COMPILATION OF DIFFERENT METHODS AND TECHNIQUES INVOLVED IN THE WOUND HEALING PROCESS

Sonu Saini[1*], Amit Nayak[2], Vikas Jogpal[2], Divyanshu[2]

Abstract
The complexity of the healing process and the diverse character of the wound environment make wound healing studies challenging. Various cells and repair phases participate in healing process include Haemostasis, proliferation & re-epithelialization, Inflammation or remodelling. To test the new therapeutic drugs there is a need to conduct pre-clinical studies on animal models, such as mice, rats, pigs & rabbits. A variety of techniques has been used to induce or create the wound. This article provides an overview of wound models to evaluate wound healing activity. The aim of this article is to help researchers design &execution the wound healing experiment.

Keywords: Wound healing, Homeostatic, Inflammatory, Remodelling, Wound healing Models

[1*]School of Medical and Allied Science, G.D Goenka University, Gurugram, Haryana, India
[2]Professor, School of Medical and Allied Sciences, G.D Goenka University, Gurugram, Haryana, India
[2]Associate Professor, School of Medical and Allied Sciences, G.D Goenka University, Gurugram, Haryana, India,
Email: vikas.jogpal@gmail.com, Ph. 9625104800

***Corresponding Author:** Sonu Saini
*School of Medical and Allied Sciences, G.D Goenka University, Gurugram, Haryana, India,
Email: sonusaini619942@gmail.com, Ph 9588524936

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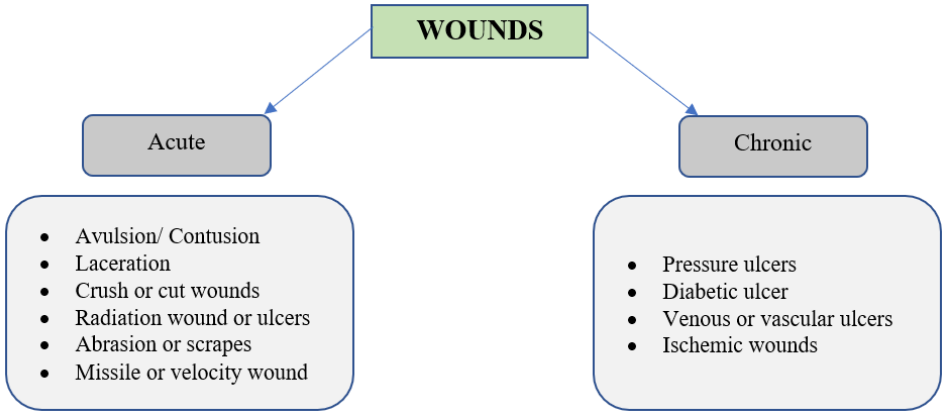
INTRODUCTION

The largest and most exposed part of the human body is the skin which is essential for various biological functions. Therefore, severe skin injury may lead to various infections in the body. A few of the causes of wounds include surgery, trauma, pathologic conditions like diabetes or vascular ailments, as well as extrinsic forces such as pressure, burns, and cuts. Recovery of skin injury is very important; many cells, growth factors, and cytokines are involved to close the lesion**[1]**. Injury-related difficulties, particularly for chronic wounds, are mostly attributable to care and treatment practices that restrict wound healing rather than tissue integrity restoration. A wound is defined as cellular, anatomical, or physiological damage in the skin; including cuts, scrapes, scratches, and punctured skin. A specific injury must have an appropriate dressing to heal more quickly and avoid infection **[2].**.A Complex and dynamic process called wound healing replaces tissue layer and cellular structure that have lost vitality. Wound healing involves the interaction of several cell types and their by-products**[3]**. Events that occur during wound healing are: inflammatory response, cell proliferation, production of the extracellular matrix's constituent parts, and the last step, referred to as remodelling**[4]**.

