understand wound healing dynamics and evaluate metrics like wound contraction, tensile strength, and histopathology, experimental models- both in vitro (fibroblast and scratch assays) and in vivo (excision, incision, and burn wound models)-are crucial. These investigations aid in the comprehension of wound healing and provide improvements in treatment.
Keywords: *Wound healing, Hemostasis, Inflammation, Cytokines, Cellular Interaction, Experimental models, Platelets*

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INTRODUCTION

Any destruction of tissue integrity may be considered a wound.[1]Wound is well-described as disorder of structural, functional, and cellular progression of living tissue, possibly due to chemical, microbial, thermal, physical, and immunological agents. A wound is a rupture in the integrity of epithelium and can be caused by a disturbance in the structure and function of normal tissue underneath it.[2] The healing of wounds includes complex interactions between several cell types, cytokine mediators, and extracellular matrix. Remodeling, proliferation, inflammation, and Hemostasis are four stages of the healing of wounds. Although each phase is distinct, they overlap in the ongoing wound-healing process. A blood supply as well as nourishment are necessary for wound healing.[3]

Classification of wounds:

Two categories are used to classify wounds. The first classification is based on the wound's composition, whereas the second is based on its cause.[4]

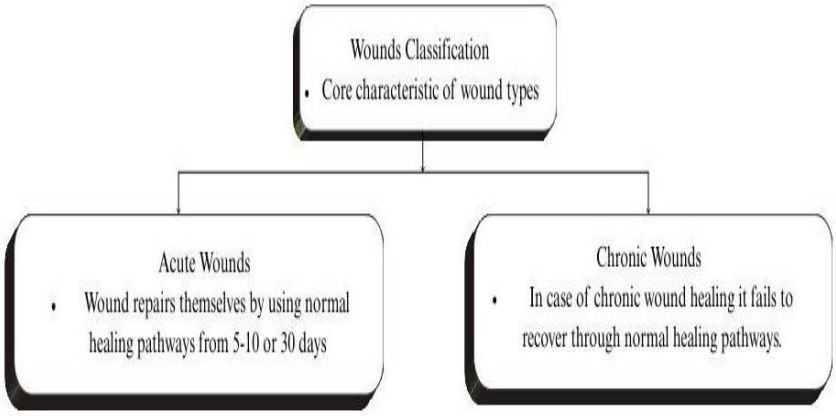

Figure 1: *Classification of wounds based on composition*

Cellular mechanism of wound healing:

Typically, wounds begin to heal right away after an accident, but occasionally, they do not heal appropriately or systematically. Wounds of this kind must be managed continuously. Typical stages of wound healing include the maturation, proliferative, and inflammatory phases.[6] Period of inflammation lasts from a few minutes to up to twenty-four minutes following an injury. Wound healing starts with hemostasis. Within minutes after the damage, numerous extrinsic and intrinsic coagulation factors will be activated; this could result in degranulation, release of growth factors (GFs) as well as chemotactic factors (chemokines), which could aid in forming clots.[7]The second stage, known as the inflammatory phase, is when neutrophils, first cells to arrive at site of injury, clean the trash as well as germs to create an environment conducive to wound healing.

