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Therapeutic Advances in Wound Healing

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Abstract

A wound is an injury to the biological form and function of an organ, such as the skin, produced by a simple or major rupture in the structure of the organ. Because a slow and ineffective repair might result in significant harm, full lesion healing necessitates rapid recovery of balanced physiological circumstances. The characteristics of the wound-healing mechanism can be used to classify wounds. A surface wound is a type of skin lesion that only affects the skin's epidermis. When the subcutaneous fat or underlying structures, such as blood arteries, sebaceous glands, and hair follicles, are compromised, full-thickness wounds develop. "Complex injuries" are wounds that are difficult to heal and cause substantial loss of skin, hair, and tissue. (Veins feeding the leg). The human body's intricate physiological process of wound healing involves coordinated sequential activation of many different cell types and signalling pathways. Chronic wounds and burns distinctly lower patients' quality of life because they are linked to an increase in physical discomfort and socioeconomic issues. As a result, improving the long-term viability of national health systems requires not just great interest but also the development of innovative and more affordable technologies and medicines.

1. Introduction

The incidence and frequency of chronic wounds have been rising, primarily because of population ageing and the consequent rise in expenses for national health systems [1]. The intricate and dynamic process of the healing of a wounded tissue which can also be viewed as an organ in some short-term ways, is an intriguing process, because of the application of developments in cell and molecular biology as well as technology, our understanding of the processes involved in vertebrate wound healing is quickly expanding [2]. Normal wound healing occurs in three distinct phases: the phase of hemostatic/inflammation, the phase of proliferation/cellular changes, and the phase of remodelling [3]. These phases are typically progressive but overlap. Massive advances have been achieved in our understanding of how wound healing works at the molecular level thanks to the identification of numerous chemical families that have shed light on the numerous processes and interactions that take place during each of these phases. Numerous cells, including cytokines, proteases, and growth factors, are involved in the healing of wounds. Wound healing usually will depend on the development of new blood vessels through angiogenesis or vasculogenesis. Proteolytic enzymes, growth-promoting or survival factors, various differentiated and ancestral cell type activators, and

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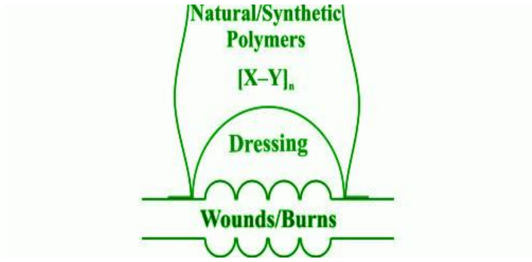
permissive microenvironments are some of the key mechanisms in neovascularization. To "transform" highly damaged and diseased wounds into those that will heal is a key goal of wound healing research.

WOUND DRESSINGS & TYPES

Wound dressings can be made to perform physiological activity on their own or to produce biochemical elements that have been added to the dressing. Healing of a wound on skin is a spectacular biological function that contains numerous cells, growth factors, and cytokines. Topical bioactive compounds in the form of solutions, lotions, and balms are worthless in delivering medication to wounds because they quickly soak water and become restless [4].

● Natural Inert Polymers: The dressing protects the wound while it heals and helps the skin and epidermal tissues regenerate. Due to its biocompatibility, biodegradability, and resemblance to macromolecules recognised by the body, some natural polymers, including polysaccharides, proteoglycans, and proteins, are frequently utilised in wound and burn therapy [5]. They are biocompatible, biodegradable, have a unique structure, and have good mechanical properties, making them the ideal habitat for cell migration, proliferation, and differentiation. As a result, regenerative medicine also uses synthetic polymers to repair and restore ligaments, circulatory systems, nerves, and bones. For the regeneration and modification of the human epidermis as well as wound healing, tissue-engineered skin is recommended, boosting the treatment in case of severe injuries to skin or in certain cases of partial burn injuries and fibroblasts and keratinocytes are biocompatible. Silk is a biopolymer made up of a rapidly repeating amino acid sequence that results in a biomaterial with exceptional mechanical and biological properties. Silk is a feasible material for surgical sutures by its biomedical applications, good biocompatibility, flexibility, adhesion, and uptake of secretions with little inflammatory response. Carrageenan, hydroxypropyl methylcellulose, and pectin are examples of natural polymers being used in wound dressings [6].