Persistent wounds reduce the quality of life, and the expense of treatment is shown in morbidity and even mortality, as well as from a psychological standpoint and in extended hospital stays. For these reasons, wounds have been called a "Silent Epidemic"**[5]**. The majority of financial expenses are related to hiring medical staff, the length and cost of hospital stays, and the selection of supplies and treatments. For all of these reasons, it is difficult to design new technologies that are meant to enhance the healing process. Various studies on wounds have been done by researchers to heal the wound faster by using various herbal **[6]** and synthetic molecules **[7]**. Various wound models have been used for preclinical studies to investigate the therapeutic effectiveness of test drug molecules or to check the particular dressing**[8]**. In addition to studying the safety, efficacy, and potency of any experimental medicines, these models utilise the research to intricate cellular and biochemical process of wound healing and repairment. It would be difficult to present all of the alternatives since the subject of using models and methodologies to evaluate wound healing is so complicated. The primary objectives of this article are to provide a variety of techniques, including image analysis, wound healing rate, histopathological, immunological, and biochemical assays, biophysical assays as well as a few commonly used in - Vivo models (such as excisional, impaired and excisional wound models). The models and its techniques presented in this review paper are meant to offer researchers a useful framework for their experimental protocols that may eventually lead to translational studies.

Classification of wounds



Acute wound

An acute wound can occur suddenly, for a short time, and may heal on its own and it takes short time to heal**[9].**

- **Avulsion:** Wounds are the wounds in which top layer of skin is torn. These are the traumatic injury in which tissue of the body get detached**.[10]**
- **Laceration:** Laceration is formed when a deep cut is formed by knife and other tools **[11]**
- **Crush or cut wounds** When force or pressure is applied to a bodily part, a crush injury occur**[12]**.
- **Radiation wound**: These wounds are refers to damage to the skin and underlying tissues as a result of acute exposure to a high external dose of radiation**.[13]**
- **Abrasion:** A specific type of open wound called an abrasion is produced when the skin rubs against with a rough surface. **[14]**

- **Missile/Velocity wounds**: These Injuries produced by sharp items that pierce the skin, such as nails, tacks, knives, needles, teeth, and ice picks are referred to as missile wounds or puncture wounds**[15].**

Chronic wounds

Chronic wounds are those in which one or more stages of the phases of haemostasis, inflammation, proliferation, and remodelling have interrupted the normal process of healing**[16]**.

- **Pressure ulcer** Whenever you are restricted to a bed or chair, pressure injuries, commonly known as pressure sores or bedsores, can appear. Pressure on specific body areas over time causes these sores to form**[17].**
- **Diabetic ulcer:** A diabetic foot ulcer is an open painful or wound that naturally grows on the bottommost of the foot and affects 15% of people through diabetes**[18].**
- **Venous ulcers:** venous ulcers are open, non-healing lesions. They frequently develop when blood is not circulated adequately and starts to collect in certain areas. Mostly they occur on leg or ankles**[19].**
- **Ischemic wounds/ Arterial ulcers:** Ischemic ulcers refers to the decrease in blood flow in a specific region of the body. In Ischemic ulcers type of lesions are formed that heal slowly. They often appear on the feet, ankles, or legs and are brought on by the legs' arteries' inability to give enough blood. Arterial ulcers are another name for ischemic ulcers.**[20].**

Process of wound healing

Wound healing is a active physiological progression which requires a sequence of controlled relationships between cells with in dermis and epidermis, as well as heavily regulated phases of biological activities. Many medical conditions like diabetes, haemophilia is linked to anomalies in fibrous tissue, which can impede tissue repair and lead to the development of a persistent ulcer **[21].** The fundamental four interconnected wound healing mechanisms are briefly discussed below (Figure)