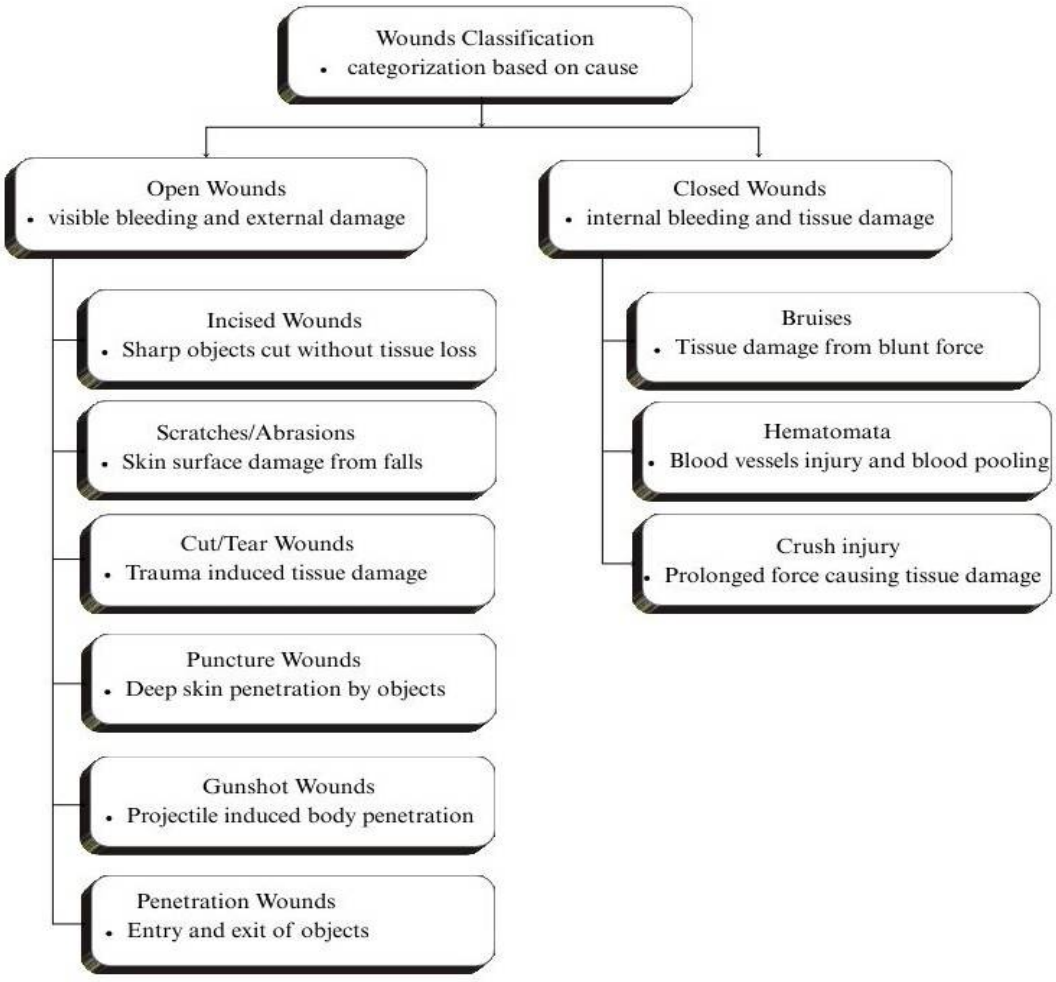

Figure 2: *Classification of wounds based on the cause of the wound*

At last step of inflammatory phase, macrophages act, causing harm to the tissue. Macrophages collect and aid in the engulfment of bacteria while also causing damage to the tissue. Macrophages initiate 2 important features of healing, which are angiogenesis as well asfibroplasia. [8, 28] After three days of injury, the proliferative phase begins and lasts for 2 ± 4 weeks. The fibroblast-stimulating factor is activated during the macrophage stage. Fibroblasts were discharged. Fibroblasts, activated, create collagen and proteoglycan and have an impact on granulation tissue remodeling. Granulation tissue is essential for the healing of wounds because it decreases the size of the injured epithelization and raises the strength of tensile of the wound.[9]Wound healing ends with maturation. The maturation phase ended about two years ago. It relies on ongoing collagen synthesis. Tensile strength increases steadily and at a contraction rate. [10,11]

