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Review Article

Nanotechnology-based Approaches for Efficient Wound Monitoring and Healing

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ABSTRACT

Wound healing is a complex physiological process consisting of several biological and immunological mechanisms which are mutually inclusive. Wounds are commonly categorized as acute and chronic wounds. Acute wound healing is dynamic and chronic wound healing proceeds in a prolonged and irregular manner; thus, it calls for proper management. Certain problems associated to wound healing have triggered the researchers to come up with a promising approach and so nanotechnology-based approaches have evolved as a driving force in wound healing. Nanotechnology has led to the fabrication of nanoparticles, biomolecule loaded dressings and smart dressings to accelerate the wound healing. Nanobiosensors are also being developed which can monitor wound conditions with great precision and incredible sensitivity. This review concentrates on novel nanoscale approaches for instance, nanoparticles such as gold, silver, polystyrene, chitosan, zinc peroxide and nanomaterials such as nano-sensors, nanoflares, nanofibers, etc. for effective wound monitoring and healing. The efficacy of nanomaterial based therapeutic agents in wound healing has been expressed herein. The significance of nanoscale systems in wound healing in terms of anti-microbial activity, angiogenesis, drug delivery, collagen deposition and stem cell delivery has also been addressed.

INTRODUCTION

The term "wound" refers to the alteration of living tissues caused by some physical impact which causes skin to cut open, as the skin is most vulnerable to tissue damage. Wound healing is the body's natural and normal reaction to injury. It is a complicated and dynamic process that aids injured tissues to regenerate quickly and restore normal function [1]. The skin wound healing process is classified into four highly interrelated and overlapping phases: haemostasis, inflammation, proliferation, and remodeling. Figure 1 shows the schematic representation of cutaneous wound healing.

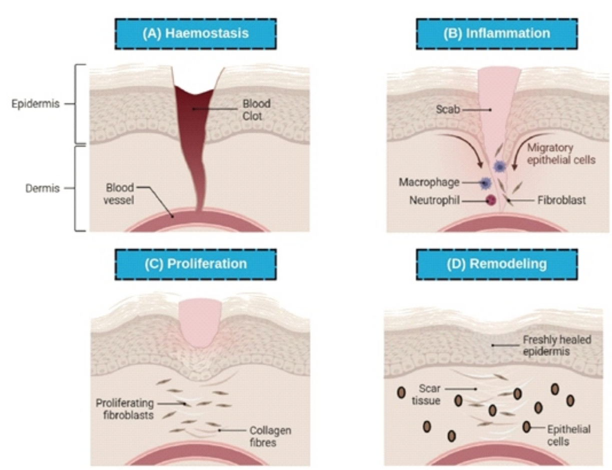

Figure 1: Schematic representation of the cutaneous wound healing

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(A) Haemostasis: A wound causes blood clot formation (B) Inflammation: Recruitment of macrophages and neutrophils (C) Proliferation: Fibroblast proliferation induces epithelial cell generation (D) Remodeling: Wound closure.

Various bio-physiological events and prominent cells determine these stages at varying intervals, with some significant overlap [2]. The skin wounds are categorized as acute or chronic on the basis of pathophysiology and outcomes [3]. Acute wounds go through a sequence of molecular processes that finally lead to structural integrity restoration [4]. A distinctive characteristic of unhealed wounds is chronic inflammation which is mediated by recruitment of pro-inflammatory immune cells [5]. Chronic wound management, on the other hand, has always been a challenge as the prolonged inflammation in these wounds is difficult to mitigate [6]. Thus, developing techniques centered on immune cell function control has been an appropriate strategy in regenerative medicine for curing chronic wounds such as diabetic, vascular, and pressure ulcers [7]. Numerous researches have been carried out across the years to develop more efficient wound treatments that might restore the injured cells, enable scar-free healing, conserve medical expenses, while offering long-term comfort [8]. Nanotechnology has emerged as one of the most optimistic innovations of the 21st century. Nanotechnology has administered on the nano-scale with multiple practical applications. It has correlated the design and application of chemical, physical, and biological systems at the range that varies from individual molecules or atoms to submicron proportions, along with the incorporation of the resulting nanostructures into larger systems [9]. Nano-medicine, a nanotechnology application, has operated in the realm of health and medicine by utilizing nanomaterials and nano-electronic biosensors [10]. Pertaining to wound monitoring and healing, nano-scaled materials are more preferable. The evidence has indicated that nano-grooves and nano-fibers are helpful for organizing cells down the orientation of bundles, limiting the random buildup of collagen in regenerating wound regions. Furthermore, they target cell migration towards wound openings, which provide new alternatives to wound healing [11]. Nanofibers have been used in tissue technology, artificial organ development, operative fabrics and implants, and wound dressing. Smart dressings have been developed by researchers, which integrate into the tissue once the wound has recovered. Nanofibers containing embedded coagulation, antibiotics, with detectors that sense sepsis manifestations possibly present inside such advanced bandages [12-14]. Henceforth, by analyzing remarkable wonders of nanotechnology, it has been demonstrated that nano-scaled specific therapies will account for prompt and effective response in wound monitoring and healing.