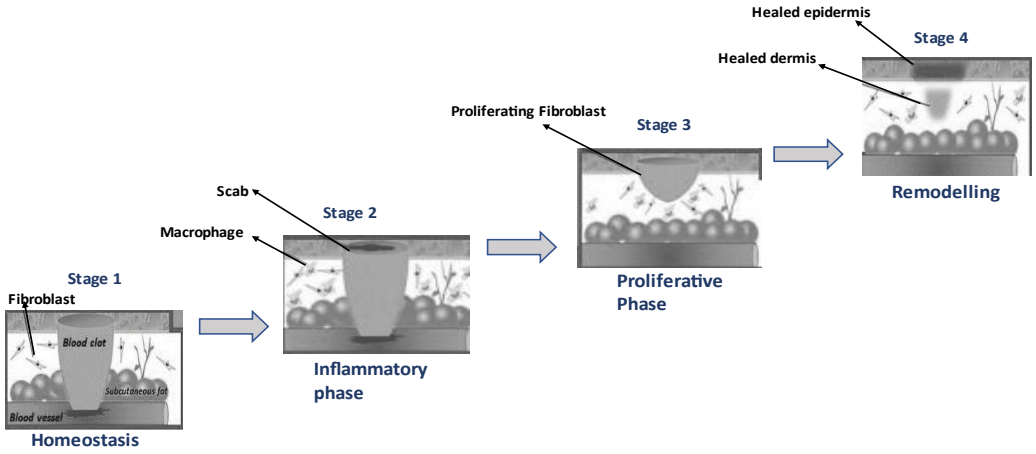


Figure: Different phases of wound healing**[22].**

Haemostatic phase

In this phase platelets bind to type 1 collagen just after injury and become stimulated, cells secrete membrane proteins that cause blood clotting. The cells secretes components that encourage the clotting cascade by producing protease, which makes the combination of fibrinogen from glycoprotein. A stable haemostasis plug is formed when fibrin mesh and platelets combine. It is well recognized that blood arteries contract immediately after injury, lowering the degree of haemorrhage and allowing embolization to be obtained by several procedures **[23].**

Inflammatory phase

At the time of injury, the inflammation begins. Haemorrhage is brought on by surgery or trauma injuries that alter the structure and organisation of the tissue. Blood fills the injured area, and exposure to protein in the wound causes platelet dysregulation and Hageman factor activation. This in turn activates several biological amplification systems, such as the supplement, kinin, and coagulation cascades, as well as the production of plasmin. This state amplifies the initial injury signal and causes the build-up of a variety of period of at least and chemotherapy inducers at the wound site in addition to clot formation, which contract the wound **[24].**

Proliferative phase

In this phase an epithelium barrier is being create to stimulate keratinocytes although falling the size of the lesioned material area over reduction and

granulation tissue. Endothelial dysfunction, interstitial fibrosis, and re - epithelialization are a part of this stage. These progressions initiate in the microenvironment of the lesion within the first forty-eight hours and can reveal up to the fourteen days after the beginning of the lesion **[25].**

Remodelling phase

The previous stage of healing is remodelling, through which the granulation tissue converts into a mark and the tissue's tensile strength rises. A number of cytokines, such as converting growth factor-, platelet-derived growth factor, and basic fibroblast growth influence, impact wound contraction through contacts between fibrosis and the underlying matrix proteins **[26].**

Factor affecting wound healing

Several factors are accountable for decreased wound healing. Major factors that affect wound healing are; Local factors, genetic, systemic and post-therapy.