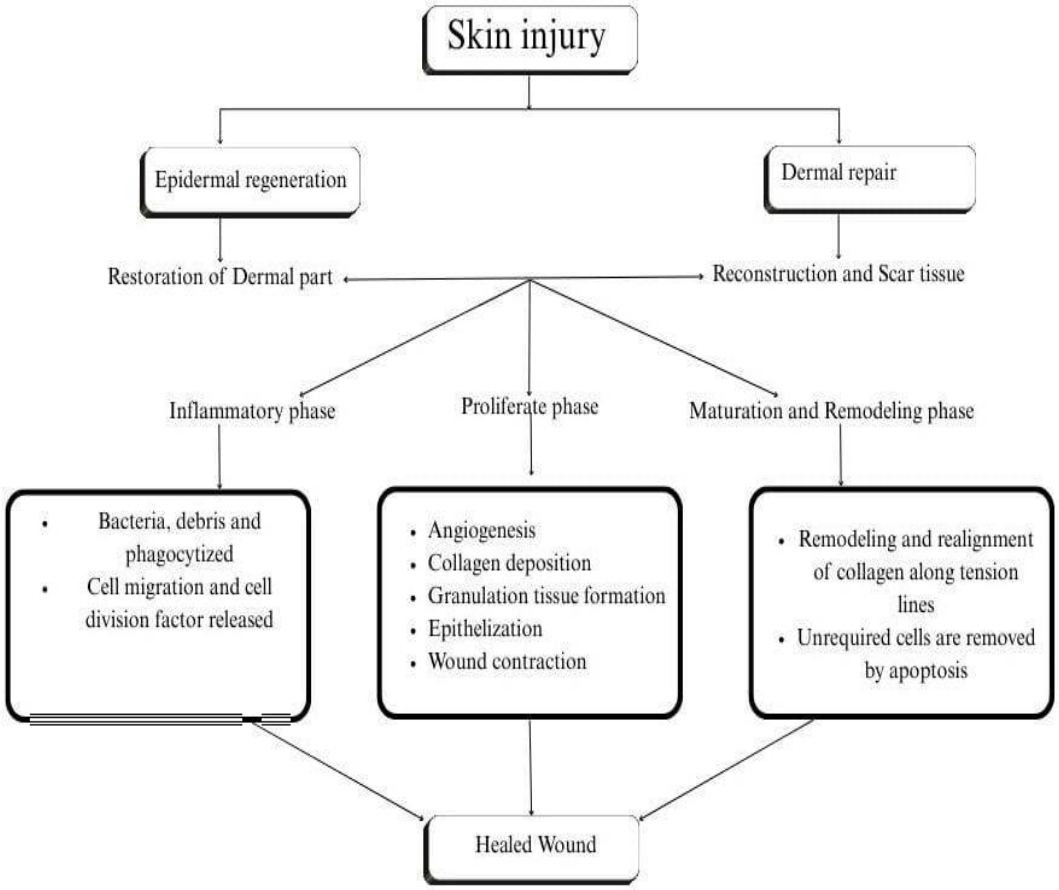

Figure 3: *Mechanism of Wound Healing*

Molecular mechanism of wound healing:

Following tissue damage, halting the bleeding and starting the healing cascade should be the top priorities. Through adhesion and aggregation, platelets create a transient clot at the wound site, playing a crucial part in this process. In order to improve platelets adherence, they release von Willebrand factor (vWF), and serotonin causes vasoconstriction, which lowers blood flow to the afflicted area. Platelets-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) are also secreted by platelets and serve as signals for further healing processes. Within minutes following the damage, this phase happens quickly. The inflammatory phase begins to prevent infection and remove debris from the wound after the bleeding has been stopped. The initial immune responders, neutrophils, enter the wound site in a matter of hours and use phagocytosis to eliminate infections and dead cells. They increase the inflammatory response by secreting tumor necrosis factor-alpha (TNF-ά) and interleukin-1 (IL-1). Following this, macrophages release IL-6 and TNF-ά, which initially contribute to inflammation. Later, they change into pro-healing cells by secreting PDGF and TGF-β, which promote collagen production and fibroblast activity. The histamine released by mast cells increases vascular permeability, which permits the invasion of immune cells. More neutrophils are attracted to the wound site by interleukin-8 (IL-8). The proliferative phase, which is marked by fibroblast activity, angiogenesis, and tissue healing, is

preceded by the inflammatory reaction. In response to PDGF and fibroblast growth factor (FGF), fibroblasts migrate to the wound site and create granulation tissue by manufacturing collagen and extracellular matrix components. Basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) promote angiogenesis, which creates new blood vessels to carry nutrients and oxygen. T and B cells are examples of lymphocytes that regulate the immune response, guaranteeing the removal of infections and fostering healing. FGF stimulates the proliferation of keratinocytes, which re-epithelialize the lesion. Remodeling, the last stage, makes the repaired tissue stronger. TGF-β keeps encouraging the formation of collagen, which increases the tensile strength of the tissue. Myofibroblasts, which develop from fibroblasts, shrink the wound's edges. As oxygen and nutrient needs decrease, newly created blood vessels stabilize and excess vessels regress. This stages restores functional integrity by transforming the brittle granulation tissue into a more robust and organized extracellular matrix.[12]

