ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

Therapeutic Advances in Wound Healing

Received: 25 October 2022, **Revised:** 28 November 2022, **Accepted:** 30 December 2022

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Keywords

Subcutaneous, circumstances, ineffective, technologies, physiological, coordinated

Abstract

A wound is an injury to an organ's biological form and function, such as the skin, produced by a simple or significant rupture in the organ's structure. 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 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 signaling pathways. Chronic wounds and burns significantly lower patients' quality of life because they are linked to increased physical discomfort and socioeconomic issues. As a result, improving the long-term viability of national health systems requires great interest and 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 intriguing; 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]. Routine 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 multiple processes and interactions during each phase. Multiple cells, including growth factors, cytokines, proteases, and, are involved in the healing of wounds. Wound healing usually depends on developing new blood vessels through angiogenesis or vasculogenesis. Proteolytic enzymes, growth-promoting or survival factors, various differentiated and ancestral cell type activators, and permissive microenvironments are vital mechanisms in neovascularization. To "transform" highly damaged and diseased wounds into those that will heal is a crucial goal of wound healing research.

2. 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 the skin is a spectacular biological function that contains numerous cells, growth factors, and cytokines. Topical bioactive compounds in 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. Natural polymers, like proteins polysaccharides, and proteoglycans, are commonly utilised in treating wounds and burns because of their biocompatibility, biodegradability, and similarity to macromolecules recognised by the body. [5]. They are biocompatible and biodegradable, have a unique structure, and have good mechanical properties, making them the ideal habitat for cell migration, differentiation, and proliferation. Correspondingly, 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 and wound healing, tissue-engineered skin is recommended, boosting the treatment in case of severe injuries to the skin or in some instances 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 natural polymers 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 provide an environment favourable for the healing process, including antibacterial, immune-modulatory, angiogenic and cell proliferative. The adaptability of biopolymers, including chitosan, cellulose, hyaluronic acid, alginate, and collagen, 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 most used material in biomedical research and bioengineering [6]. Technological developments in science, tissue regeneration technology, nanotechnology, and bioengineering have made this conceivable. [7]. Creating an "egg box" results from 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 and is a biodegradable and non-toxic natural tissue matrix constituent [8].

- Synthetic Polymers: Modern wound dressing currently mainly comprises synthetic polymers due to recent advancements in the field. Both passive and interactive forms of dressings

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
Journal of Coastal Life Medicine

comprised of synthetic polymers are available. In addition to helping recover 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 entering this area. They can be films, foams, hydrocolloids, or hydrogels [10]. Synthetic materials are routinely mixed with organic or bioactive polymers to enhance the final wound dressing's physical characteristics.

- Foams: Occlusive polymeric dressings include foam dressings as their category. Foam, readily available for use in the treatment of oozing wounds beginning in the middle of 1979, was one of the first "modern" treatments for wound dressings. Foams have several benefits that typical gauze dressings do not have, including the fact that they do not lose their viability and may be used for a substantially more protracted amount of time without getting macerated [9]. Foam dressings are essential in creating an environment that is conducive to the healing of wounds because of the properties that they possess. [11]. Foam dressings are designed to overcome the difficulties of occlusive dressings to absorb exudates while still providing the moist environment necessary for tissue healing [12].

- Hydrocolloids: They are absorbent, occlusive, and semi-permeable to vapour. Hydrocolloids are polymers with hydrophilic properties due to many hydroxyl groups in their structures. Hydrocolloids can be obtained either in their natural state or by synthetic means. Polysaccharides are the hydrocolloid type that is most frequently used in applications in the real world. [13]. Hydrocolloid dressings, due to their occlusive nature, ensure an oxygen-free environment, which leads to the liquefaction of necrotic tissue and makes autolytic clearance easier. This view has been strengthened by case studies indicating the ease of autolytic debridement of diabetic foot ulcers after using hydrocolloid dressing. [14].