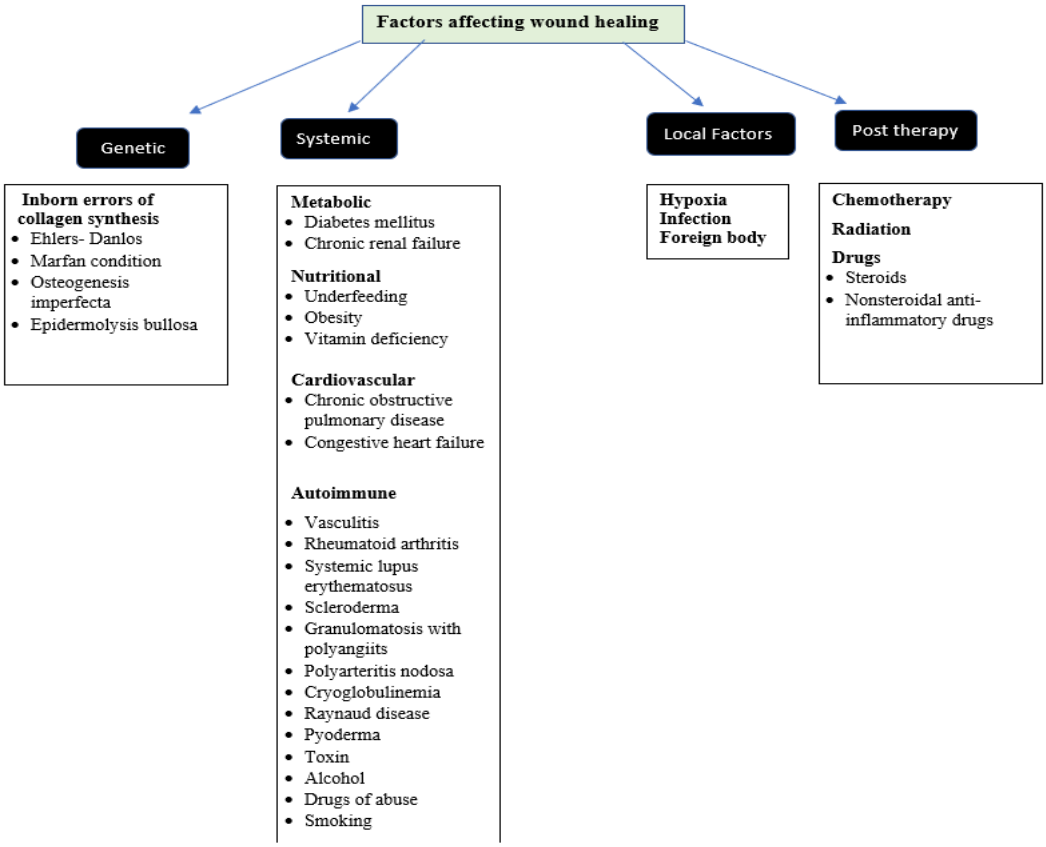


Figure: Flowchart of factors affecting wound healing

Local factors that affect wound healing

Hypoxia

In wound healing proper gaseous exchange is necessary so that wound can heal faster. Healing is delayed in lesions where hypoxic condition has been established. After an wound, provisional hypoxia promotes wound healing, whereas determined or chronic hypoxia inhibits wound healing. The creation of cytokines and progress factors by macrophages, keratinocytes, and fibroblasts can be stimulated by hypoxia. PDGF, TGF-, VEGF, tumour necrosis factor (TNF), and endothelin-1 are that are essential to promote the healing of wounds**[27].**

Infection

When skin is injured, microorganisms that are often limited at the skin's surface get access to the tissues underneath the skin. The arrangement of the wound as having adulteration, colonisation, local infection/critical colonisation, and/or expanding aggressive infection depends on the level of infection and the microorganisms' size for replication **[28].**

Genetic factor

Syndrome of Ehlers-Danlos

The Ehlers-Danlos syndrome (EDS) is a disease in which the theirs is problem with collagen synthesis and it is characterised by delayed wound healing and hyperaemic fragility of the skin. The alpha chains of collagen type V contain genetic problems in more than half of the afflicted patients. The diseases are characterised by thin, crumbly skin with visible veins, easy bruising, slow wound healing, creation of atrophic scars, recurring

hernias, and hyperextensible joints. 1,2 Rectal prolapse, intestinal diverticula, hiatal hernia, and bleeding are all examples of digestive system issues **[29].**

Marfan syndrome: Marfan syndrome is an autosomal-dominant genetic condition that is caused because of defect in gene that synthesize fibrillin-1**[30].** Tall height, arachnodactyly, loose ligaments, myopia, scoliosis, pectus excavatum, and ascending aorta are symptoms of the condition in patients**[31].** Patients with this condition can also develop hernias**[32].** Fibrillin proteins are involved in storage and activation of TGF-β which are required to heal the wound **[33].**

Epidermolysis bullosa: The epidermis, basement membrane, or dermis may have impaired tissue adhesion, which can lead to tissue separation and blistering with little to no damage. The COL7A1 gene, which encodes type 7 collagen and is crucial for tying the epidermis to the dermis **[34].**

Systemic factor

Diabetes mellitus

Diabetes patients have abnormal molecular signalling and complications in Cell activation and migration creation of granulation tissue, angiogenesis, epithelialization, and collagen deposition. Also interfere with activity of matrix metalloproteases and changes in collagen turnover **[35].**

Chronic renal failure

The most frequent conditions that lead to acute kidney damage are severe trauma (particularly crush injuries), burns, surgical wounds, and infectious infections**.** Most of the animal studies revealed that acute kidney damage inhibits fibroblast and capillary growth, these abnormalities are more noticeable in individuals who develop severe uraemia **[36].** In chronic renal illness, inadequate angiogenesis, persistent inflammation, and cell proliferation also impair wound healing **[37].**