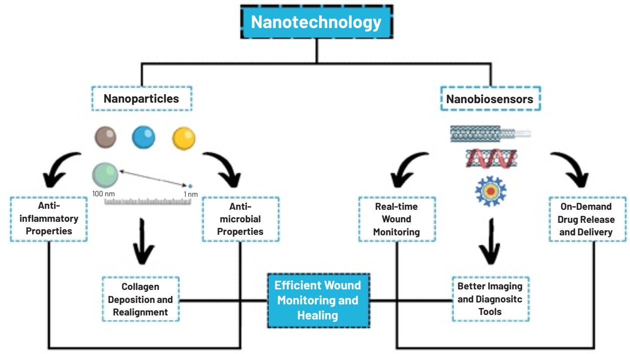

Figure 2: Nanotechnology-based Approaches for Efficient Wound Monitoring and Healing

Nanoparticles can be effective in treating wounds due to their properties such as anti-inflammatory, anti-microbial, etc. Nanobiosensors can also be efficient in treatment of wounds attributing to their properties such as real-time monitoring and on demand drug release and delivery.

Nanotechnology in Wound Monitoring

Nanotechnology has played a pivotal role in wound monitoring by introducing innovative materials and techniques to enhance the assessment and management of wounds. Advanced wound dressings, infused with nanoparticles, release therapeutic agents or change their properties in response to specific wound conditions, promoting healing while simultaneously providing real-time information on the wound's status [15]. Nano-scale imaging technologies has enabled healthcare professionals to visualize wounds at the cellular and molecular levels, aiding in precise diagnosis and treatment planning [16]. "Smart" wound dressings equipped with nano-sensors possess the ability to wirelessly transmit data on factors like pH, temperature, or bacterial load to remote healthcare providers, facilitating proactive intervention. In essence, nanotechnology has revolutionized wound monitoring by combining cutting-edge materials and monitoring technologies, ultimately improving patient outcomes in wound care [17].

Nano-sensors for Real-time Wound Monitoring

A study has examined the use of nano-flares (NFs), a nano-sensor based on the Spherical Nucleic Acid (SNA) platform, to measure the expression of connective tissue growth factor (CTGF) as an indicator of hypertrophic scars and keloids [18]. These optical sensors can penetrate skin layers, target and measure cellular mRNA biomarkers, providing non-invasive information. Compared to traditional visual observation and biopsy methods, this optical approach has been more accurate, timely, and convenient. The study has also explored the application of

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NFs for real-time monitoring of tissue status. Researchers have synthesized four types of NFs that identify mRNA biomarkers corresponding to different wound healing stages. In vitro experiments have established a correlation between cellular changes and fluorescence signals from these NFs, and in vivo tests have assessed the ability of topically applied NFs to accurately identify normal or abnormal wound healing [19]. Another study has reported the use of a one-step coaxial electro-spinning method to embed single-stranded DNA (ssDNA)-wrapped single-walled carbon nanotube (SWCNT) nano-sensors into separate microfibers, creating wearable optical micro-fibrous bandages. These bandages have served as a sensing layer to monitor oxidative stress in wounds. Through confocal Raman microscopy of individual fibers, the researchers have found that the SWCNT nano-sensors remained intact within the fibers over time. Furthermore, only a minimal amount of nano-sensor material had released from the three-dimensional fibrous matrix after 21 days, suggesting the long-term stability and retention of the nano-sensors within the textile-based sensing layer [20].