● Natural Bioactive Polymers: Biopolymers are naturally occurring macromolecules produced to the utmost level of biocompatibility by microorganisms, plants, and animals. The bioactive qualities of the polymers, Such substances provide an environment that is favourable for the healing process, including antibacterial, immune-modulatory, cell proliferative, and angiogenic. The adaptability of biopolymers including cellulose, alginate, hyaluronic acid, collagen, and chitosan, among others, has been utilised by the wound care business today. To better satisfy the requirements of contemporary wound healing, including tissue restoration, restoring damaged tissue consistency, and scarless healing, biopolymers' structural and functional qualities can be improved. Alginate is likely the material that is used the most in biomedical research and bioengineering [6]. Technological developments in the fields of science, tissue regeneration technology, nanotechnology, and bioengineering have made this conceivable. [7]. The creation of an "egg-box" is the outcome of the interplay of guluronic acid (G)-rich regions on neighbouring polymer chains. Pressure, diabetes, venous ulcers, holes, and certain oozing wounds can all benefit from alginate-based hydrophilic medical applications. It also has a high water-holding ability and offers a humid environment that helps wound healing by preventing the damaged tissue surface from drying up. Try mixing it with gauze, foams, or creams to utilize it. Collagen, as hyaluronic acid, provides tensile strength to the skin as well as being a biodegradable and non-toxic natural tissue matrix constituent [8].

● Synthetic Polymers: Modern wound dressing currently mostly comprises of synthetic polymers due to recent advancements in the field. Both passive and interactive forms of dressings comprised of synthetic polymers are available. In addition to helping with the recovery of function under the polymer covering, non-occlusive passive synthetic polymer bandages are utilised to treat wounds. Gauze and tulle are two examples of these passive artificial polymers [9]. Artificial polymer bandages that are interactive and can form a clot thus serve as a barrier to stop bacteria from enterin this area. They can take the form of films, foams, hydrocolloids, hydrogels, or hydrogels [10]. Synthetic materials are routinely mixed with organic or bioactive polymers to enhance the final wound dressing's physical characteristics.

● Foams: Foam dressings are a subclass of occlusive polymeric dressings. One of the initial "contemporary" methods to be utilized for wound dressings was foam, which became readily accessible in the mid-1979s for exuding wounds. Foams have many benefits over conventional gauze dressings, including the fact that they don't lose their viability and can be used for a much longer period without developing maceration [9]. The characteristics of foam dressings are crucial in generating an environment that promotes wound healing [11]. Foam dressings aim to address the occlusive dressing's inability to absorb exudates while maintaining the moist environment required for tissue healing [12].

● Hydrocolloids: They are semi-permeable to vapour, absorbent, and occlusive. Because they include a large number of hydroxyl groups, hydrocolloids are polymers with hydrophilic characteristics. You can get hydrocolloids either naturally or synthetically. Polysaccharides are typically the hydrocolloid form employed in practical applications [13]. Because they are occlusive, hydrocolloid dressings make sure there is a no-oxygen environment that causes the liquefaction of the necrotic tissue and facilitates autolytic clearance. This notion has been bolstered by case studies demonstrating the simplicity of autolytic debridement of diabetic foot ulcers after hydrocolloid dressing application [14].

● Hydrogels: Crosslinked hydrophilic polymers including polyvinylpyrrolidone, polyacrylamide, and polyethylene oxide are used to create hydrogels. Hydrogels have the intrinsic ability to swell when in contact with water and do not dissolve in water [15]. Most hydrogels need a second layer to hold them in place because they don't naturally cling to skin. Three different forms of dressings that can be used in case of burns are—a new silver hydrogel dressing, a polymer film dressing, and a polymer foam dressing—have been compared in in vitro antimicrobial investigations. Despite having comparable silver contents in all three, it has been demonstrated that the silver hydrogel dressing has better antibacterial action than the other two dressings [16].