Nutritional

Malnutrition

Protein and energy substrates are necessary for the proper completion of all phases of healing. Additionally, electrolytes, minerals, and vitamins are all restricted in situations of malnutrition and work as cofactors in the healing of wounds. For example, precursor of proline, which is essential for collagen deposition, angiogenesis, and wound contraction, arginine has a role in immunological, endocrine, and endothelial processes required for wound healing**[38].**

Obesity

Obesity-related wound healing complications include pressure and venous ulcers, hematoma and seroma development, infection, and dehiscence. Adipose tissue's avascular structure causes localised hypoxia, which impairs neutrophil function and bacterial clearance as well as the transport of medications to the lesion**.** Reduced wound mechanical strength and reparative collagen deposition are observed in healthy obese animals, demonstrating that even simple obesity hinders healing **[39]**

Autoimmune disease

The creation of the cytokines interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-a as well as immune complex deposition cause autoimmune-mediated tissue harm in rheumatoid arthritis, which is typically confined to the synovial membranes. Disease-modifying antirheumatic medications, such as methotrexate, hydroxychloroquine, and anti-TNF-a monoclonal antibodies, are widely used to treat rheumatoid arthritis. However, these medications all carry the risk of post-operative infections or delayed wound healing. Immunosuppression may accelerate chronic wound healing or may slow down acute wound healing **[40].**

Chemotherapy

Corticosteroids are routinely administered to cancer patients; they are well recognised for inhibiting the inflammatory response and consequent fibroplasia, melanocytes, endothelium, and immune cells are affected by radiotherapy and chemotherapy. Various types of dressings, biomaterials, growth factors, and cell treatments are only a few of the current methods used to speed up wound healing in cancer patients **[41].**

Radiation

Radiotherapy and chemotherapy have an impact on the majority of quickly distributing skin cells, including keratinocytes, as well as fibroblasts, melanocytes, endothelium, and immune cells. Current techniques for accelerating wound healing in cancer patients include a variety of dressings, biomaterials, growth factors, and cell therapies, to name just a few**[42].**

Drugs

Medication

Numerous medications, such as those that interfere with platelet function, clot formation, inflammatory reactions, and cell proliferation, as well as other biological processes, have the potential to affect wound healing. There is many

drug based and plant based medicines**[43],** , **[44]**and **dressings [45].**, that have the ability to heal the wound faster. Plant medicines reduce the chances of side effects to the wound patients. Glucocorticoids, non-steroidal anti-inflammatory drugs, and chemotherapeutic drugs are just a few of the commonly prescribed medications in the medical sector **[46]**

Non-steroidal Anti-inflammatory Drugs (NSAIDs)

Non-steroidal anti-inflammatory medicines (NSAIDs), including ibuprofen, used to relieve inflammation, control pain, and treat rheumatoid arthritis. Low-dose aspirin is frequently used as a preventative therapy for cardiovascular disease but not as an anti-inflammatory medicine because of its anti-platelet activity. The issue of whether long-term NSAID use impairs wound healing is still up for debate. Ibuprofen has been revealed to have an anti-proliferative effect on wound healing in animal models **[47].** Ibuprofen-foam is a topical NSAID that may be applied locally to the surfaces of chronic wounds to promote humid wound healing, lessen transient and persistent wound pain, and aid in the recovery of chronic venous leg ulcers **[48].**

Glucocorticoid Steroids

Systemic glucocorticoids which are recurrently used as anti-inflammatory drugs, are known to impair wound healing by suppressing cellular wound responses, such as fibroblast growth and collagen synthesis, as well as by having broad-based anti-inflammatory effects **[49].**

Chemotherapeutic drugs

Chemotherapeutic medications aim to block angiogenesis, fast cell division, and cellular metabolism, hence blocking many of the processes necessary for effective wound healing **[50].**

Animal Wound Models

Wound healing animal models have been used over many decades in experiments to recognize the tissue restoration progression and test original therapeutics.