Imaging Techniques for Wound Monitoring Using Nanotechnology

Nanotechnology has also facilitated the development of advanced imaging techniques for wounds, allowing for more precise and detailed monitoring of wounds. Nanotechnology has enabled the use of scanning probe microscopy techniques, such as atomic force microscopy (AFM) and scanning tunneling microscopy (STM), to visualize wounds at the nano-scale. These techniques can provide high-resolution images of cellular and molecular structures within the wound, helping researchers and clinicians in understanding the intricate processes involved in healing. Moreover, nanoparticles can serve as contrast agents in various medical imaging techniques, such as magnetic resonance imaging (MRI), computed tomography (CT), and ultrasound. These nanoparticles can be functionalized to target specific cellular markers or processes related to wound healing, improving the imaging's specificity and accuracy [16]. Quantum dots are nano-scale semiconductor particles that emit specific wavelengths of light when excited. They are being used as imaging agents to track cellular processes and tissue regeneration in real time. Quantum dot imaging has provided detailed information about cell migration, proliferation, and differentiation during wound healing [21].

Table 1: Different Types of Nano-sensors Developed for Efficient Wound Monitoring

Nano-sensor Type	Sensitivity	Function	Ref.
Nano-sensor for infection monitoring	High	Infection monitoring, detecting and tracking infections at a molecular level. Designed to detect specific biomarkers or pathogens associated with infections.	[22]
Nano-sensors for pH detection	Exceptionally high	Designed to measure the acidity or alkalinity of a solution, offering high sensitivity and precision.	[23]
Nano-sensors for glucose monitoring in diabetic ulcers	High	Measure glucose levels in the wound microenvironment of diabetics	[24]
Temperature sensitive nano-sensors	Extreme sensitivity	Designed to detect and respond to changes in temperature at the nanometer level, offering high sensitivity and versatility.	[25]
Oxygen concentration monitoring nano-sensors	Highly sensitive to changes in oxygen level	Monitors oxygen level in ischemic wounds.	[26]
Uric acid concentration monitoring nano-sensors	Highly sensitive to uric acid concentration between 100–800 µM.	Designed to detect uric acid levels in wounded area and exudate.	[27]

Nanoparticles in Wound Healing

Wounds, especially the chronic and refractory wounds are difficult to manage as they mostly involve the risk of microbial contamination and infection, which can slow down the healing process [28]. The surge in multi-drug resistance in pathogens has led to an increase in the application of nanoparticles for their antimicrobial and other pro-healing properties (Figure 3).

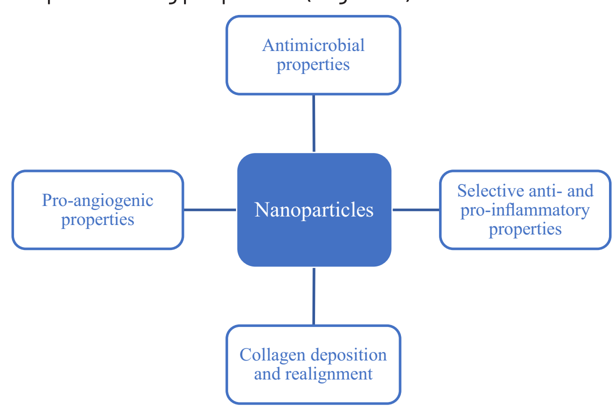

Figure 3: Properties of nanoparticles which help in accelerating wound healing

Antimicrobial properties can prevent infections, selective anti- and pro-inflammatory properties can manage the pain and suffering of the patients, while pro-angiogenic and collagen deposition properties can accelerate the wound healing and closure.

Presently, metallic nanoparticles are being studied, most extensively, for their potential in killing microbes, the efficacy of which is attributed to their surface area, which is in contact with the microbes [29].