- Hydrogels: For the purpose of manufacturing hydrogels, crosslinked hydrophilic polymers such as polyacrylamide, polyethylene, and polyvinylpyrrolidone oxide are often utilised. Hydrogels, unlike other gels, swell up when they come into contact with water but do not dissolve in it. [15]. Since hydrogels do not naturally attach to the skin, most hydrogels require an additional layer in order to maintain their position. Three different forms of dressings that can be used in case of burns—a new silver hydrogel dressing, a polymer film dressing, and a polymer foam dressing—have been compared 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].

3. Determinants of Wound Healing

A few causes can hamper the healing of wounds. Each element is essential for diagnosing and managing injuries of all sorts. This article examines the many local and systemic factors that could hinder or postpone the healing process. Local factors impeding wound recovery include trauma, maceration, desiccation, infection or atypical bacterial activity, stress, oedema, and necrosis [17]. Infection and oxygenation at the site directly impact 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 harmful impacts on tissue damage more than cancel out their positive benefits. [18].

Systemic elements are crucial in assessing a person's general well-being during wound healing. A risk factor for slowed wound healing is getting older. Compared to young mice, it alters inflammatory reactions, re-epithelialization, collagen synthesis, and angiogenesis, slowing down the process. Wound healing is significantly influenced by both male and female androgens and estrogen. Inflammation, matrix synthesis, protease inhibition,

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epidermal activities, and regeneration are all known to be regulated by estrogen [19].

Wound healing is significantly delayed because 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 experimental and clinical research as a hazard factor for poor wound healing. Alcohol intake compromises the body's defenses, leaving the wound open to additional infection. The most crucial impairment is caused by decreased angiogenesis [21]. Like 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 has 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. If the wound is kept moist using a dressing that retains moisture, epidermal cell migration will be sped up, which will help the epithelialization process.

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

❖ Necrosis: Dead, lifeless tissue known as necrosis can obstruct the healing process. Slough and eschar are two kinds of necrotic tissue that may manifest in a wound. Slough typically comprises dry, stringy, necrotic tissue and a bit lose. Eschar can be a dark colour and mimics a dry, leathery tissue. Necrotic tissue typically needs to be removed for healing and repair to occur.

❖ Trauma and edoema: When wounds are frequently wounded or destitute of a local blood supply by recovery is sluggish oedema, and in many cases, it does not occur at all.

There is a possibility that delayed wound healing might be caused by systemic factors with little to no direct link to the wound site. These include radiation therapy, vascular insufficiencies, immunosuppression, body type, nutritional state, age, 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, compromised immune, respiratory, and circulatory systems.

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

❖ Values from a lab: When assessing healing, laboratory results other than nutritional markers must also be considered. 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 several lesions or ulcers, including venous ulcers, diabetic, arterial, and pressure. These ulcers typically manifest themselves because of reduced blood flow. The practitioner must determine the kind of ulcer to choose appropriate topical and supportive drugs.

4. Traditional Dressings in Wounds

Due to the general extracellular matrix's complex structure and the existence of many cell types in an organized manner, functioning and healthy skin regeneration still needs to be improved. 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 new therapeutic avenues for skin disorders. While improving healthcare access and removing some drawbacks of contemporary products and treatments, such as their expensive prices, protracted manufacturing processes, and rise in bacterial resistance [23].

5. Dressings as Drug Delivery Systems:

- Wounds: The wound site can be directly treated with antibiotics, growth factors (GFs), probiotics, analgesics, proteins, and nutrients using wafers, hydrogels, foams, hydrocolloids, and films. Varied dressings have different properties, such as different fluid absorption levels, wound healing length, 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 kill bacteria and fungal infections aggressively, 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 a lesion site with no immune reaction first from the patient is known as wound colonization. Cellulitis, bacteremia, and septicemia may occur due to insufficient control mechanisms for infected wounds. One of the primary contributors to the development of chronic wounds is the formation of bacterial biofilms; 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 Staphylococcus aureus and Pseudomonas aeruginosa 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 with reduced migration, internal death of microorganisms, and phagocytosis. 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 the 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 previously 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]. In addition to killing germs, silver-infused dressings have been shown to kill fungus. 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 merely update current biocompatible wet medical applications containing silver in the pure state, as ions, or as nanomaterials. It enumerates the numerous silver-loaded dressings now available. The bulk of them has been shown to have antiseptic activity in vitro 154,155 and in vivo in most cases, according to peer-reviewed research journals [27].