Different types of wound models are used in wound healing studies
Excision wound model
Burn wound model
Incision wound
Dead space wound model
Ear wound model
Rabbit ear wound
Blister wound model
Tape striping wound model

Excision wound model:

In this excisional model, it is possible to study haemorrhage, inflammation, the development of granulation tissue, re-epithelialization, angiogenesis, and remodelling. Over time, wound area can be monitored (frequently photographed), and wound closure is determined realised on the size of the wound in relation to its initial dimensions. Excision wound model useful for estimating collagen creation, such as hexosamine and hydroxyproline estimate, cover epithelization, area of wound contraction, and wound index **[51].** Animals anesthetized with the help of ketamine HCl at a dose of 80 mg/kg of body weight in i.p route and the hair of the back region are detached with the help of shaving cream. After that an impression is made on the dorsal thoracic region of the rats and a 300 mm^2 circulararеais removed with the help of surgical blade and scissor. Wound of depth not more than 2 mm is created **[52].**

Burn wound model

In this model, the rats or animals are anaesthetized with the help of ketamine HCL at a dose of 80 mg/kg of body weight in i.p route and the hairs of the back region are removed. The shaved area is sterile with the help of 70% v/v ethanol. In this model the wound formed by the help of a cylindrical metal rod about 10 mm in diameter, actuality heated for 30 s. In open flame firstly and immediately pressed to the shaved skin of rats under the aesthesia. The treatment is applied as per dose selection, followed by continuous treatment of skin/tissue integrity. The percentage wound contraction and the epithelization times are evaluated by using this model **[53].**

Incision wound model

To create the incision model selected animals are divided into similar groups and given the same care as in the excision wound model. Ketamine hydrochloride can be used to numb all rats (50 mg/kg, i.p., body weight). Using a shrill scalpel and the complete depth of the shaved skin, a 6 cm long paravertebral incision have to create on either side of the rat's spinal column. Following full haemostasis, the incision was closed with interrupted sutures that were spaced around 1 cm apart. The stitching has been done by means of black silk surgical thread (number 000) and a curved needle (number 11). Afterward stitching, the incision consumes left naked for 10 days while the animals received regular care. On 10^{th} day All rats were put under anaesthesia on the tenth day, the sutures were taken out, and a tensiometer was used to evaluate the tensile strength of the healed wound skin**[54].**

Dead space wound model

The animals were housed in separate cages and into five groups of six rats into five groups of six rats. Polypropylene tubes (2.5 cm 0.5 cm) were subcutaneously implanted in the lumbar area on the dorsal side to establish the dead space wound. Animals were given test extract from the first post-wounding 0 day to the 9th. The granulation tissue taken from each implanted tube was judiciously dissected out through the tube on the 10th post-wounding day and used to calculate the hydroxyproline concentration and determine the breaking strength **[55].**

Ear wound model

The mice were housed separately and given unrestricted access to both tap water and typical rodent chow. A 12-hour light/dark cycle was used to keep the chamber at a constant 24 ° C. Every day, the mice were watched to note their overall health, appearance, and wound care. Ketamine (50 mg/kg; Ketalar) and xylazine (Rumpun; 5 mg/kg) were combined and administered intramuscularly for all procedures. The anesthetized mice were positioned prone on a specially made platform, and standard excisional incisions (width 2.25 mm, depth 0.12 mm) were made on the dorsum of the ears. On top of one ear was a translucent cylinder that was closed and had seven tiny holes in it. The cylinder was kept under negative pressure such that suction from the seven holes held the ear firmly in place on the viewing slide. A circular punch-type knife was used to make full thickness skin incisions on the dorsum of the ears.All cuts were made on the ear's middle and anterior vascular bundles. A microsurgical method and an operating microscope were used to incise and remove the epidermis, dermis, and the subcutaneous layer up to the cartilage layer, but not past it (Zeiss, OPMI 6). By using chilled saline and mild pressure for 10 seconds with a cotton swab, haemostasis was achieved at the wound edge **[56].**

Rabbit ear model

The rabbit ear wound model was first presented in 1991 **[57].** This is comparable to the model of a mouse ear wound without hair. This model have been used to study hyper granulation as well as to study ischemia conditions. Multiple wounds on each ear can act as treatment groups or controls in this paradigm. In culture, tissue explants from the new tissue can be marked for the creation of new collagen, proteins, glycosaminoglycans, or DNA. The structure of the three main vascular pedicles is very stable in the rabbit ear, which is an added benefit. When two of these are split in half, the ear becomes reproducibly ischemic while still surviving completely. This enables the investigation of several drugs in ischemia situations with poor healing **[58]**