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Table 2: Different types of nanoparticles and their useful biological properties

Nanoparticle Type	Biological Properties	Ref.
Silver Nanoparticles (AgNPs)	Antibacterial activity, anti-inflammatory effects, and wound healing efficacy	[30]
Gold Nanoparticles (AuNPs)	Antimicrobial property, promote healing and increase in the skin absorptivity of nanoparticles	[31]
Polystyrene Nanoparticles (PS-NPs)	Stimulate angiogenesis and enhance cell proliferation during re-epithelization	[32]
Chitosan Nanostructures (Ch-NPs)	Accelerating effects in wound healing	[33]
Zinc peroxide Nanoparticles (ZnO2-NPs)	Antimicrobial, anti-elastase, anti-keratinase, and anti-inflammatory properties	[34]

Some of the major functions performed by nanoparticles in wound healing, are discussed below:

Anti-microbial Activity

Silver nanoparticles are the most vastly investigated nanoparticles for their antimicrobial properties. The efficacy of AgNPs against bacterial as well as viral and fungal contaminations and infections has been confirmed by various studies [35-38]. The ability of AgNPs to inactivate viruses such as Hepatitis B and HIV viruses. is generally attributed to different forms of silver, which react with amino, carboxyl, phosphate and sulfhydryl groups, etc., to denature necessary enzymes. Apart from AgNPs, gold (Au), copper (Cu), titanium oxide (TiO_2), zinc oxide (ZnO), fibrin, graphene and graphene oxide nanoparticles are found to possess antimicrobial properties [39-44]. These nanoparticles have also been used as wound dressings after combining them with biocompatible scaffolds. Graphene-based nanoparticles, for instance, in combination with other biomaterials, can be used to form nanocomposites which can then be used to deliver growth factor, to enhance the bioactivity of other materials or to promote angiogenesis via the intracellular formation of reactive oxygen and nitrogen species (ROS and RNS) and the activation of phospho-Akt and phospho-eNOS antibodies which promote angiogenesis [45-48].

Angiogenesis

Angiogenesis is the formation of new blood vessels, a process critical for wound healing as the transport of oxygen and necessary nutrients to the proliferating cells, is carried out via the new vessels. In the past, metallic nanoparticles, particularly gold nanoparticles (AuNPs), were found to be having anti-angiogenic properties [49]. However, recent studies aimed at synthesizing AuNPs via green synthesis approaches, have suggested pro-angiogenic properties of AuNPs, along with better stability and biocompatibility [50]. In one study, a combination of AuNPs with α-lipoic acid and epigallocatechin gallate, exhibited accelerated healing of diabetic cutaneous wounds, via anti-inflammatory effects and regulation of angiogenesis. An initial increase in vascular endothelial growth factor (VEGF) and angiopoietin-2 expression was also attributed to the same combination [51].

Drug Delivery

Wound healing being a complex process, requires various bioactive compounds especially growth factors (GFs) for properly inducing cell proliferation, migration, angiogenesis and collagen deposition [52]. Nanoparticles have developed into efficient delivery systems for these bioactives. The novel characteristics of NPs make them a suitable option for delivery of GFs to the wound sites. Various studies have confirmed the potential of NP-based delivery systems by delivering GFs such as vascular endothelial growth factor (VEGF), recombinant human epidermal growth factor (rhEGF), basic fibroblast growth factor (bFGF), granulocyte colony stimulating factor (GCSF), keratinocyte growth factor (KGF), platelet-derived growth factor (PDGF), and platelet-rich plasma (PRP), which contains various GFs. NP-based vectors have been constructed by incorporating rhEGF, VEGF, PDGF, and bFGF with either collagen-hyaluronic acid (HA) in embedded form or with gelatin NPs via encapsulation. These constructs offer slow controlled release of GFs for up to 1 month. Application of these NP-based delivery systems on artificially inflicted wounds on diabetic rats has exhibit accelerated wound closure [53].

Table 3: Growth Factors Incorporated Nanoparticles-based Studies for Diabetic Wound Healing

