Comprehensive Review of Wound Healing Approaches and Techniques

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Abstract

Wound healing is a natural biological process in the human body, accomplished through four precisely and highly programmed phases: hemostasis, inflammation, proliferation, and remodeling. For successful wound healing, all four phases must occur in the correct sequence and time frame. Various factors can disrupt one or more of these phases, leading to improper or impaired wound healing. One of the primary problems in wound management is that while most wounds contain microbes, it does not mean that infection will occur in every case. Medicinal plants are crucial in aiding the wound healing process. This article points out the study of the importance of wound management and its treatment.

1. INTRODUCTION

A wound is an injury to the skin or tissues caused by factors like cuts, abrasions, and punctures. A wound can affect the function and structure of the skin. The structure of the skin can be restored by maintaining Homeostasis (Stuart Enoch et al., 2007 & John Leaper et al., 2007). According to World Health Organization (WHO) data, approximately 30,000 deaths occur globally each year due to burns, scalds, and other skin injuries (Aldalbahi et al., 2020). The Healing of the wound involves a well-organized series of events. A Healed wound must be:

a) The connective tissues are repaired and the wound is completely re-covered by replication.
b) The wound can be returned to its normal anatomical structure and function without the need for simultaneous dressing. Some wounds which fail to heal in the correct time and manner lead to chronic wounds (Stuart Enoch et al., 2007 & David John Leaper et al., 2007).

2. TYPES OF WOUNDS

2.1 Acute Wounds

These wounds are associated with external factors like bites, burns, minor cuts, post-surgical wounds and severe traumatic injuries. Studies have consistently shown that acute wounds typically heal within an estimated timeline but it is based on the type or severity of the wound. The primary treatment for the wound is; It should be clean dressing and sanitation which leads to the natural healing quickly. Traumatic injuries like burns, and gunshot wounds have weakened tissues that are contaminated with some foreign materials it requires surgical and antimicrobial therapy (Okur et al., 2019 & Ioannis D. Karantas et al., 2019)

2.2 Chronic Wounds

Most chronic wounds are ulcers that are linked with various diseases like ischemia, diabetes mellitus, and venous stasis disease. In urban areas, 57.89 % of people and in rural areas, 42.1 %

of people were affected by chronic wounds in India (Sharma et al., 2024 & Vivek Srivastava et al., 2024). Non-healing wounds led to enormous health expenditure, total cost valuation of up to ₹3 billion per year (Guo et al., 2010; DiPietro et al., 2010; Mathieu et al., 2006 & Menke et al., 2007). This review will discuss the wound healing mechanisms, treatment, factors affecting and scar healing.

3. WOUND HEALING

Wound healing is a complicated process. Chronic wound healing such as diabetic wounds, and leg ulcers cause health and economic consequences (Lindholm et al., 2016 & Searle et al., 2016). Four phases in the healing of wounds are hemostasis, inflammation, proliferation, and remodeling (Shaw et al., 2009 & Wichaiyo et al., 2019). After the skin injury, the process of platelet aggregation and blood coagulation jointly plug the injured vessels to stop the bleeding and form the protective layer called a wound scab (Surasak Wichaiyo et al., 2024). After several hours, neutrophils are carried over to the wound area to remove invading microbes, which promotes inflammation (Wichaiyo et al., 2019; Wichaiyo et al., 2021 & Maiuthed et al., 2023). These cells produce some substances such as reactive oxygen species (ROS) and proteases which unintentionally cause harm or injury to nearby cells, tissues, or organs.

3.1 Types of Wound Healing

3.1.1 Primary healing

It occurs when a wound is closed within 12-24 h of its creation. The wound edges are closed by using sutures, tapes, mechanical devices and surgical tapes. The incision causes localized damage to the tissue cells. As a result of fibrosis (formation of fibrous connective tissue) and also there is appropriate balance between the phases of healing it raises the chance of wound healing quickly to complete closure.

3.1.2 Delayed primary healing

This type of healing occurs in a contaminated wound. These wounds are closed after 3-4 days because the phagocytic cells and inflammatory cells are moved to the wound area and destroy the contaminating bacteria. The wound edges can be closed in several days. The collagen metabolism cannot be affected and the tensile strength of the skin is retained.

3.1.3 Secondary healing

It occurs when a wound with excessive loss of tissue it can be caused by severe burns, trauma and some surgical process. The reformation of epithelial cells alone cannot restore the original structure of the skin, the growth of granulation tissue and the collection of extracellular matrix components like collagen can restore the original structure of the skin. The fully opened wounds are closed by wound contraction and epithelialization.

3.1.4 Superficial wound healing

Superficial wounds are seen in the severe burns and split thickness donor graft sites. The superficial part of the dermis can be affected by these wounds. So, the basal layer cells remain uninjured. The dermis can be covered by dermal appendages like hair follicles and the sebaceous gland. The cells migrate from the basal layer to surround the wound and the healing process is initiated.

3.1.5 Acute wound healing

These types of wounds can be treated by following some cellular activities like Phagocytosis, chemotaxis [Migration of cell], mitogenesis [division of cells] and synthesis components of extracellular matrix. These activities occur in a series of events that correlate with the different types of cells involved in the various stages of the wound healing process (Stuart Enoch et al., 2007 & David John Leaper et al., 2007).

3.2 Phases of Wound Healing

3.2.1 Hemostasis (Immediate)

Hemostasis is the first phase of wound healing (Pool et al., 1977). It stops the bleeding after the damage to the vesicles. It can be done in three main steps vasoconstriction, primary hemostasis, and secondary hemostasis (Rumbaut et al., 2010 & Thiagarajan et al., 2010). The cell involved in the process is called platelet and the matrix involved in the process is called fibrinogen. When the skin is damaged the quick response to stop the bleeding is vasoconstriction of the vessel walls. After that primary hemostasis and secondary hemostasis occur. The primary hemostasis process involves platelet aggregation and platelet plug formation which is done by the production of collagen within the sub-endothelial matrix. Secondary hemostasis involves the activation of a coagulation event where the fibrinogen is converted to insoluble strands that produce the fibrin mesh. When the platelet plug and the fibrin mesh combine to form the thrombus it helps to stop the bleeding (Melanie Rodrigues et al., 2018 & Nina Kosaric et al., 2018). In this phase the wound healing process is done by four major amplification systems complement cascade, clotting mechanism, kinin cascade, and plasmin generation which contribute to the healing process (Stuart Enoch et al., 2007 & David John Leaper et al., 2007).