Blister wound model

This model may be applied to both animals and people to assess epidermal regeneration and the effects of various substances and medications. Small, uniform epidermal blebs are manufactured by suction utilising a variety of techniques to create blisters. Thus, transdermal invasion is prevented. Numerous blisters may form in various regions on the body or in the same anatomical area. 120 hours following the development of suction blisters, the hairless hamster has completely rebuilt its acanthotic epidermis **[59].**A vacuum of 20 cm Hg can elevate the blisters in the mi volar forearms of people **[60].**Under these circumstances, typical human skin will start to blister after thirty five to fifty five minutes. Blister roofs can then be removed with a scalpel blade. Through this process, identical superficial wounds with a consistent depth and diameter are produced. **[61].**This model may be used to conduct a variety of experiments, such as assays for molecular weight or the absorption of medications or substances in various solutions. These findings may be utilised to explore a variety of medications via passive diffusion and offer a quick method for peptide and protein medications that would normally be poorly absorbed to be delivered temporarily **[62].**

Tape striping model

The lowest layer of the stratum corneum contains the epidermal barrier. This barrier may be destroyed in this model by repeatedly peeling the epidermis using sticky tape. An evaporimeter that measures TEWL can be used to assess this disintegration. A moist skin surface is typically produced by 20 repeated stripping operations using sticky tape. This approach causes deviations in physiological methods including TEWL, which is enhanced in comparison to the blister wound, and is fewer harmful to the epidermis than the blister model **[63].**

Wound Healing Evaluation Parameters

Measurement of wound area.

The progressive change in the wound area is monitored on a full HD camera on pre-determined days such as, 2, 4, 8, 12, 16, and 20 and so on until the wound is completely healed. Take the trace on a trace paper and calculate the area with the help of mm scale graph paper **[64].**

$$\% \text{ wound contraction} = \frac{\text{initial wound size} - \text{specific day wound size} \times 100}{\text{initial wound size}}$$

Determination of period of epithelization

The dropping of the scab from the wound is careful as indicator of wound healed, or as the end point of complete epithelization. The number of days is mandatory for this is known as epithelization period **[65].**

Determination of wound index

Wound index is estimated by an arbitrary scoring system as presented in the table **[66].**

S No.	Gross change	Score
1.	Complete healing of wounds	0
2.	Imperfect but healthy healing	1
3.	Late but healthy healing	2
4.	Healing has not yet been started but the environment is healthy	3
5.	Formation of pus – evidence of necrosis	4
	Total	10

Measurement of tensile strength

The animals were sacrificed on the 10^{th} day, and their tensile strength was determined as follows: Sutures were carefully removed after the animals were sacrificed and put under anaesthesia. Each animal's two wounds were properly cleaned out. Then, using a knife with two fixed blades at a given distance, wound strips of equal size (width) were cut. A pair of steel clips were used to secure each strip's two ends. One clip was permitted to dangle from a stand, and a plastic bottle was then permitted to fill with water progressively until the wound strip broke where the wound was. The sum of water needed to breakdown the wound was measured and represented as the tensile strength of the wound in grams **[67].**

Hydroxyproline estimation

The content of hydroxyproline, a fundamental component of collagen, was examined in wound tissues. The tissues were hydrolysed in 6 N HCl at 130°C for 4 hours in sealed tubes after being dried in a hot air oven at 60–70°C to constant weight. After neutralizing the hydrolysate at pH 7, it underwent a 20-minute chloramine-T oxidation process. The Ehrlich reagent was used to create colour at 60°C, and the reaction was stopped by adding 0.4 M perchloric acid. The colour was read at 557 nm by an ultraviolet (Cintra) spectrophotometer **[68].**

Histopathology

The rats are sacrificed with the high dose of ketamine HCl and tissue is excised as of the wound site of each animal of the group. These tissue samples are distinctly stored in the formalin solution, for microscopic examination **[69].**

Conclusion

Many animal models & techniques to assess the wound healing have better improved over the years. In this study we looked at some of popular experiment animal models & tecniques for wound healing. We believe that, this information can help researchers to serve as a starting point in the selection of models & techniques to test the new therapeutic drugs. Before they can be taken from the bench to beside & help millions of injured patients, particularly these wound which are difficult to heal.

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