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THE NEXT GENERATION OF WOUND HEALING: PIONEERING APPROACHES

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Abstract

Wound healing is a complex, multi-phase process involving physical, chemical, and biological mechanisms that restore damaged tissue. When this process is disrupted, it can lead to chronic wounds and abnormal scar formation, which are more susceptible to infection. Acute and chronic wound infections remain a global health concern due to high morbidity, mortality, and the rise of antibiotic-resistant pathogens. Nanomaterials have recently emerged as promising agents in wound healing due to their unique properties, including antimicrobial activity, enhanced tissue regeneration, and controlled drug delivery. These characteristics make them especially effective against biofilm-forming bacteria, which are a major barrier in chronic wound management. Despite their potential, nanomaterial-based therapies face several challenges. Concerns around toxicity, long-term stability, biocompatibility, and scalable production must be addressed. Further research is needed to better understand how these materials interact with biological systems and to ensure safety through rigorous preclinical and clinical testing. Recent advancements in wound care extend beyond nanotechnology, incorporating stem cell therapy, bioengineered skin grafts, and 3D bioprinting to promote skin regeneration and improve healing outcomes. These innovative strategies aim to minimize side effects while enhancing therapeutic effectiveness. In summary, nanomaterials offer exciting possibilities for revolutionizing wound care. However, their clinical translation will require a careful balance between innovation, safety, and regulatory approval. Continued interdisciplinary research is essential to fully realize their potential in managing both acute and chronic wounds.

Keywords: Nano medicine, wound healing, Dressing for infectious control.

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Introduction

Wounds are injuries which occur when sudden, rash and mostly unexpected accidents affect the integrity of skin. The injury may result from different causes such as cuts, crushes It is estimated that 2% of the population in developed countries suffer from a chronic wound during their lifetime. In Europe, according to the European Wound Management Association (EWMA), the prevalence of chronic wounds is 3–4/1000 (1.5–2.0 million out of 491 million inhabitants), the incidence being 4 million patients/year [1]. Patients suffering from chronic wounds may experience continuous pain, loss of mobility and functionality, increased stress level, social isolation, depression, anxiety, prolonged hospitalizations, impairment of work capacity, and negative financial impact. Moreover, if chronic wounds are located in the lower limbs (e.g., diabetic foot ulcer), amputation occurs in 85% of patients and the mortality rate increases to 40% after 5 years [2, 3].

Wound infection

- Types of wound: Depending on the duration and methods of the healing process, wounds are generally classified into two categories: acute and chronic wounds. Wounds resulting from corrosive chemicals, radioactivity, mechanical injury, heat, or electrical shock are considered acute wounds; they usually heal with proper wound-care treatment in a fairly short period of time. Chronic wounds, however, are associated with specific diseases, such as diabetes mellitus, and do not follow the orderly set of stages and predictable amount of time that characterize the normal wound-healing process.
- Wound dressing: The main purpose behind wound dressing is to protect the wound from external contamination. It also retains hydration in the wound to enhance regeneration and prevent exposing the origin of the wound [4]. Therefore,

wound-dressing materials should be biocom patible, semi-permeable to water and oxygen, hypoallergenic, and cost-effective in their case.

Pathophysiology of wound healing

Immediately after injury, a cascade of physiological reactions is triggered in order to restore the physical and functional integrity of the affected area [5]. Wound healing involves four steps: hemostasis, inflammation, proliferation, and remodeling. The ability of the body to restore its homeostasis after a traumatic event depends on maintaining the balance between the endogenous substances and the cells that mediate the healing process. The healing process is influenced by several factors such as mass index body, local anatomy, associated medication, infection, dysmetabolism, and patient compliance. In addition, the associated comorbidities (diabetes mellitus, high blood pressure, obesity, autoimmune diseases, peripheral vascular dysfunctions) interfere with healing physiological process and can impact the outcome of the treatment [6]. The Wound Healing Foundation (WHF) classifies chronic wounds in several categories, depending on their etiology: pressure ulcers, venous ulcers, diabetic ulcers, and arterial insufficiency ulcers as well as radiation, surgical, and infectious wounds.

Nanomaterials in Wound Healing

The use of nano materials in wound healing is expanding rapidly; furthermore, nano therapy- based wound-healing treatments are under clinical investigation [7]. The basic reason underlying the increased use of nano materials can be attributed to their physi ochemical properties including nano size, large surface area, and high surface area-to-volume ratios. Moreover, the size and shape of nano materials are conducive to their use in wound healing because they play a role in active drug delivery, penetrability, and cellular responses [8]. Two types of nanomaterials are commonly used in wound therapy [9]. nanomaterials with intrinsic properties that typically promote wound treatment, and nanomaterials as vehicles for the delivery of therapeutic agents.