Phases of wound healing:

Hemostasis: When a blood vessel is wounded, it rapidly contracts, and a clot forms to stop extreme bleeding. Platelets, which help with clotting, adhere to the injured area by interacting with proteins like collagen and von Willebrand factor. This causes their activation, leading to the release of molecules that support the clot. The clot is composite of fibrin and other proteins, closing the wound, preventing infection, and providing a basis for immune cells. Platelets also release signals that attract immune cells and stimulate skin repair. They help fight infection by releasing antimicrobial peptides. Once the clot forms, the body stops excessive clotting by various inhibitors. In the meantime, smooth muscle and endothelial cells, along with specialized progenitor cells, repair the blood vessel, directed by platelet-derived growth factors.[13]

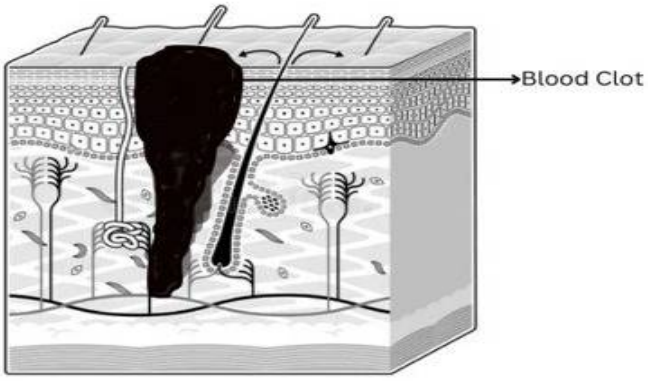

Figure 4: *Hemostasis*

Inflammation: Native inflammation is the body's first defense in contradiction of infection in a wound. It begins when injury releases signals from damaged cells (DAMPs) and bacteria (PAMPs), which trigger immune cells like mast cells, T cells, and macrophages. These cells stimulate pro-inflammatory molecules that attract more immune system cells and enlarge blood vessels to help white blood cells penetrate the wound. Using phagocytosis and antimicrobial traps, neutrophils arrive first to eliminate dead cells and bacteria. Though too much inflammation can slow healing, too little can leave the wound weak to infection. Neutrophils start to disappear after a few days, either by becoming extinct, being removed by macrophages, or returning to circulation. Monocytes enter the wound and change into macrophages, which help to clean up debris and support healing. Primarily, macrophages help inflammation by releasing cytokines and growth factors. Later, they change to an anti-inflammatory state, producing molecules that promote tissue repair, blood vessel growth, and skin regeneration. These immune responses maintain infection control and tissue repair, confirming proper wound healing.[13]