2. Determinants Of Wound Healing

The healing of wounds can be hampered by a number of causes. Each element is essential for diagnosing and managing wounds of all sorts. In this article, we examine the many local and systemic factors that could hinder or postpone the healing process. Local factors that can impede the healing of a wound include desiccation, infection or atypical bacterial activity, maceration, necrosis, stress, trauma, and oedema [17]. Infection and oxygenation at the site have a direct impact on how well a wound heals. All stages of wound healing depend on oxygen for cell metabolism, energy synthesis, and other processes. Leukocytes create superoxide, which is required for the oxidative destruction of infections. Vascular disruption in a wounded area results in oxygen deprivation and hypoxia. While chronic hypoxia slows wound healing, temporary hypoxia promotes it. When oxygenation is normal, reactive oxygen species promote wound healing. However, as their levels rise in cells under hypoxia, their beneficial effects are countered by their detrimental effects on tissue damage [18].

In assessing a person's general well-being during wound healing, systemic elements are crucial. A risk factor for slowed wound healing is getting older. When compared to young mice, it alters inflammatory reactions, re-epithelialization, collagen synthesis, and angiogenesis, which slows down the process. Wound healing is significantly

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influenced by both male and female androgens and estrogen. Inflammation, matrix synthesis, protease inhibition, epidermal activities, and regeneration are all known to be regulated by estrogen [19].

Wound healing is significantly delayed as a result of stress. In times of stress, the production of glucocorticoids is upregulated, which lowers the amounts of chemoattractants and pro-inflammatory cytokines needed for the inflammatory stage of wound healing. Glucocorticoids stimulate decreased transcription of gene-regulating molecules, cell adhesion compounds, and immune cell proliferation and differentiation[20].

Alcohol use is implicated in both experimental and clinical research as a risk factor for poor wound healing. Alcohol intake compromises the body's defenses, leaving the wound open to additional infection. The most important impairment is caused by decreased angiogenesis [21]. Similar to drinking, smoking has negative impacts on how quickly wounds heal. Smoke-related chemicals obstruct the process. Vasoconstriction brought on by nicotine lowers blood perfusion. Oxygen uptake is hampered by carbon monoxide. Recent research have suggested using modest doses of nicotine to promote angiogenesis despite overall unfavourable results [22].

❖ Desiccation: In a moist environment, wounds heal more quickly and painlessly than in a dry one, where cells typically dry out and perish. Desiccation promotes coagulation, which inhibits healing. Epidermal cell migration is accelerated, supporting epithelialization, if the wound is kept wet with a moisture-retentive dressing.

❖ The presence of uncommon bacteria or an infection: A wound culture should be collected to identify the causative bacteria and decide the best course of antibiotic treatment in case of purulent leakage or exudate, hardness of the skin, erythema, or fever are present. In the event that a stress ulcer or packed damage that reaches to the bone does not heal, patients should be checked for osteomyelitis symptoms.Your doctor must be informed of any atypical culture or lab tests in order to treat your infection with the proper drugs.

❖ Necrosis: Dead, lifeless tissue known as necrosis can obstruct the healing process. Slough and eschar are the two forms of necrotic tissue which might appear in a wound. Slough is frequently composed of stringy, necrotic, moist, loose tissue. Eschar can be a dark colour and mimics a dry, leathery tissue. Necrotic tissue typically needs to be removed in order for healing and repair to occur.

❖ Trauma and edoema: Wounds recover slowly and often not at all in conditions when they are repeatedly damaged or deprived of a local supply of blood by oedema.

Systemic variables with little to no direct connection to the site of the wound itself might cause wound healing to be delayed. These include vascular insufficiencies, radiation therapy, nutritional state, age, body type, chronic disease, immunosuppression, and chronic disease.

❖ Age: Wounds may heal relatively slowly in older people than in younger people due to comorbidities that arise with age. Age-related risk factors for skin damage and sluggish wound healing include inadequate food consumption, hormonal changes, dehydration, and compromised immune, circulatory, and respiratory systems.

❖ Chronic illnesses: Chronic conditions that might hinder wound healing include cancer, diabetes mellitus, peripheral vascular disease, coronary artery disease, and others. The optimum treatment strategy should be continuously monitored throughout the course of treatment for patients with chronic conditions.

❖ Values from a lab: When assessing healing, laboratory results other than nutritional markers must also be taken into account. In order to establish the patient's ability to heal, it may be essential to evaluate the patient's hepatic, renal, and thyroid functions in addition to the hemoglobin level.