Current advances and challenges in treating wound healing

- **Clinical diagnosis**: Clinical diagnosis is the first step to prevent further complications. However, classification of wound infections remains a challenge in practice. In general, almost all wounds contain microorganisms, but not all wounds develop infections. A clinical report by Leaper et al. showed that ~50% of patients who have a local wound infection do not show any sign of systemic infection [12], making diagnosis difficult [13]. Currently, there is a lack of objective clinical diagnostic criteria for wound infection, and clinicians usually make subjective judgments based on e0xperience. Diagnostic criteria (e.g. foul odour friable or discolored granular tissue) are highly subjective, resulting in high rates of misdiagnosis or overtreatment with antibiotics. As a result, patients can be at risk of developing multi-resistance bacterial strains.
- **Clinical wound dressing**: Materials Wound dressings are used to temporarily cover wounds and to prevent or manage wound infections. However, wound dressing may become a favorable place for microorganisms and biofilm formation, resulting in increased microbial load and delayed wound healing [14]. The ideal wound dressing should be flexible and immune-com patible, forming a physical defensive barrier but allowing oxygen exchange [15]. Many novel clinical wound dressings have been developed and are utilized, including sponges, hydrofibers, hydrocolloids, fucoidan, collagen, hydrogels and films. Antimicrobial wound dressings can be categorized as antiseptic, ionic/nanocrystalline silver and antibiotic. An antiseptic wound dressing is a treatment that releases antiseptics to eliminate microorganisms within the tolerance limits of living tissue. Products can contain either silver (e.g. Aquacel AG), nano-crystalline silver (e.g. ACTICOAT) or cadexomer iodine (e.g. Iodosorb™) as antimicrobials.
- **Current treatment of chronic wounds**: Current treatment of chronic wounds depends on the wound etiology. In all cases, an adequate wound cleaning and debridement, a control of possible infections, and the use of wound dressings are needed. NHPU treatments include dressings that accelerate the wound healing and relieve the tissue pressure. However, DFUs and VU focus on dressing that maintains the moist environment conducive to wound healing a compression [16]. Conventional dressings, such as gauze or gauze-woven cotton composite dressings, provide wound protection from bacterial contamination and allow gaseous/fluid exchange. They are used as secondary dressings to cover complex dressings or for the treatment of superficial and no infected wounds. Specifically, compression leg bandages are used in VUs to improve the vein circulation [17].

Wound care management and protocol

Given the diversity of causes, types of wounds, and the individual characteristics of patients, wound management is difficult to standardize. However, it is imperative that this process be carried out as objectively as possible, so that the established treatment protocol can be effective. The treatment should be closely related to type of wound and its healing phase and in correlation with the patient's comorbidity.

Nanomaterials -based growth factors for wound healing

Growth factors can be defined as biologically active polypeptides which play a pivotal role in modulating and coordinating cellular processes such as cell growth, differentiation, and migration during all stages of wound healing [18]. It is worthy to note that recombinant human platelet derived growth factor (rhPDGF) is the only available growth factor approved by the FDA. Another major hurdle regarding growth factors is that they fail to protect themselves from enzymatic degradation in the proteolytic wound environment. To resolve this issue, PLGA NPs, chitosan NPs, and solid-lipid NPs could be used to protect the growth factors from enzymatic degradation. Chu et al. [19], successfully showed that PLGA NPs could be used as a carrier in the preparation of rhEGF nanoparticles. In a similar way of study, rhEGF growth factor was incorporated into chitosan NPs within a fibrin gel for stable and sustained release of the growth factor Furthermore, Xie et al. [20].

Biological like polymers

Self-assembling peptides (SAPs) Peptides are comprised from aminoacid residues linked through peptide bonds, with a molecular weight of less than 10,000 Da. Peptides are ubiquitously present in both vegetal and animal regna and are essential for life cycles. Every physio/pathological process is regulated by various types of peptides with one or more functions. So, there are antibiotic peptides which are part of natural immune systems of prokaryotes and eukaryotes, cancer/anticancer peptides, immune/inflammatory peptides, endocrine peptides, gastrointestinal peptides, cardiovascular peptides, renal peptides, respiratory peptides, opioid peptides, and blood–brain peptides. In organisms, peptides are synthesized through ribosomal translation (antibiotics in microorganisms–microcines and bacteriocines), hormones and other signaling molecules (in the human body), or by enzymatic processes (glutathione) [21]. The resulting structures are highly biocompatible and may be used in tissues regeneration, scaffolds for drugs carriers and controlled release, and modulation of APIs to overcome adverse effects and enhance their stability [22]. The discovery of the first SAP, coded Ac-(AEAEAKAK)2-CONH2 (A-alanine, Eglutamic acid, K-lysine), in a yeast protein zuotin in 1990 was regarded as a big innovation and a valuable tool to design new materials for a wide variety of applications.