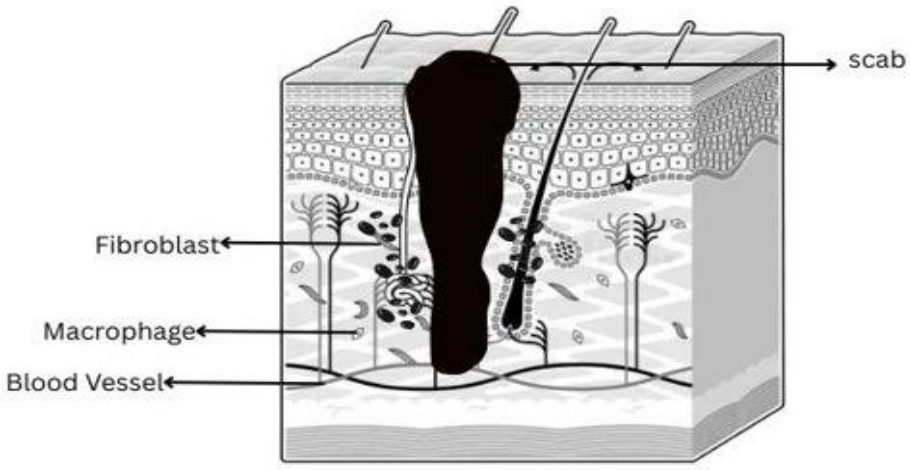

Figure 5: *Inflammation*

Proliferation: The stage of wound healing referred to as proliferative includes dermal cells such as endothelial, macrophages, keratinocytes, andfibroblast cells working together to permanently fix the injury, create new tissue, and form blood vessels. Within 12 hours of injury, keratinocytes at the wound edge become more moveable due to mechanical, chemical, and electrical signals. They travel across the wound in a process called re-epithelization, using enzymes (MMPs) to clear debris and lay down a new basement membrane. Hair follicle steam cells also pay contribute to new epidermis formation. Fibroblasts change the provisional fibrin matrix into granulation tissue, rich in collagen as well as fibronectin. Some fibroblasts transform into myofibroblasts, increasing wound healing to speed closure. Oxygen deprivation (hypoxia) activates VEGF release, stimulating endothelial cells to form new blood vessels. Macrophages fund this process by releasing enzymes (MMPs) and growth factors. They also help change new vessels by supervisory their formation and preventing excessive growth. Nerve fibers renew after injury, assisted by neuropeptides like substance P, which supports cell growth and blood vessel formation. Reduced nerve signaling, as seen in diabetes, postponements healing. Together, these processes return skin structure and function, formulating for the final remodeling phase.[13]

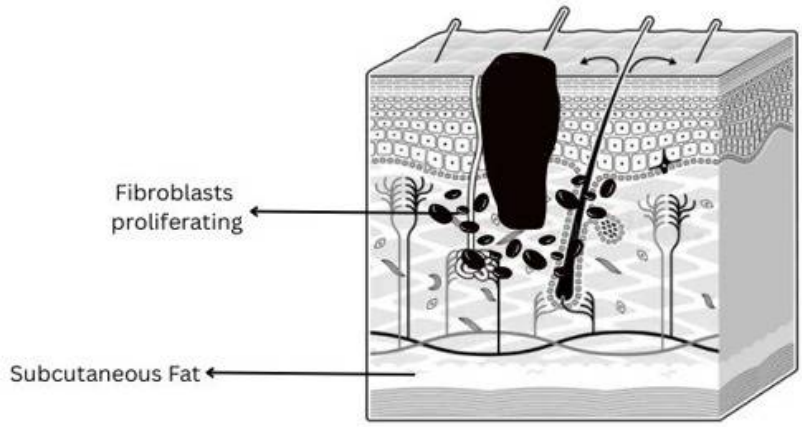

Figure 6: *Proliferation*

Remodeling: The remodeling phase of wound healing begins with forming fibrin clot and lasts for years, ending with a mature, collagen-rich scar. Fibroblasts change initial fibrin clot with fibronectin, proteoglycans, as well ashyaluronan, later forming mature collagen fibrils. Initial granulation tissue contains more collagen type III (30%) than normal skin (10%). Over time, type III is changed by type-I, firming scar. However, scar tissue never fully recovers the structure or strength of unwounded skin (only up to 80%). Matrix metalloproteinases (MMPs) balance collagen synthesis and breakdown, confirming proper ECM remodeling. Elastic fibers take months to progress, with elastin fragments (elastokines)

acting as signaling molecules during repair. Myofibroblasts, triggered by TGF-β and mechanical tension, initiative wound contraction. They usage actin filaments to pull the ECM composed, reducing wound size. As wound healing is completed, all the cells leave a scar. Though the wound closes, the healed skin never fully recovers its original structure or elasticity.[13]