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
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6. 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 worldwide 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 predict how gases behave in the atmosphere roughly. 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 adverse 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 appropriately cleaned and debrided. The sponge clogs by thick pus; however, some fibrous material and thin exudates can be managed. Visceral organs should usually be protected, and the sponge should not cover critical vascular structures. The outer layers 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 previously challenging to manage or 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; Angiotensin-converting enzyme-2 is the glycoprotein antigen associated with the host or human body cell receptor. This is the receptor for various viruses, including the coronavirus. When the virus enters the host cell, the spike protein of the virus is cleaved, which results in the protein's degradation. This is because the host cell contains an enzyme called transmembrane proteases, which are present in the human body. Serine now attaches to the ACE-2 receptor and the S2 subunit, which triggers the formation of viral coating with the host cell sheath. The only component of serine responsible for this effect is called serine. After that, the virus makes its way into the oral mucosa's epithelial cells and the lungs' alveolar cells. The coronavirus that causes it can also be discovered in the cells of the heart, endothelium, kidney, and intestines. Because of this, a patient with an infection caused by the coronavirus will have extrapulmonary and 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. Compared to other iodine-based dressings, both had lower iodine levels but equivalent antibacterial characteristics [32].

- Nanotechnology in wound healing: Diagnostic and therapeutic solutions based on nanotechnology make it possible to target the intricate cell type specificity, normal wound-healing process, the number of regulatory molecules, and the pathophysiology of chronic wounds. Numerous cutting-edge remedies powered by nanotechnology have been developed to address issues with the healing of chronic wounds. For the standardization of nanotechnologies, more learning 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 to heal wounds [34]. Scaffolds are created using a variety of nanotechnology processes, such as electrospinning, phase separation, and

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
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self-assembly. The most popular technique for creating nanofibers is electrospinning [35]. Electrospinning is a tried-and-true method for creating porous polymeric nanofibers, which has produced nano scaffolds with structural and physical characteristics similar to those of the extracellular matrix [36]. Electrospun nanofibers of silk fibroin were used as hybrid scaffolds to promote fibroblast adhesion and proliferation, improving wound healing in diabetes patients [37].

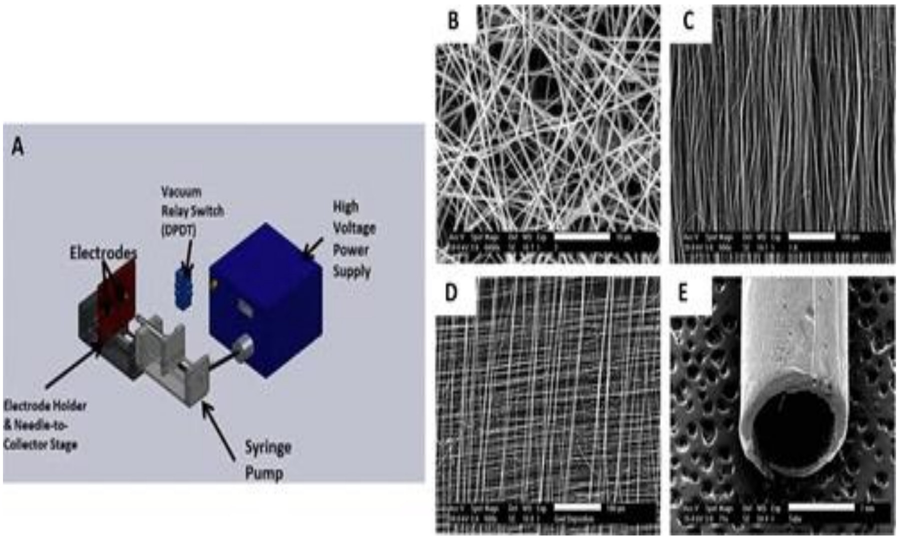

Figure 1. (A) Visual images of an electrospinning apparatus. (B) A microscopy image of electro spun scaffold, (C) with aligned fibre orientation, (D) with gridded fibre alignment, and (E) a tubular scaffold [33].