The chemical composition of SAPs consists of alternating hydrophobic aminoacids (alanine, valine, leucine, isoleucine, and phenylalanine) with hydrophilic aminoacids (lysine, arginine, histidine, aspartic acids, and glutamic acids), having very well-defined arrangements of negative and positive charges [23]. The temperature induces different 3D organizations of the peptide aggregates which influence the water uptake and mechanical strengths of hydrogels. For instance, amyloid beta peptide (C16-KKFFVLK) exhibits different self-arrangements at 20 ◦C (helical ribbons and nanotubes) compared to its exposure to 55 ◦C (twisted tapes). In addition, peptide RADA 16-I maintains beta sheets assembling through 25 ◦C to 70 ◦C, but small-sized globular aggregates were obtained at much higher temperatures [22, 23]. Targeting microorganism resistance to antibiotherapy, SAPs nanofibers with antimicrobial effects have been developed. It was shown that diphenylalanine-SAP inhibits bacterial growth through cell membrane disruption, depolarization, and enhanced permeation resulting in elevated levels of ROS. The addition of short SAPs to natural or synthetic polymers allows the design of SHs with improved benefits on wound healing. Arg-Gly-Asp-(RGD), cytosine-guanine-adenine (CAG), Arg-Glu- Asp-Va (REDV), and Tyr-Ile-Gly-Ser-Arg (YIGSR) are short SAPs used to activate the physiological cascade of wound healing because they are recognized by integrin receptors (RGD) or endothelial cells and promote cell migration, granulation tissue formation, selective cell adhesion, and neoangiogenesis in damaged tissues [24].

- **Nanoparticles:** NPs, with a diameter of 1–100 nm, are highly explored in the field of biomedicine and tissue engineering. In wound healing, they can be subdivided in two main categories: NPs with intrinsic properties positive for wound healing and NPs as drug delivery systems. Their main advantages are the controlled and sustained release, increase in drug half-life, and bioavailability. NPs with intrinsic activity for wound healing when developing strategies to address the healing of chronic wounds, technologies not using drugs or biologics are attractive to lower product fabrication costs and reduced time to market. Metallic NPs made of silver, copper oxide, gold, iron oxide, zinc oxide (ZnO), aluminum oxide, titanium dioxide, and gallium have proved their antibacterial properties.Its activity is caused by the production of ROS and the interaction with RNA, DNA, and enzymes (inhibitory), which all together provoke bacterial death. Other materials with intrinsic activity are cerium, bioactive glass (BG), and carbon-based and -bearing nitric oxide (NO) NPs.
- **Nanofibers:** Nanofibers are filaments with diameters within the nanoscale. They are usually produced by the electrospinning technique due to its low cost and simplicity. This technique uses a high electric force between a needle point capillary tip and a collector to spin the polymeric solutions and obtain fiber meshes. Indeed, its high surface areato-volume ratio and tunable porous morphology can promote the wound homeostasis, as well as allow the gas/nutrient interchange. Moreover, nanofiber meshes should also provide moisture to avoid the wound dehydration and bacterial contamination. They can also encapsulate biological molecules,

drugs, or nanocarriers encapsulating those, which consequently allow their topical administration with the subsequent advantages (lower dose and less side effects). In contrast, nanofiber meshes have also been tested as artificial skin. When MSCs are used they can differentiate into endothelial cells or release GFs to trigger the wound healing process. Nanofibers can be categorized depending on their composition (natural polymers, artificial polymers). Table 3 describes the strategies followed for diabetic wound healing.

Innovative herbal medicine

Herbal medicine has been used clinically since 5000 BC. Herbal medicine has minimal side effects and a low risk of drug resistance in treating wound infections. Natural products derived from insects such as periplaneta Americana extract, manuka honey and the natural product chitin have been clinically used in the treatment of various types of wound infection. A list of herbal medicines with antibacterial effects including herbal monomer and herbal compound is given in. The therapeutic effect of herbal medicine is attributed to certain chemical components. Among them, natural tannins have shown remarkable antibacterial and antioxidant activities. Tannins are polyphenolic compounds that are widely distributed in plants. A study showed that the total tannin content in phaseoloides (L.) Merr extract was found to be ~76.18%. Transmission electron microscopy observations demonstrated that tannins could interfere with S. aureus and destroy the cell membranes, releasing their intracellular cytoplasm. This study showed that tannin promoted wound healing in rats infected with S. aureus. Subsequent to these investigations, tannic acid has been approved by the US FDA and clinically used for skin ulcers and burns due to its favorable antioxidant, hemostatic and antibacterial properties.