3.2.2 Inflammatory phase

In this phase, the body's immune system responds to the injury. WBC cells [neutrophils and macrophages] migrate from the wound site to the infected area and destroy the microorganisms. This phase begins within an hour to lasts for three to four days. Quick activation of the immune cells in the tissue occurs by mastocytes, gamma, delta cells, and Langerhans cells which secrete chemokines and cytokines which are helpful for wound healing. Inflammatory cells play an important role in wound healing (Gonzalez et al., 2016; Medrado et al., 2003 & Pugliese et al., 2003).

The inflammatory phase can be classified into the early phase (1-2 days) and late (2-3 days) depending on the time and duration of response of the inflammatory cell cooperated (Stuart Enoch et al., 2007 & David John Leaper et al., 2007).

3.2.3 Neutrophils in wound healing

Neutrophils are produced in the bone marrow. Neutrophils are also known as first responders because they respond quickly during the injury. On the day of injury, neutrophils produce 50% of all cells in the wound. The activated neutrophils can release some factors to prolong the activity of the neutrophil cells. Neutrophil cells destroy infectious microbes by releasing toxic granules and initiating phagocytosis. Neutrophils develop some unique granules each granule contains a specific set of anti-microbial agents (Melanie Rodrigues et al., 2018).

3.3 Cells Involves in Wound Healing

3.3.1 Mast cells

Paul Ehrlich discovered the mast cells in 1978. Originators for the mast cells are derived from the bone marrow and migrate to the connective tissues of skin and mucosa. In the skin the mast cells act as effectors for allergic reactions, mediating immunoglobulin E (Ig E) reactions and fighting against parasitic worm infection. In wound healing the mast cells interact with various cell types. Mast cells are responsible for the compression, contraction, and stretch of the cells, tissues and organisms. In the early stages of wound healing, mast cells produce antimicrobial agents to prevent infections of the skin and they release chymase and tryptase for the ECM breakdown. Mast cell histamine stimulates keratinocyte proliferation and re-epithelialization (Weller et al., 2006 & Foitzik et al., 2006). Mast cell tryptase and histamine induce the fibroblast proliferation and synthesis of collagen which enhances wound contraction (Abe et al., 2000 & Garbuzenko et al., 2002).

3.3.2 Dendritic cells

Dendritic cells are crucial antigen-presenting cells that play a central role in initiating and regulating adaptive immune responses, particularly T-cell responses. Langerhans cells are a subset of dendritic cells specifically located within the epidermis the outermost layer of the skin. Paul Langerhans found special cells in the skin called Langerhans cells. At first, he thought they helped with the nerve signals, but scientists later learned they help to fight infections (Romani N et al., 2003). Both Langerhans cells and dendritic cells are present in the skin at the time of infections. Dendritic cells and macrophages are both important immune cells that share some similarities. However, they have distinct roles and functions, with the dendritic cells specializing in antigen presentation and the macrophages focusing on phagocytosis under tissue repair (Hume et al., 2008). Macrophages are a type of phagocytic cell responsible for the clearance of cellular debris, ECM degradation intermediates, and pathogenic microorganisms. Dendritic cells have stronger antigen presenting abilities than macrophages. Antigen presentation occurs in the dermis under lymph nodes. The dendritic cells activate the T cell responses to recognize and target the specific invaders (Tamoutonour et al., 2013 & Guilliams et al., 2013).

3.3.3 T cells

There are two different variants of T cells present in the human epidermis and dermis: Alpha beta (αβ) and Gamma delta (γδ) (Bos et al., 1990 & Teunissen et al., 1990). The distribution of T-cells in the human and murine skin differs significantly. Humans have T cells mainly in the dermis, whereas mice have gamma delta T-cells specifically dendritic epidermal cells [DETCs] in the epidermis distinguished by their morphology (Mestas et al., 2004 & Bergstresser et al., 1983). Research on T cell involvement in wound healing primarily centres on dendritic epidermal T cells largely due to their unique capacity to produce cytokine and growth factors that promote keratinocyte proliferation only facilitate wound re-epithelialization (Jameson et al., 2007 & Jameson et al., 2004).

3.4 Proliferative Phase (day 3 - week 2)

Proliferation is the main phase it focuses on closing the wound surface (re-epithelialization) and restoring the vascular network and granulation tissue (Ning Xu Landen et al., 2016). Re-epithelialization needs the migration of keratinocytes. The migrating keratinocytes produce more

cells to cover the wounds (Lau et al., 2009 & Paus et al., 2009). Migration is triggered by the loss of physical tension and contact inhibition in the cell structure like desmosomes and hemi desmosomes (Martinez-Arias et al., 2001 & Jacinto et al., 2001)

Migration stops when the cells get new adhesion structures and contact with the cells. The re-epithelialization can be stimulated by getting wound based signals, e.g., nitric oxide is produced by macrophages and nerve growth factor, synthesized from various cell types in the wound (Barbul et al., 2002; Witte et al., 2002). The reformation of blood vessels is very important for the wound healing process because nutrients and oxygen are very important for wound repair. Formations of new blood vessels are known as angiogenesis it is initiated by basic fibroblast growth factor (bFGF) and platelet derivate growth factor (PDGF) (Kirsner et al., 2003 & Zhang et al., 2003).