Vascular dysfunction: The lower extremities may be affected by a number of lesions or ulcers, including arterial, diabetic, pressure, and venous ulcers. These ulcers frequently develop as a result of decreased blood flow. To ensure that the topical

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and supportive medicines are suitable, the practitioner must determine the type of ulcer.

3. Traditional Dressings In Wounds

Due to the general extracellular matrix's complex structure and the existence of many cell types in an organised manner, functioning and healthy skin regeneration remains extremely difficult. Traditional organic-based therapies, such as leaf extracts, honey, and larval stage, provide appealing alternative solutions to newly invented wound care solutions. These therapies may open up new therapeutic avenues for skin disorders. while improving healthcare access and removing some of the drawbacks of contemporary products and therapies, such as their expensive prices, protracted manufacturing processes, and rise in bacterial resistance [23].

4. Dressings As Drug Delivery Systems

- Wounds: The wound site can be directly treated with antibiotics, probiotics, analgesics, growth factors (GFs), proteins, and nutrients using hydrogels, hydrocolloids, foams, films, and wafers. Varied types of dressings have different properties, such as different levels of fluid absorption, length of wound healing, and mechanical toughness. The impact of these substances, along with the dressing's physical characteristics, may expedite the healing of wounds. [24].
- Antimicrobials: During wound healing, wound assessment, surgical treatments, and dressing changes wound dressings are designed to aggressively kill bacteria and fungal infections, minimize bacterial bioburden and avoid recontamination. In the last 20 years, several innovative wound dressings comprising antimicrobial medications have been produced, leveraging the features of modern dressing technology [24].
- Wound Infection: The existence of microbes on the site of a lesion with no immune reaction first from the patient is known as wound colonization. Cellulitis, bacteremia, and septicemia may occur due to insufficient control mechanisms in the care of infected wounds. The production of bacterial biofilms is one of the main causes of chronic wounds, and even a microbial population burden can significantly slow tissue repair [24]. Microorganisms via sebaceous glands and hair follicles, the digestive and oropharyngeal tracts, and the existence of Pseudomonas aeruginosa and Staphylococcus aureus together include a chance of disease in around 75% of burn injuries. Injuries are vulnerable to infection caused by the accumulation of a considerable microbial biomass concentration and the incapacity of leukocytes to cope to reduced migration, phagocytosis, and internal death of microorganisms. Wound contamination is aided by localized degradation, hypoxia, ischemia, and immunological deficits, like those induced by the human immunodeficiency virus (HIV) and chemotherapy [24].
- Antibiotic Drugs: Antibiotics are increasingly being used for local treatment of wounds, at least according to scientific papers. Antibiotic combinations can be used to cure multidrug resistant microorganisms [25]. Antibiotic-resistant bacteria have necessitated the development of alternative therapies for wound infections, such as nonantibiotic dressings, which are constantly being developed and can help to minimize antimicrobial resistance [25].
- Silver: Silver is now identified as the ideal candidate for treating diseases that have previously been treated with antibiotics. Silver's antibacterial effect has been attributed to a variety of processes. The first suggested mechanism involves the inactivation of bacterial membrane enzyme proteins via thiol group binding [26]. Silver-loaded dressings have been reported to be effective against nonbacterial targets such as fungi. The wound healing characteristics of chitin and polymeric pyrrolidone-based film dressing including silver oxide were examined functionally. Nylon nanofibers with AgNPs electrically spun for wound healing displayed antibacterial efficacy against Gram-negative S. aureus and E. coli [27]. Many wound dressings in curing and/or avoiding sickness are merely updates of current biocompatible wet medical applications containing silver in pure state, as ions, or as nanomaterials. It enumerates the numerous silver-loaded dressings now available. The bulk of them have been shown to have

antibacterial activity in vitro 154,155 and in vivo in the majority of cases, according to peer-reviewed research journals [27].