The combination of clove oil and sandalwood oil enhances antibacterial activity against S. aureus and E. coli by 98%. In addition to its direct bactericidal effect, it can also mediate the secretion of antimicrobial peptides from HBD3 and LL-37 through the olfactory receptor OR2AT4 to methicillin- sensitive S. aureus, MRSA and purulent. In summary, it is expected that herbal derivatives are a group from which strong candidates for future treatment of chronic wound infections and biofilms will be selected. This study suggests that the activity of antibiotics can be increased by boosting systemic immune responses against drug-resistant pathogens. Another study demonstrated that polysaccharides isolated from Moringa oleifera seeds can be used to stabilize silver nanoparticles (AgNPs). Moringa oleifera seed polysaccharides have strong antimicrobial activity against pathogens collected from wounds, with minimal cytotoxicity toward mouse fibroblasts cells, and promote the migration of cells.

Future directions and challenges

Future efforts should focus at enhancing site specificity and targeting efficiency for more effective wound-healing applications as per the nanomaterial used. Therefore, researchers should aim at developing biocompatible and biodegradable nanomaterials capable of correcting all phases of wound healing.

Early diagnosis

An accurate diagnosis of wound infections is crucial to prescribe appropriate wound treatment. However, current approaches are speculative and time-consuming,with varying specificity and sensitivity. Novel diagnostic methods have been developed using the methods of PCR and auto-fluorescent imaging. A PCR kit, DxWound, has been developed to detect anaerobic bacteria, aerobic bacteria and fungi, allowing on-time monitoring for wound infections [138], while a portable autofluorescence imaging devices (e.g. MolecuLight™) has been utilized clinically for diagnosing wound infections. Future directions may involve denaturing gradient-gel electrophoresis, fluorescence in situ hybridization, metabolomics and genomics, techniques currently demonstrating great potential for the development of accurate, rapid, simple, noninvasive, inexpensive and specific diagnosis in wound infections [25].

Combined therapies for wound infection

For the treatment of acute or chronic wound infection, monotherapies, such as using antimicrobials, still have a high risk of antimicrobial resistance. Moreover, the spatial distributions of the microorganisms in the wound are complicated, the community behaviours of the bacteria are dynamic and the interactions between the polymicrobial and human immunity are undefined.The appearance of new bio-molecules active in wound healing, such as GFs or nucleic acids, shows the necessity of designing new formulations to protect them from degradation and to deliver them at specific rates. The emergence of nanotechnology, especially the fabrication and characterization of nanoparticulate systems, has increased the number of available interventions for healing of chronic wounds.

Challenges

Despite the numerous advantages of nanomaterial-based wound healing therapies, several challenges need to be addressed. These include toxicity concerns, regulatory considerations, scalability of production, and the long-term stability of nanomaterials . Further research is needed to optimise the design and formulation of nanomaterials, understand their interactions with biological systems, and conduct rigorous preclinical and clinical studies to ensure their safety and efficacy. These difficulties include cost-effectiveness, scalability, safety issues, and regulatory constraints.

Conclusion

The prevalence of acute and chronic wounds is increasing every year because of the aging population and the growing incidence of wound-related comorbidities, and remains a continuous concern of health systems worldwide. Overtime, medical specialists have developed and implemented various protocols and tools to overcome misinterpretation in wound assessment, which lead to impaired healing processes and complications. Choosing the appropriate topical approach has proved to be crucial for the entire output of the treatment. Nanomaterials have enabled the development of cutting-edge wound dressings, scaffolds, and various therapies due to their exceptional features, such as their tunable physicochemical features and specific targeting abilities. Infection remains a challenge in both acute and chronic wounds, leading to increased morbidity, mortality and healthcare-associated costs. Gram-positive bacteria, such as E. coli and P. aeruginosa, and Gram-negative bacteria, like S, aureus,are found to be the most predominant pathogens.Early detection of wound infections, combination therapies and understanding the skin microbiome can also aid in the treatment and prevention of wound infections. The main purpose of this review was to highlight the advantages of using nanomaterials for the wound-healing process. It is noteworthy that the unique physiochemical properties of nanomaterials render them ideal candidates for wound-healing applications Despite the extensive research and enhanced knowledge regarding wound treatment strategies for quality wound healing, the treatment of hard-to-heal chronic wounds and larger wounds still remains a major challenge in the skin regeneration and wound care domain.

Author Contributions

All authors are contributed equally

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