In this phase, a wound matrix is formed during the hemostasis phase that is replaced by granulation tissue, containing a huge amount of fibroblast, blood vessels, that are connected with collagen bundles it slightly recovers the structure and function of the skin (Schultz et al., 2009 & Wysocki et al., 2009). Fibroblast plays a major role in the formation of granulation tissue which migrates from the dermis to the wound (Schultz et al., 2009 & Wysocki et al., 2009). Collagens are produced by fibroblasts and it is the most important protein present in the body. Collagen provides strength and integrity to all tissues of the body and it plays a vital role in the wound repair mechanism. Collagens are composed of three protein alpha chains combined into rope like triple helix (Stuart Enoch et al., 2007 & David John Leaper et al., 2007).

3.5 Remodeling Phase (1 week – several weeks)

The remodeling phase takes weeks to years (Laurel M. Morton et al., 2016). In this phase, shrinkage of many new blood capillaries occurs. One complex feature of remodeling phase is extracellular matrix (ECM) remodeling which helps to retrieve the normal structure of the tissue. The wound that falls on the physical contraction in the whole healing process it is done by my fibroblasts (contractile fibroblast) that are present in the wound (Gosain et al., 2004; DiPietro et al., 2004 & Campos et al., 2008).

A non-vascular, non-cellular and mature tissue environment is formed (Greenhalgh et al., 1998). Some skin segments like sweat glands, and hair follicles cannot be recovered after the traumatic injury and the original skin attains only 80% of its original tensile strength (Xu Landen et al., 2016).

The core aim of this phase is to produce maximum strength through reorganization and reepithelialization. During this process, the majority of blood vessels, fibroblasts, and inflammatory cells disappear from the wound area due to mechanisms of cell death. It leads to the formation of scars with reduced no of cells.

4. PRINCIPLES OF WOUND HEALING

Five generalized principles for achieving timely wound healing they are (Holden et al. 2019 &

Ward et al., 2019)

1. Wound assessment
2. Wound cleansing
3. Dressing change

4. Dressing choice
5. Antibiotic stewardship

4.1 Wound Assessment

Preliminary assessment is the main step and it considers all perspectives of the patient's health that impact the healing process (Collier M et al., 2003). The health care professionals should check for any venous or articular disorders, poor diabetic control, and insufficient nutrition that are present in the patient which may delay wound healing (Guo et al., 2010 & DiPietro et al., 2010). Once the reason for the wound is identified, checked to its nature that is main for the treatment management (Ousey and Cook, 2012 & Cook et al., 2012). Models which are used to guide the wound assessment, the tissue, infection and inflammation, moisture, epidermal advancement, and surrounding skin (TIMES) tool are suggested based on their relative simplicity (Wounds et al., 2016). When a wound fails to heal on high quality wound management and the cause is also not identified, there is a chance of cancerous change that should always be considered (Sundaram et al., 2018).

4.2 Wound Cleansing

It is the main aspect of wound care that decreases the bacterial loads and removes contaminations (Lloyd-Jones et al., 2012). Wound cleansing should be performed by following every dressing removal. Cleaning the wounds using a syringe or a bag of sterile saline pour over the wounds. A Cochrane systemic review shows that tap water is as effective as sterile water for wound cleansing; there is no significant difference between potable water and sterile water. Potable water does not increase the risk of infection (Valente et al, 2003; Fernandez et al., 2012 & Griffiths et al, 2001). Potable water should significantly reduce bacterial infection (Resende et al., 2016). As a readily available hypoallergenic agent and a household soap used with tap water, it shows an effect that is equivalent to normal saline in wound healing treatment, with the additional benefit of causing a less harmful effect on the granulation tissue (Najafian et al.,2015).

4.3 Essentials for Wound Dressing

There is some wound care essential for the dressing

1. Check and change the wound dressings periodically.

2. Change dressings when fluid leaks through or dressings are wet or dirty.

3. Average dressing change frequency three to four times a week.

4. Some wounds need daily dressing changes.

Regular dressing changes promote healing, prevent infections, reduce pain and order, and keep patients comfortable (Lindholm et al., 2016 & Searle et al., 2016).

Benefits: The healthcare providers check the wound's progress. Shows patient quality care. Patients know about the treatment.

Risks: too many dressing changes can increase the infection level (Lawrence et al., 1994 & Zarghooni et al, 2015).

The wound dressing is based on major factors like available resources, dressing quality, patient comfort, factors like fluid leakage wound location and the type of bacteria present in the wound (NICE et al., 2016).

4.4 Choice of Dressing

Dressing choice can be overwhelming to healthcare professionals due to the information overload, complex product options, lack of clear evidence and misleading information (Jones et al., 2007). An ideal wound dressing protects the wound from harm and keeps the bacteria out of the wounds it is gentle on the skin and it maintains the moisture balance; removes the dead tissue and helps to heal the wound faster (Richards et al., 2014 & Dafydd et al., 2014). Healthcare professionals face a crucial decision when selecting a wound dressing. To ensure optimal healing consider the following factors Effective wound management: Promotes healing, prevents infection. Affordability: Balances cost with quality. Non traumatic: Minimizes discomfort and pain. Availability: Accessible in clinical settings (Ashton et al., 2006 & Price et al., 2006).

Healthcare professionals should involve patients in their dressing choices to increase their comfort and ensure the dressing does not impact their activities of daily living. National Health Service [NHS] spends approximately more than ₹100 million annually in wound dressing. Inefficient dressing choices can lead to prolonged healing times and an increase in wound dressing costs (Lindholm et al., 2016).

4.5 Considered Antibiotic Prescription

Healthcare professionals often prescribe antibiotics unnecessarily for wounds due to the uncertainty about the diagnosis and limited experience with the wound. This can lead to overuse of antibiotics, increased antibiotic resistance, delayed healing, and adverse reactions. Improved wound assessment skills and diagnostic confidence can help to reduce unnecessary antibiotic prescription usage (Richards et al., 2014 & Howell-Jones et al., 2006).