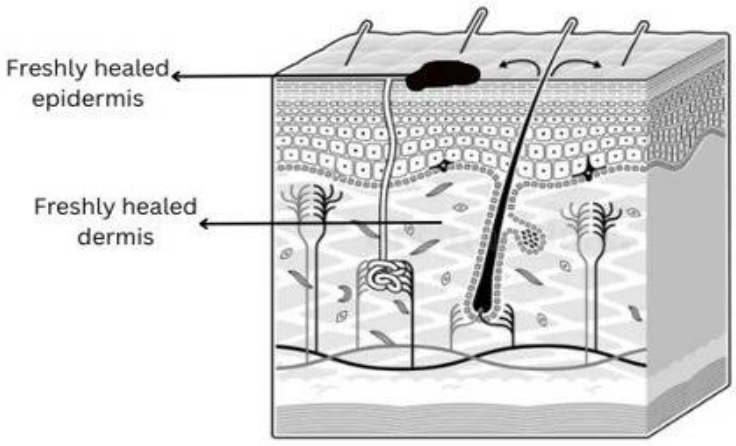

Figure 7: *Remodeling*

Various wound healing model:

Studies on wound healing come in two varieties. In vitro investigations come first, followed by in vivo research. The following are some of the wound healing models used in this study:

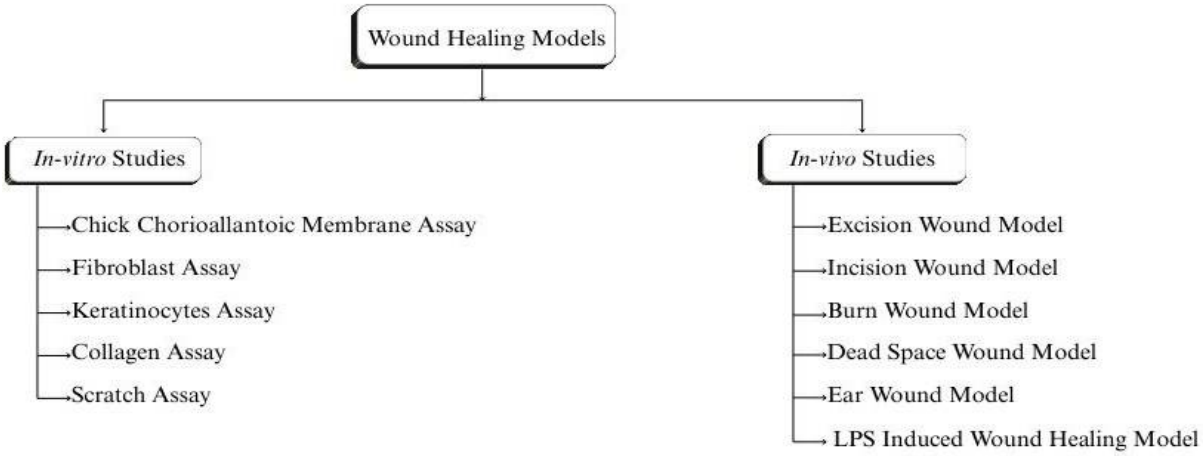

Figure 8: *Classification of wound healing models*

***In-vitro* research:** The Latin phrase "the technique which is performed outside the living animal" is the source of the term *"in-vitro." In this kind of research, tissue is separated from the animal body as well as kept in the proper growth medium for a few days to several months*. The in vitro assay is useful for identifying compounds that promote healing and antibacterial actions. [5,16]

Chick chorioallantoic membrane assay: In the CAM model, it stimulates development of new blood vessels. For wounds to heal, the angiogenesis process is essential. They provide tissue healing and the restoration of regular blood flow.[17] Nine-day-old fertilized chick eggs are assembled in this model, and a tiny window (1.0 cm2) is created on the shell's surface. A hole is made so that air can be drawn out via the rubber bulb. The window is open, the testy sample is at the intersection of two sizable vessels, and the methylcellulose is securely fastened. After sealing the window with the tape, eggs are incubated in well-humidified environment at 37°C for 72 hours. Observe the creation of new blood vessels when the eggs are open. Contrasting the drug-containing and drug-free egg disks. Fibroblast growth factor, or FGF, is the industry standard. [5,18]