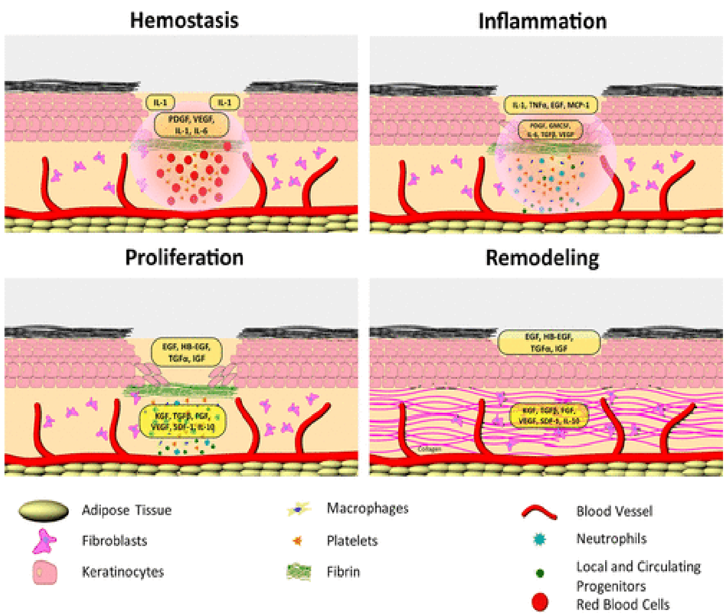

Figure 2: Skin wound healing stages that show the molecules and cells in charge of reestablishing a healthy barrier [33].

ISSN: 2309-5288 (Print)
ISSN: 2309-6152 (Online)
CODEN: JCLMC4
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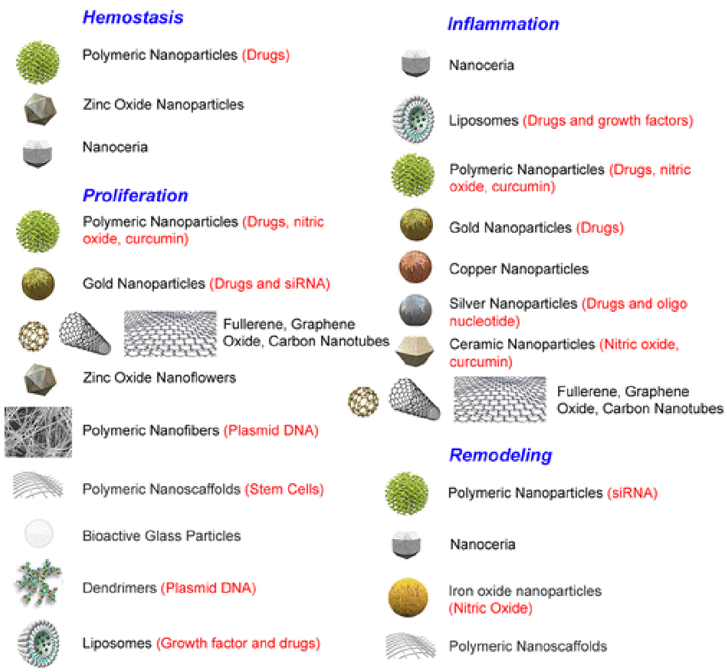

Figure 3: Diagrammatic evidence of therapies based on nano-technology used in wound healing [33]

7. 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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