The unnecessary use of antibiotics in wound care is a growing concern. To combat antibiotic resistance healthcare professionals should only prescribe antibiotics when clear means of infection are present, such as increased pain, wound discharge, spreading redness or fever. Before prescribing, wound scabs should be taken to identify the causative Organism. Antibiotics should be used for the shortest possible period, come up with the regular clinical and microbiological review to adjust treatment as needed. Healthcare professionals can reduce the risk of drug-resistant healthcare associated infections and prevent antibiotic overuse and misuse.

It is essential to prioritize responsible antibiotic use to protect patients (Doron et al., 2011; Davidson et al., 2011 & Lipsky et al, 2016). As an essential perspective of medical practice wound care is a skill set for all health professionals, no matter their background (Holden et al. 2019 & Ward et al., 2019).

5 FACTORS AFFECTING WOUND HEALING

Many factors lead to the unhealed wound. In simple terms, the factors that affect wound healing can be classified into systemic and local. Local factors directly affect the wound characteristics, Meanwhile, systemic factors are involved in the overall health or disease condition of the individual that affects the healing mechanisms.

5.1 Local Factors

5.1.1 Oxygenation

Oxygen is the main factor because it is involved in cell metabolism, particularly energy production using ATP and is the major need for all types of wound healing processes. It prevents wounds from infection, stimulates angiogenesis, increases keratinocyte differentiation, reepithelialization and migration improves fibroblast proliferation and collagen synthesis and enhances wound contraction (Bishop et al., 2008 & Rodriguez et al., 2008). Due to the vascular breakdown and high oxygen utilization by metabolically active cells.

Some systemic factors also involved in vascular breakdown like age and diabetes it led to poor tissue oxygenation (Tandara et al., 2004 & Mustoe et al., 2004). On the stage of poor vascular flow that creates hypoxic wounds, chronic wounds are particularly hypoxic. Oxygenation is not restored in the wounds, healing is impaired. Temporary hypoxia does not affect wound healing but chronic hypoxia delays wound healing (Bishop et al., 2008 & Rodriguez et al., 2008). In acute wounds, hypoxia acts as a signal that triggers many aspects of the healing process. Hypoxia can stimulate cytokines and growth hormone production from fibroblasts, macrophages, and keratinocytes (Bishop et al., 2008). In normally healing wounds, ROS such as hydrogen peroxide and superoxide act as messengers to stimulate the main process in the healing process including angiogenesis and cell motility. Both hypoxia and hyperoxia raise ROS production, but the increased level of ROS has both beneficial causes and also leads to tissue damage.

5.1.2 Infections

Once the skinny is wounded, Microorganisms normally present on the skin surface can infect a wound. Infection severity depends on the microorganism replication and tissue response. Wound infections changes range from harmless contamination to severe contamination.

Wound infection stages are:

a) Contamination: Non replicating microorganisms present on the wound surface.

b) Colonization: Replicating microorganisms from the wound surface but no tissue damage.

c) Local infection or critical colonization: Microorganisms replicate, causing local tissue damage and response.

d) Spreading invasive infection: Microorganisms invade deeper tissues, causing harm (Edwards et al., 2004 & Harding et al., 2004).

The inflammatory response plays a vital role in wound healing by eliminating contaminating microorganisms. However, if the wound is not properly cleaned, inflammation can persist because the microbes are not fully eliminated. The presence of bacteria and endotoxins stimulates an extended release of pro-inflammatory cytokines including interleukin 1 and tumor necrosis factor alpha. The prolonged inflammatory response can affect wound healing, leading to chronic wound formation and potentially resulting in non-healing of lesions. The presence of inflammation in chronic wounds breaks down the balance between proteases and protease inhibitors. Especially the elevated level of matrix metalloproteases [MMP] degrade the extracellular matrix, while decreased levels of naturally occurring protease inhibitors (e.g., tissue inhibitors of metalloproteases) the growth factors that are crucial for wound healing are rapidly degraded and slow down the healing process (Edwards et al., 2004 & Menke et al., 2007)

5.2 Systemic Factors

5.2.1 Age

The geriatric people (age above 60 years) are the faster growing group than other age group people (World Health Organization [WHO, www.who.int/topics/ageing]), and the increased age is the main factor for impaired wound healing. Numerous clinical and animal studies have investigated aids related changes in wound healing at the cellular and molecular levels. These findings indicate that they are in healthy older individuals aging primarily causes a delay temporal delay in wound healing without compromising the quality of healing (Keylock et al., 2008). Ageing slows wound healing due to the changes in inflammation, including delayed immune cell arrival (T-cells), disrupted chemical signals (chemokines) and the reduced ability of macrophages to clean up damaged tissue (Swift et al., 2001).

A comprehensive review of age-related changes in wound healing reveals there is a difference between young and aged individuals the alterations occur in each healing phase including enhanced platelet aggregation, increased inflammatory mediator secretion, delayed macrophage and lymphocyte infiltration, impaired macrophage function, decreased growth factor production, delayed epithelialization, angiogenesis, and collagen disposition reduced collagen turnover and the remodeling decreased wound strength (Gosain and DiPietro et al., 2004).