5. Advance Therapies

● Negative Pressure Wound Therapy: Recent years have seen a rise in the popularity of negative pressure wound therapy (NPWT), commonly referred to as external negative pressure therapy or pneumatic closure. Hospitals all throughout the world use it frequently to treat 300 million serious wounds annually. By applying suction and enhancing blood circulation to the area with a specially designed sealed bandage, NPWT accelerates wound healing [28]. The ideal gas equation can be used to roughly predict how gases behave in the atmosphere. At sea level, a chest tube connected to a 20-mmHg suction would have an absolute pressure of 740 mm, or a gauge pressure of 20 mmHg[29]. Fluid elimination, bringing the wound together, micro deformation, and moist wound healing is some of the methods through which negative-pressure wound therapy functions. Numerous randomized clinical research backs the application of negative pressure wound treatment in particular types of wounds. The U.S. Food and Drug Administration has lately revealed rare cases of patients experiencing severe side effects, including bleeding and infection [30]. Stimulation of wound healing pathways through shear stress mechanisms has been one of the main reasons this treatment has become so successful [31]. With negative pressure wound therapy difficulties are easy to avoid. Before applying a sponge, wounds should be properly cleaned and debrided. The sponge clogs by thick pus, however, some fibrous material and thin exudates can be managed. Visceral organs should normally be protected, and important vascular structures should not be covered by the sponge. The outer layers of these can rip due to the sponge's adhesion; reports of substantial bleeding or exsanguination have been made. NPWT has established itself as a ground-breaking innovation in wound care. Wounds that were previously difficult to manage or were in a chronic, non-healing state are now controllable. Additionally, many supplementary uses have been mentioned, demonstrating the adaptability and dependability of this approach to wound treatment.

● Oxygen Associated Therapy; Glycoprotein antigen with the host cell or human body cell receptor which is angiotensin-converting enzyme-2. This is the receptor for many viruses including the coronavirus, when the virus enters the host cell its spike protein gets cleavage and it breaks down and it happens due to the host cell proteases enzyme found in the human body that is called transmembrane proteases serine now the one part of the serine binds to the ACE-2 receptor and S2 subunit which causes synthesis of viral covering with the host cell sheath. Then the virus enters the alveolar cells in the lungs and on the epithelial cells of the oral mucosa and its coronavirus is also found in the cells of the heart, kidney, endothelium and intestine. That is why a patient with the infection of the coronavirus has extrapulmonary manifestation in addition to respiratory symptoms [32]. An enzyme-activated hydrogel bandage called Oxymel (Crawford Healthcare Ltd.) promotes wound healing. For patients with chronic illnesses or bacterial bioburden, a similar product with the same basic concept has been developed; the only distinction is the amount of iodine produced. When compared to other iodine-based dressings, both dressings had lower iodine levels but equivalent antibacterial characteristics [32].

● Nanotechnology in wound healing: Nanotechnology-based diagnostic and therapeutic strategies enable targeting of the complex normal wound-healing process, cell type specificity, the abundance of regulatory molecules, as well as the pathophysiology of chronic wounds. Numerous cutting-edge remedies powered by nanotechnology have been developed to address particular issues with the healing of chronic wounds. For the standardization of nanotechnologies, more study is still needed before these therapies can be used in the clinic [33]. Nanoparticles with inherent qualities that are helpful for treating wounds and nanomaterials utilized as therapeutic agent delivery systems are the groups of nanomaterials used in the healing of wounds [34]. Scaffolds are created using a variety of nanotechnology processes, such as electrospinning, self-assembly, and phase separation. The most popular technique for creating nanofibers is electrospinning [35]. A tried-and-true method for creating porous polymeric nanofibers is electrospinning, which has produced nano scaffolds with structural and physical characteristics similar to those of the extracellular matrix [36]. Silk fibroin electrospun nanofibers were employed as hybrid scaffolds to encourage fibroblast adhesion and proliferation for better healing of diabetic wounds [37].