Fibroblast assay: In this technique, suspended cells are fertilized with Fetal Calf Serum (FCS) as well as left for three days to balance each after being incubated in CO2 conditions in an atmosphere and air at 37°C in tissue culture incubator. On the third day, a typical medication is added to the medium. The media is changed as well as cleaned using phosphate-buffered saline solution on the nineteenth day. Cells are

divided into two sections. Trepan blue dye is one reagent used to measure the concentration of hydroxyproline. [5,19]

Keratinocytes assay: The epidermal layer is covered by keratinocytes, which also stop fluid loss and delay attacks by bacteria. Keratinocytes free in serum growth medium (KGM) are used to cultivate keratinocyte cells at 37°C while carbon dioxide is consumed. Twenty-four well plates are used to cultivate vascular permeability factor (VPF) cells. Following overnight culture, the medium is combined, the cell lyser is extracted using lysis buffer, the samples are centrifuged, and they are kept at 70°C for immunochemical testing. [5,20,15]

Collagen assay: TGF-3 (transforming growth factor type-3) is essential to tissue repair and inflammation when present in cells or cell fragments. Dulbecco's modified Eagle's medium (DMEM) as well as calf serum maintain NRK 49F cells. When the cells reach confluence, growth factors are added to HCL, which contains albumin from bovine serum. Medium is changed to Minimal Essential Medium (MEM), which includesHepes, plasma-derived serum, buffer, and glutamine. After 16 iterations, the media is transformed into ascorbate and supplements without plasma. Reintroduced are growth factors. After 15 minutes, proline is added, as well as the incubation process continues for three hours at 37°C. [5,21,22]

Scratch assay: Creatinga "scratch" on the cell monolayer is the basis for the model's name. To "scratch" until fresh cell-cell interactions are known again, the edge of cell is employed to move forward and backward. In a 24-well cell culture plate, keratinocytes HaCaT (2–104 cells) and fibroblasts L929 (1–104 cells) are maintained. Pipette slope is used to create a linear scratch in the cell monolayer. The remaining cell is washed away with DME solution. The positive control group is the standard medication. The gap in time intervals is used to estimate the cellular gap. [5,23,24]

***In-vivo* studies:** The term comes from the Latin phrase “inside the living body.” The test is conducted on living organisms (mice, rats, rabbits, etc.), and its pharmacological action is the same in humans as in animals. As a result, nonclinical research in animals is necessary before administering the test to humans. [5,25]

Excision wound model: In this specific model, rats' depilated dorsal regions are infected with circular wounds about 3 cm in diameter. The wounds should be assessed immediately by covering the area with transparent polythene or graph paper. This is the introductory or starting reading. Drugs must be administered as a test as well as astandard, and observations are made by tracking wound area and calculating wound closure area on alternate post-wounding days. [26,27,28,29]

Incision wound model: This model is carried out under anesthetic conditions, and the animal’s skin is sliced. Two paravertebral incisions, each 6 cm long, were created on each side of the rats, around 1.5 cm from the center, through cutaneous muscles and skin. Following the skin incision, skin is held together as well as sewn tightly and continuously at 0.5 cm intervals using a curved needle (No. 11) as well as suture thread (No. 000). On day nine, later the wound has healed, the sutures should be removed. On10thday, the tensile strength of wound should be assessed using a continuous and steady water flow approach. [26,30]

Burn wound model: Animals that fast overnight develop burn wounds. Under anesthesia, a 300 mm2 circular cylinder using hot, molten wax at 80°C is poured onto the animal’s shaved dorsal region until the wax solidifies. Wax takes 10–12 minutes to solidify. Now that the cylinder has disengaged, the marked partial thickness circular burn model remains. [26,31,32]

Dead space wound model: The granuloma tissue undergoes physical alterations in this specific model. Subcutaneous dead space wounds create a pouch through a tiny skin snip in the groin and axilla regions. Cylindrical grass piths of 2.5cm (length) and 0.3cm (diameter) are packed inside pouch.2 grass piths are taken by each animal at various places. Grass pith attachments induce granuloma development. An alcoholic swab was used to mop the wounds and stitch them. Granulomas were removed and cut open close to the grass piths. On the tenth post-winding day, the continuous water flow technique was used to assess tensile strength of tissue piece (obtained by trimming the rectangular strip of granular tissue) that measured roughly 15mm (length) and 8mm (width). [26,32,33,34,35]