5.3 Diseases

5.3.1 Diabetes

Globally, diabetes is a prevalent condition that impacts hundreds of millions of people. One of the critical issues faced by diabetics is the documented delay in acute wound healing. This often results in the development of chronic non-healing diabetic foot ulcers (DFUs), which occur in approximately 15% of diabetics. These ulcers are a severe complication, preceding 84% of all diabetes-related lower leg amputations (Brem et al., 2007). The impaired healing process in diabetic foot ulcers (DFUs) and acute cutaneous wounds in diabetic patients involves multiple complex pathophysiological mechanisms. DFUs, akin to venous stasis disease and pressure-related chronic non-healing wounds, are invariably linked with hypoxia (Tandara et al., 2004). In diabetic wounds, numerous cellular dysfunctions are observed, such as impaired T-cell immunity, defective leukocyte chemotaxis, reduced phagocytosis, and diminished bactericidal capability, along with dysfunctions in fibroblasts and epidermal cells. These defects lead to insufficient bacterial clearance and delayed or impaired healing in diabetic individuals (Loots et al., 1998 & Sibbald et al., 2008). The healing impairment seen in diabetic individuals includes hypoxia, dysfunction in both fibroblasts and epidermal cells, impaired angiogenesis and new blood vessel formation, increased metalloprotease levels, damage caused by reactive oxygen species (ROS) and advanced glycation end-products (AGEs), reduced immune system resistance, and neuropathy.

5.4 Treatment for Wound Healing

5.4.1 Wound Dressing

Wound Dressing is one of the most common treatment procedures used in the healing of wounds (Marjan Mirhaj et al., 2022). It depends on the type, depth, location, and size of the wound. Wound dressing acts as a physical barrier between the wound and the outer environment which

can protect the wound from microbes, and other damages and improve the healing process (Varaprasad K et al., 2020 & Jayaramudu T et al., 2020). The presence of microbes in the wound it leads to slow down the healing process. The important key factor of the wound dressing is its anti-microbial properties. It prevents the wound from infection and penetration of bacteria and microbes into the wounds and enables the natural healing process (Liang et al., 2019; Natarajan et al., 2019 & Harini et al., 2019).

Wound dressing is broadly classified into three categories 1.Traditional 2. Passive 3. Modern wound dressings. In ancient times, traditional wound dressings were made from tree leaves, plants, spider webs, and honey. These materials were used to stop bleeding and protect the wound from the external environment (Gizaw et al., 2018 & Thompson et al., 2018). Passive dressing such as sterile gauze, cotton pads, and bandages, primarily covers the wound surface and absorbs the exudates. However, they can adhere to newly formed granulation tissue, causing pain during removal. Modern wound dressings include films, foams, hydrocolloids, and hydrogels. These dressings can be made from biological materials like collagen or synthetic materials, which offer more durability and lower costs (Brumberg et al., 2021 & Soleymani Eil Bakhtiari et al., 2021).

5.4.2 Skin graft

Skin grafts are used as a treatment when a wound is too large to heal on its own. In this procedure, skin is harvested from another area of the patient body typically the upper leg and transplanted to the wound. Additionally, there are grafts made from human cell products and synthetic materials. Skin grafts improve the chances of rapid closure for venous leg ulcers that are healing poorly. They also promote faster healing of chronic foot ulcers in people with diabetes (https://www.ncbi.nlm.nih.gov/books/NBK326436/).

5.4.3 Moist wound treatment

George Winter, associated with Smith & Nephew Inc. in 1962, proved that wounds could epithelialize faster when covered with occlusive dressings that preserved moisture (Winter et al., 1962). Numerous studies show that wound occlusion and moisture improve all phases of healing (Mertz et al., 1984 & Eaglstein et al., 1984). Advantages of moist wound treatment (Eaglstein et al., 2001)

1. Moist treatment decreases the risk of scarring by avoiding the development of scabs.
2. Moisture plays a crucial role in activating growth factors and proteolytic enzymes, as well as facilitating surface oxygen and nutrient delivery. Moisture enhances the migration and proliferation phases of healing by enabling cells to move across the wound surface more effectively, promoting faster epithelialization and angiogenesis**.** This treatment can be done with various moisture dressings like occlusive dressings, hydrogels, hydrocolloids and foams.

a) Occlusive dressings - Occlusive dressings, also known as films, are semi-permeable polyurethane coverings with an adhesive layer. They are designed for use on minor exuding wounds. Their main functions are to protect against bacterial infection, absorb small amounts of exudate, and maintain a moist environment conducive to the growth of new epithelial tissue. Additionally, these dressings allow for gaseous exchange, facilitating the evaporation of excess moisture (Singh et al., 2013) (Fig. 1)

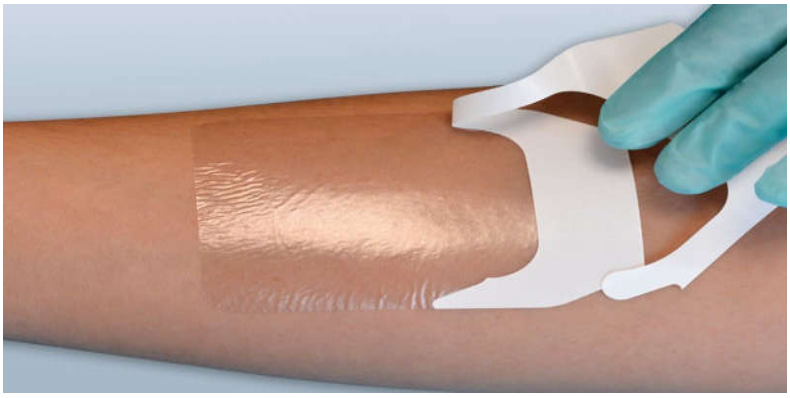

Fig.1: Semi-permeable Film Dressing

b) **Hydrogels -** Hydrogels are primarily used for wounds with low levels of exudate, as they contain high water content. These dressings are typically made from sodium carboxymethyl cellulose or polyacrylates, which form an amorphous gel in a propylene glycol and water mixture. Hydrogels help hydrate necrotic tissue, and remove dead tissues, while also having the ability to absorb exudates (Singh et al., 2011).

c) **Hydrocolloids -** Hydrocolloids are used for wounds with moderate exudation. They consist of a layer of hydrocolloid, which includes liquid-absorbing particles embedded in a flexible, self-adhesive mass. These particles are typically made of sodium carboxymethyl cellulose, calcium alginate, pectin, and gelatin. The elastic mass also contains various synthetic polymers. When wound exudate interacts with the hydrocolloid particles, it forms a cohesive gel that helps maintain a moist environment for healing. Most hydrocolloid dressings are topped with a semi-permeable polyurethane film.

d) **Foams** - These double-layer dressings consist of a polyurethane film carrier and a foam layer on the wound side. They are ideal for wounds that absorb moderate to heavy fluid, and specialty absorbent dressings can act as secondary coverings.