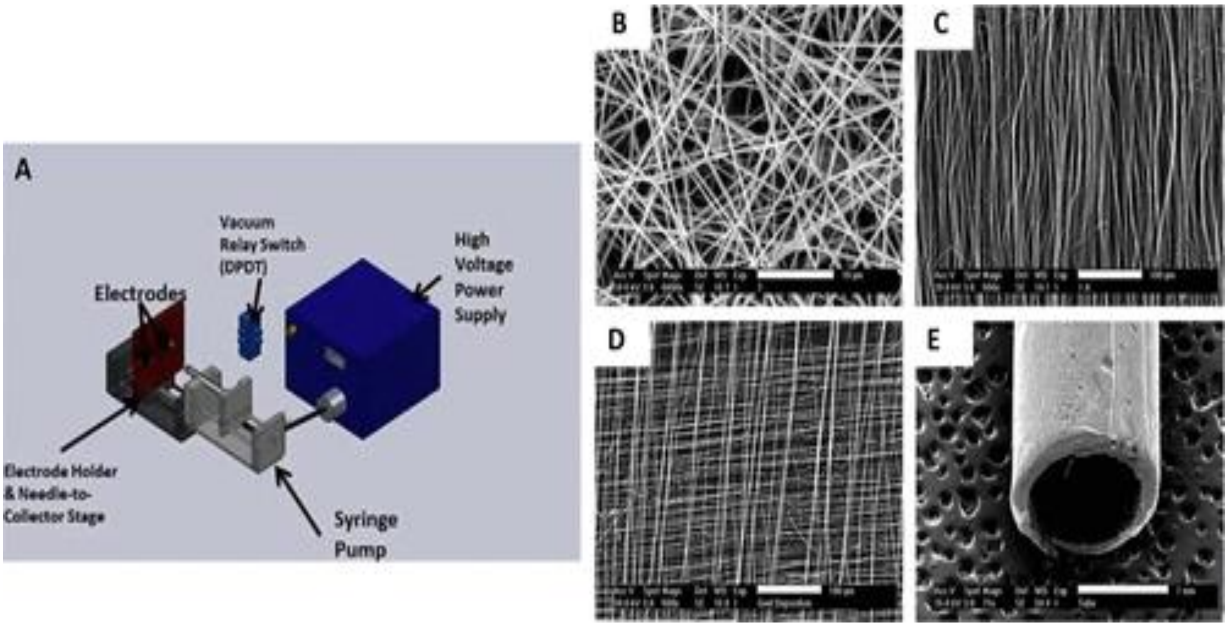

Fig. 1. (A) Visual images of an electrospinning apparatus. (B) A microscopy image of electro spun scaffold, (C) with aligned fibre orientation, (D) with gridded fibre alignment, and (E) a tubular scaffold [33].

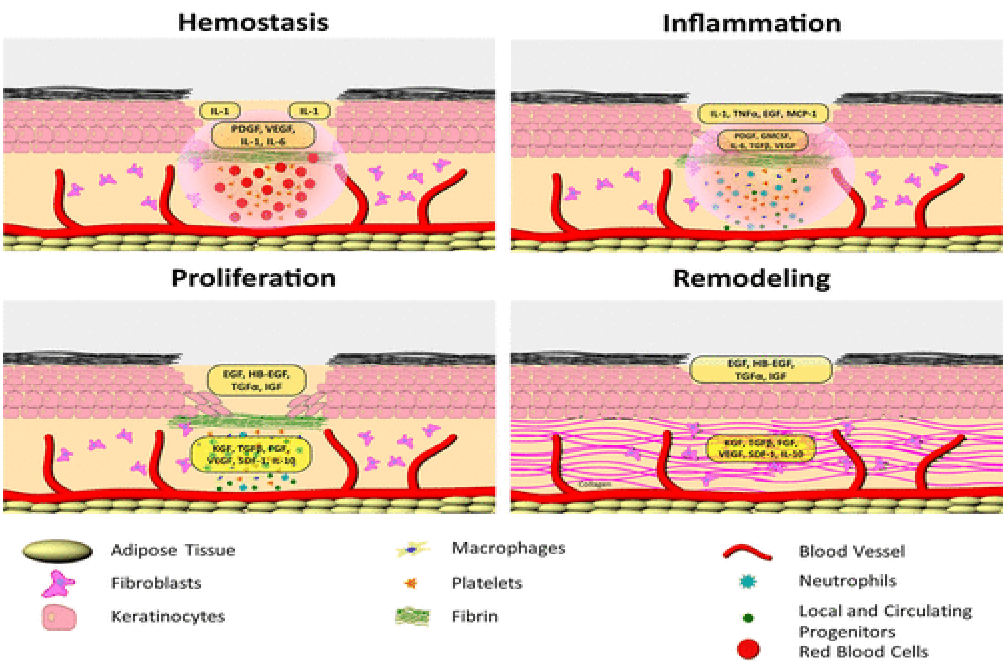

Fig. 2: Skin wound healing stages that show the molecules and cells in charge of reestablishing a healthy barrier [33].