Ear wound model: Since the ear wound model contains a vascular cartilage wound bed and heals without contraction, it may be appropriate in some of the few instances where human healing is solely dependent on epithelialization and granulation development without contraction. [26,36]

LPS induced wound healing model: This specific model involves creating circular wounds around 3 cm in diameter on the rat’s depilated dorsal area while maintaining aseptic conditions. LPS is then applied to the lesion topically or intradermally. Apply the standard medicine and the test drug based on the animal grouping immediately.[37]

Assessment metric of wound healing:

Measurement of wound area/rate of wound contraction: Until the wound is fully healed, progressive change in the wound area is tracked on a full HD camera on specific days, such as 2, 4, 8, 12, 16, and 20. The trace is taken on paper, and the area is calculated using mm-scale graph paper. [14,38]

$$wound\ closure\ (\%) = \frac{Initial\ wound\ area - Remaining\ wound\ area}{Initial\ wound\ area} \times 100$$

Determination of period of epithelization: Scab falling off the wound is thought to be a sign that wound is healing or that full epithelization has occurred. Epithelization time is number of days needed for this. [14,39]

Calculation of the wound index: Table shows that the wound index may be predicted using an arbitrary scoring system. [14,40]

Table-1: arbitrary scoring system

Change in gross	Score
Pus formation-a sign of necrosis	4
Healing has not yet begun, but the surrounding is safe	3
Healthy but delayed recovery	2
A partial but sound recovery	1
Whole recovery	0
Total	10

Measurement of tensile strength: Tensile strength is assessed after animals are sacrificed on the 10thday of model after receiving high dose of ketamine HCL.Following rodents' removal, wound stripe of equal length and width is carefully eliminated from the rats and fixed to tensiometer at predetermined distance. Then, both ends of skin strips are secured with the stainless-steel clips of the tensiometer. One clip enables the stand to be hung, and another holds a plastic bottle that may be incrementally filled with water until wound strip is broken. The water content has been determined and shown as wound's tensile strength in grams. [14,43,42]

Histopathology: Tissue is taken from each animal's wound site within the group after the rats are killed with a high dosage of ketamine HCl. These tissue samples are kept apart in the formalin solution for microscopic analysis. [14,41]

CONCLUSION

Acute wounds, which are caused by physical trauma or invasive procedures, usually follow a systematic healing pathway, progressing through the distinct yet overlapping stages of hemostasis, inflammation, proliferation, and remodeling. This structural process ensures the restoration of anatomical and functional tissue integrity. Chronic wounds, on the other hand, present a unique challenge because of their prolonged inflammatory state, which disrupts the natural progression of healing. Wound healing is an essential biological process that is defined by the intricate coordination of cellular and molecular mechanisms to restore tissue integrity after injury. The biological components, such as platelets, endothelial cells, fibroblasts, neutrophils, keratinocytes, and macrophages, play key roles in wound healing. In addition to releasing signals that attract immune cells and promote skin regeneration, platelets also start the creation of clots. Together, neutrophils and macrophages eliminate pathogens and debris while producing growth factors to aid in tissue healing. To ensure the regeneration of skin and blood vessels, fibroblasts and endothelial cells aid in creating granulation tissue and angiogenesis. In vitro as well as in vivo experimental models have proven invaluable for study of wound healing dynamics. In vitro methods enable researchers to investigate cellular responses and biochemical interactions in controlled environments, while in vivo models offer insights into the healing process within living organisms, closely resembling human physiology. These models make it easier to evaluate wound healing metrics. Understanding the principles behind wound healing and creating novel therapies has been greatly aided by applying sophisticated experimental approaches. Recovery results have been demonstrated to be improved by therapies that target inflammation, angiogenesis, and cellular responses. Furthermore, improving existing procedures and investigating novel ways are necessary for tackling the obstacles of chronic wounds and boosting the quality of repaired tissue.

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