5.4.4 Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy has been applied in wound healing based on its ability to stimulate fibroblast proliferation, boost immune function, and promote angiogenesis, among other effects. However, these expectations have not consistently translated into practice, leading to some debate over its efficacy. Importantly, this therapy is applied in a hyperbaric oxygen chamber (Fig.2), as localized oxygen delivery has not been effective, potentially resulting in serious side effects such as myopia, oxygen toxicity in the brain leading to seizures, and pneumothorax (Wu SC et al., 2010). According to a Cochrane review, there was only a slight increase in the chances of diabetic foot ulcers healing after one year (Kranke et al., 2004). Currently, hyperbaric oxygen therapy should only be considered for wounds where an ischemic diabetic ulcer shows signs of hypoxia (Fonder et al., 2008). Since that study was not designed to assess outcomes like amputation, a clinical trial is currently in progress. This trial aims to compare standard wound care with and without hyperbaric oxygen therapy to evaluate its effectiveness in preventing amputations in diabetic patients with non-healing ulcers (O'Reilly et al., 2011).

Fig. 2: Hyperbaric Oxygen Chamber

5.4.5 Negative Pressure Therapy

Negative pressure wound therapy, known as vacuum-assisted closure, has been widely used since 1997. By keeping the wound moist, improving blood flow, eliminating exudate, and applying pressure to encourage closure, these devices mitigate various shortcomings often found in chronic wounds. Additionally, many studies have shown that they are associated with lower infection rates in such wounds (Streubel et al., 2012). Dressing changes can also be made easier, saving money by reducing the need for surgical cleaning over time. Generally, these devices have foam dressing that needs changing every couple of days and a tube to help with drainage. There are specific materials and fluids designed for these systems, which can range from basic home units to more advanced hospital machines. An emerging application for negative pressure wound therapy is in managing complicated surgical wounds. It can help decrease the wound's volume temporarily, which simplifies the later surgical repair (Venturi et al., 2005).

5.4.6 Cold Atmospheric Plasma Based Treatment

For the last 25 years, plasma-based treatments have been used in biomedical engineering, mainly for ulcers and cancer. Plasma is a fourth state of matter and comes in two types: thermal and non-thermal (cold). In thermal plasma, all particles are in balance, while in non-thermal plasma, the particles are not. Recently, plasma therapy for wound healing has become popular because of its helpful effects. Cold plasmas, also known as non-thermal plasma, gas plasma, or physical plasma, are widely used in biomedical research because they operate at lower temperatures (below 40°C), making them suitable for medical applications (Emmert et al., 2021). Additionally, the plasma mixture includes UV irradiation and an electric field that, together with different ions and reactive species, mediate the biological effects required for tissue regeneration (Lu X et al.,

2012). Additionally, cold atmospheric plasma (CAP) is an innovative approach that utilizes various mechanisms to treat chronic wounds and promote healing (Braný et al., 2020). Cold plasma can help reduce bacteria and support the healing process by producing anti-infective reactive oxygen and nitrogen species. It also inactivates microbes through reactive oxygen species (ROS) and reactive nitrogen species (RNS), showing potential for regenerating tissue in wounds. Nitric oxide (NO), a common reactive nitrogen species, is particularly effective in reducing bacterial load, aiding ECM remodeling, and promoting angiogenesis (Cheng K.Y et al., 2018). The combination of ROS and nitric oxide (NO) promotes greater expression of growth factors in wound sites, which helps manage wound contraction and the process of re-epithelialization (Nasruddin et al., 2014). Currently, there are three certified and approved cold plasma devices for biomedical use. In 2013,kINPen®MED was certified as a Class IIa medical device in 2013 by INP Greifswald/Neoplas Tools GmbH in Greifswald, Germany. In 2010, Dielectric barrier discharge source (DBD) PlasmaDerm® VU-2010 (CINOGY GmbH plasma technology for health, Duderstadt, Germany. Consequently, the medical device SteriPlas was developed by Adtec Ltd., London, UK for the reduction of bacterial load and the treatment of acute and chronic wounds (Bernhardt T et al., 2019 & Praveen Kolimi et al., 2022).