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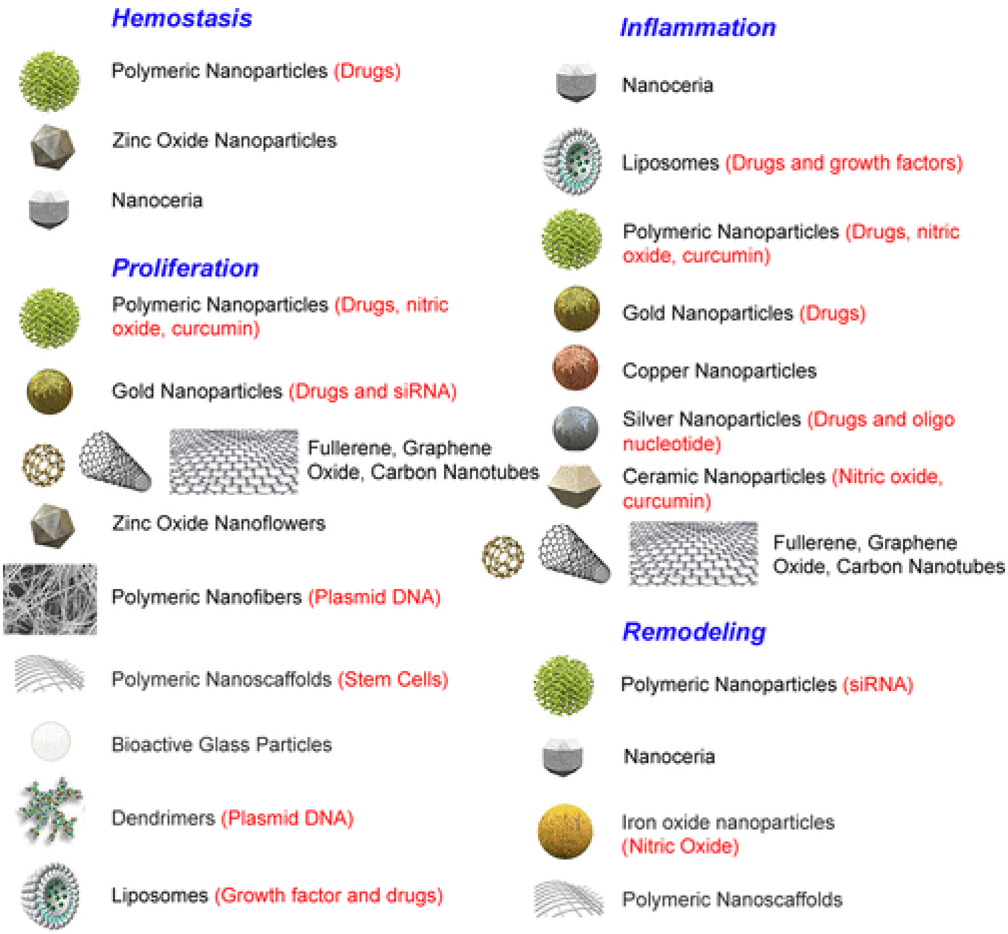

Fig 3: Diagrammatic evidence of therapies based on nano-technology used in wound healing [33]

6. Conclusion

The complex physiological process of healing wounds takes place in humans which involves a coordinated sequential activation of numerous cell types and signalling pathways. Chronic wounds and burns distinctly lower patients' quality of life because they are linked to an increase in physical discomfort and socioeconomic problems. In addition, unlike burns, the incidence and frequency of chronic wounds have been rising, primarily because of population ageing and the consequent rise in expenses for national health systems. As a result, improving the long-term viability of national health systems requires not just great interest but also the development of innovative and more affordable technologies and medicines. Additionally, innovative formulations utilizing metallic nanoparticles and topical insulin are described here as future trends in wound treatment. These new formulations have proven to be therapeutic choices with the potential to shift the way wounds are ptreated soon.

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