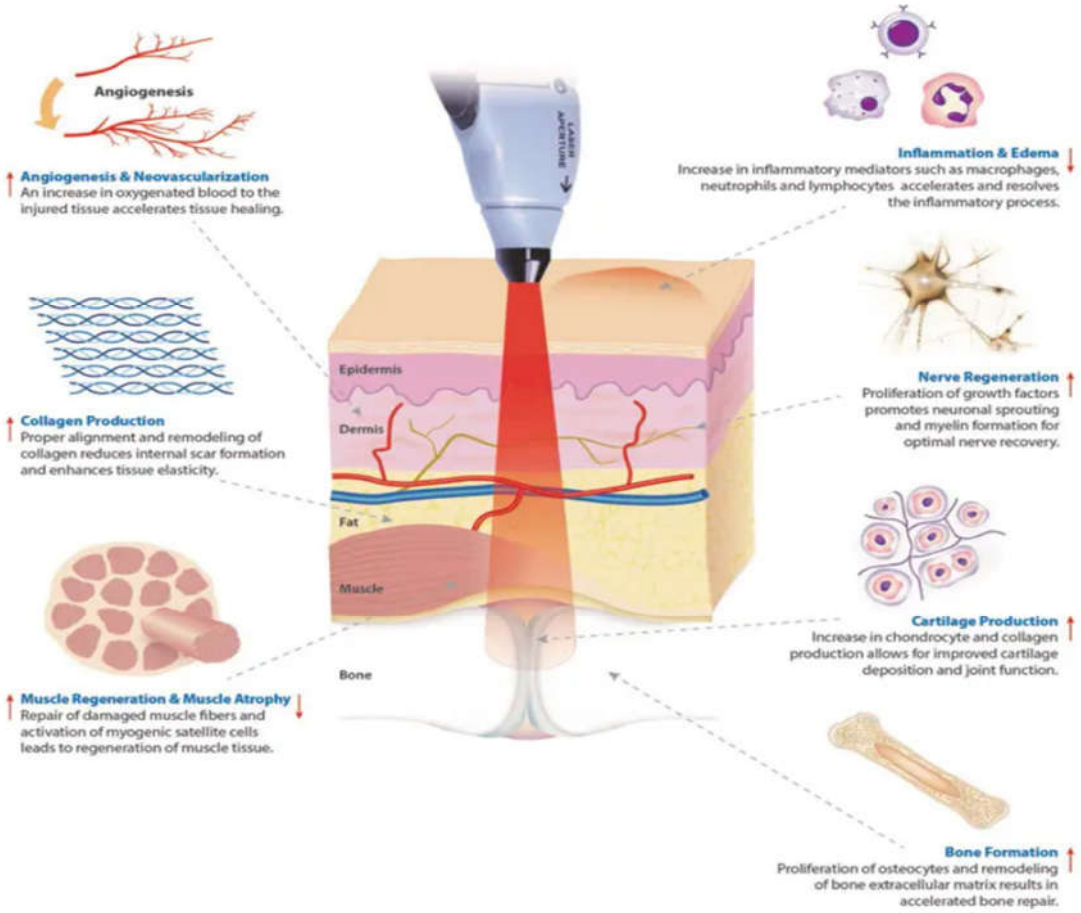

Fig. 3: Mechanisms of Lower Laser Therapy

5.4.7 Low-Level Laser Therapy

Low-level laser therapy (LLLT) is a phototherapy method that employs different gas components. Common types include helium, gallium, aluminum, arsenide, and neon each producing different wavelengths to reach specific tissue depths (Fig.4) (Hartmann D et al., 2021). The specific mechanism of LLLT is not completely understood it seems to reduce inflammation in wounds by decreasing the production of specific chemicals and enzymes linked to pain. Key factors influencing this method include the optimal wavelength, radiation dose, duration, and treatment location. LLLT has been reported to be effective in treating acute, chronic, and postoperative wounds (Elvir-Lazo et al., 2020). Some clinical trials have found positive effects of LLLT on wound healing, but there are also studies emerging that indicate LLLT may not result in significant improvements in healing (Vitse et al., 2017 & Marjan Mirhaj et al., 2022).

5.5 Biomaterials for 3D Scaffolds

Biomaterials used in 3D scaffolds are essential for tissue engineering and regenerative medicine. These materials form structures that facilitate cell attachment, growth, and differentiation, thereby promoting tissue repair and regeneration.

5.5.1 Synthetic Biomaterials

Synthetic materials have two main benefits: they can be made in large quantities with controlled qualities, like strength and how long they last, and we can adjust their chemical properties to make them better at sticking, linking together, and breaking down naturally (Eltom et al., 2019). Polymeric materials such as biodegradable polyesters have greater compatibility with body tissues and these are widely used in tissue engineering. Synthetic polymers such as polycaprolactone (PCL), polylactic acid (PLA), polyglycolic acid (PGA), and related copolymers (polylactic-co-glycolic acids (PLGA)) can compose the matrices. Initially, PCL was applied in the production of degradable films and moulds; however, it is now extensively used across multiple sectors, such as in making absorbable sutures, drug delivery systems, and scaffolds for tissue regeneration. PGA is a type of crystalline polymer that doesn’t dissolve in many organic solvents. Due to its water-attracting properties, it rapidly loses strength and gets reabsorbed within 4 weeks after being implanted (Chaudhari et al.,2016). Studies focused on composite systems containing synthetic polymers and bioactive substances to boost cell growth and healing efficiency (Ferri al., 2018 & Jordá, et al., 2018). Poly (3-hydroxyoctanoate) nano-sized 45S5 Bioglass® scaffolds, with their high wettability and rough texture, support cell growth and quicken blood clotting. Studies on mesoporous bioactive glass (MBG) fibers using polyethylene oxide focused on aiding skin tissue regeneration and managing inflammation (Chaudhari et al., 2016).

5.5.2 Natural Biomaterials

Natural materials have gained attention in recent studies aimed to show the drawbacks of synthetic materials. They possess the advantage of incorporating signal sequences that support and maintain cell adhesion and functions. The most frequently used natural biomaterials derived from proteins for tissue engineering are collagen, gelatin, silk fibroin, and fibrin, all of which are integral to the human body's extracellular matrix (ECM). While extraction from human or animal sources is the common method for obtaining these materials, their availability is restricted, and

they carry potential risks of pathogen contamination**.** Collagen is a naturally derived material known for its strong mechanical properties and biocompatibility. It is susceptible to crosslinking and degrades through physiological processes. Unfortunately, this biological nature also leads to some disadvantages, such as its quick degradation by enzymes like collagenase and gelatinase (Chaudhari et al., 2016). Gelatin offers advantages over collagen due to its lower immunogenicity and enhanced potential for cellular adhesion, due to the presence of arginine–glycine–aspartic acid sequences (Mota et al., 2014). Scaffolds made from gelatin nanofibers may be useful for healing wounds. Various types of gelatins, including sponges mixed with alginate, those containing epidermal growth factor (EGF), and films, have the potential to treat burns (Chaudhari et al., 2016). Fibrin is a promising bioengineering material obtained from fibrinogen extracted from patients. It is immunocompatible and functions as a temporary scaffold. Fibrin gels are used to release growth factors, cytokines, and other bioactive molecules that influence cell adhesion, proliferation, migration, differentiation, and extracellular matrix production. Many growth factors, particularly basic fibroblast growth factor (BFGF) and vascular endothelial growth factor (VEGF), can bind to fibrin (Kober et al., 2015; Gugerell et al., 2015). Biomaterials such as keratin, bovine serum albumin, eggshell, and membrane proteins are being investigated for skin regeneration applications. Keratin and its derivatives are utilized to create scaffolds that facilitate the delivery of antibiotics or growth factors. Meanwhile, eggshell provides an ideal extracellular matrix (ECM) environment for human skin fibroblast cells (Ohto-Fujita et al., 2011 & Konno et al., 2011). Natural biomaterials are used with the combination of other natural or synthetic biomaterial and combine with other bioactive molecules and drugs (Tottoli EM et al., 2020 & Dorati et al., 2020).

5.6 Medicinal Plants Used in Wound Healing

5.6.1 Aloe vera

Aloe vera (*aloe barbadensis*), belongs to the *Liliaceae* family, it is one of the oldest medicinal plants having wound healing properties used to treat various skin diseases including burns as well as acute and chronic diabetic dermal wounds.

The leaves and gels of aloe vera are used to treat wounds. Components present in aloe vera include vitamins like (A, E, C and B_{12}), enzymes like bradykinesia which help to lower the excessive inflammation, minerals, sugars, anthraquinones (aloin and emodin), lignin, saponins, phenolic compounds, hormones (auxins and gibberellins help in wound healing), salicylic acid(anti-inflammatory and anti-bacterial properties) and amino acids (Surjushe et al., 2008).

5.6.2 Lawsonia inermis (henna)

Lawsonia inermis belongs to the family *Lyrthraceae* also known as henna tree. Henna is used for the treatment of burn injuries, skin infections, wounds and ulcer healing.

It also has antibacterial and anti-inflammatory properties. *Lawsonia inermis* has active compounds like carbohydrates, phenolic compounds (lawsoniaside, lalioside, and syringinoside), flavonoids (apigenin, luteolin), saponins, proteins, alkaloids (harmine and harmaline), terpenoids, quinones (lawsone, alizarin), xanthones, fat, resin and tannins. Lawsone is the major compound present in the extract of *Lawsonia inermis* flowers, leaves and branches (Muhammad et al., 2005).

5.6.3 Zingiber officinale (Ginger)

The rhizome of ginger (*Zingiber officinale*) is widely used as a spice and condiment.

It contains many active compounds, such as gingerols, shogaols, flavonoids, diterpenoids, and sesquiterpenoids. Among these, zingerone, shogaols, and gingerols are the main compounds that give ginger its spiciness. Gingerols and shogaols are particularly noted for their anti-inflammatory properties (Nurrahayu et al., 2017).

5.6.4 Curcuma longa (Turmeric)

Curcumin, a well-known active ingredient from the rhizomes of C. longa, has various biological effects. It belongs to *Zingiberaceae* family

It has anti-inflammatory, protective, and antioxidant properties, making it a promising option for wound healing research (Kabir et al., 2019). Curcumin's antibacterial properties play a key role in speeding up the wound healing process. Curcumin can prevent the formation of bacterial biofilm and the adhesion of bacteria to host receptors.

5.6.5 Centella asiatica (Gotu Kola)

Centella asiatica, commonly known as Gotu Kola, has been extensively utilized in both traditional and modern medicine to address various health issues, including scleroderma, eczema, psoriasis, leprosy, and chronic inflammatory conditions, as well as skin wounds (Gohil et al., 2010 & Somboonwong et al., 2012).

Its broad spectrum of biological activities can largely be attributed to key compounds like asiaticoside and, to a lesser extent, madecassoside. Asiaticoside, a type of saponin, plays a crucial role in the healing process. It has been shown to stimulate the synthesis of type-I collagen in human dermal fibroblast cells, which is essential for skin repair and regeneration. The presence of madecassoside further enhances these effects, contributing to the overall anti-inflammatory and healing properties of C. asiatica. Together, these compounds work synergistically to promote skin health and repair (Mukherjee et al., 2015 & Omid Yazarlu et al., 2021).

5.7 Marketed products

5.7.1 Nuvaderm

Nuvaderm is recognized by the FDA as a topical medical device. It consists of a biocompatible poly(urea-urethane) polymeric suspension that creates a uniform film when applied to wounds and skin. The polymer is mixed with organic solvents that quickly evaporate after application, allowing the polymer to adhere well to the skin’s surface. This forms a flexible, long-lasting, waterproof barrier over the wound and the surrounding area.

The film is colourless and transparent, and it allows moisture to escape, which is important for healing. Nuvaderm has been tested for biocompatibility according to ISO 10993 standards, demonstrating safety in terms of cytotoxicity, sensitization, irritation, acute systemic toxicity, and implantation (Lance Swick et al., 2017).

5.7.2 LiquiPlast®

LiquiPlast® is a liquid made up of 12% pyroxylin dissolved in ethyl acetate and alcohol. It looks like a clear, thick liquid in its container. When tested, the film formed by LiquiPlast® was smooth and showed no changes at temperatures of 25°C and 37°C. It has a tensile strength of 11.3 MPa and can stretch about 9.9% before breaking, making it flexible enough for moving skin. After application, it dries quickly, losing weight significantly in the first 10 minutes, after which it stabilizes, indicating that it dries rapidly and forms a film within that timeframe. LiquiPlast® also sticks well; it can bond two plastic caps securely under added weight. In a study with mice, when applied to a 4 mm wound, it created a clear adhesive film within 10 minutes and helped the wound contract within an hour, showing it can actively aid in healing (Surasak Wichaiyo et al., 2024).

5.8 Recent Innovative Strategies in Wound Healing

- Portable 3D skin printers
- Spray based technological approach
- Spray based technological approach (Dimple Chouhana et al., 2019).

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