Type of Nps	Growth Factors	In-Vivo Model	Administra-tion Route	Results	Ref.
Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC)	rhEGF	8 mm skin wound in diabetic male db/db mice	Topical dressing	Higher fibroblast and keratinocyte proliferation with greater resolution of inflammation	[54]
Poly (lactic-co-glycolic acid) (PLGA) Nanoparticles	VEGF, bFGF	8 mm skin wound in diabetic male db/db mice	Topical dressing	Significant granulation, tissue formation, collagen secretion and re-epithelialization	[55]
Sodium-carboxy methyl-chitosan (NaCMCh) Nanoparticles	rhEGF	20 mm skin wound in diabetic male Sprague-Dawley rats	Topical dressing	Higher cell viability with enhanced wound healing rate	[56]
Gelatin Nanoparticles	VEGF, PDGF, bFGF, EGF	15 mm skin wound in diabetic male Sprague-Dawley rats	Topical dressing	High cell proliferation and accelerated complete healing	[57]
Gold Nanoparticles (AuNPs)	KGF	10 mm in diameter skin wound in diabetic rats	Topical dressing	Promoted re-epithelialization and wound contraction along with elevated expression of Col-I, α-SMA and TGF-β1	[58]
Silver nanoparticle-coated ε-Polylysine Nanocomposites	ε-polylysine	1.5 cm skin wound in diabetic male Wistar rats	Topical dressing	Accelerated wound healing without side effects on skin tissues; no infection	[59]

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Collagen Deposition

Silver nanoparticles have been found to possess the ability to enhance collagen deposition. A study confirmed increased collagen deposition in both normal and diabetic mice wounds, treated with a polyelectrolyte multilayer (PEM) dressing containing AgNPs [60]. Similar results have been observed in different studies using AuNPs as well as calcium-based nanoparticles [61, 62].

Stem Cell Delivery with the Aid of Nanoparticles

Stem cells can revolutionize wound healing properties. The totipotent cells hold the ability to differentiate into the cells of the wound site, accelerating wound closure. The targeted delivery of different stem cells using NPs is an active research topic. NPs are being used to guide stem cells and at the same time, stem cells are being experimented as a medium to deliver NP-properties. In a stenting experiment, the migration of mesenchymal stem cells (MSCs) to the site of atherosclerosis was controlled magnetically by filling the MSCs with silicon, gold, and iron nanoparticles. The results observed were more efficient than conventional stenting [63]. In another study, epidermal stem cells (ESCs) were transfected with polyethyleneimines-linked β-cyclodextrin. Skin wounds were treated with the transfected ESCs and accelerated VEGF synthesis, follicle regeneration and skin re-epithelialization were observed [64].

Smart Dressings with Nano-materials for Wound Healing

A study carried out the development of smart bandages with wound monitoring capabilities. The objective was to make the magnetic nanoparticles within the wound dressing responsive to specific wound healing biomarkers, such as temperature. This allowed the smart bandage to detect and react to temperature variations occurring as a result of activities at the wound site. Essentially, the integration of nanoparticles onto cellulose fibers enabled the bandage to sense and respond to relevant physiological changes during the wound healing process [65]. Another study showed that nano-fibers offer a promising approach to wound healing as they can serve as a dual-purpose solution, facilitating haemostasis and providing a scaffold for cell regeneration [66]. The key idea behind nano-fibers is to design wound dressings that replicates the structure and functionality of the extracellular matrix (ECM). Typically, nano-fibers are constructed using naturally occurring molecules found in the skin's ECM, making them a common choice. This approach aims to create wound dressings that closely mimic the natural environment of the skin, promoting more effective and natural wound healing processes. A study investigated the tissue responses to nano-sensors embedded in a hydrogel matrix, with a focus on single-walled carbon nanotube (SWCNT) biosensors. It was found that the rate of acute inflammation resolution was notably influenced by the type of SWCNT wrapping, with DNA-wrapped SWCNTs leading to less severe acute inflammation. Additionally, comparison between different hydrogel formulations has suggested that modifying physical parameters like cross-link density could reduce nanoparticle release, resulting in better-tolerated implants and faster inflammation resolution. The study had also demonstrated that the SWCNT sensor's functionality has deactivated during the acute inflammatory response [67]. These findings highlight the importance of careful design considerations when formulating hydrogel-encapsulated nano-sensors. Future researches may aim to explore various hydrogel formulations to better understand the chemical factors influencing tissue responses, with the aim of identifying optimal hydrogel materials to prolong the in vivo longevity of nano-sensors.

Challenges and Future Prospective

Chronic wounds pose a global healthcare challenge, with limited Food and Drug Administration (FDA) approved therapeutic agents, hindering comprehensive solutions [68]. Nanotechnology-based approaches offer promise for wound monitoring and healing, but face challenges due to the complex pathology of wound healing, patient diversity, and intricate trial designs [69]. Physicochemical considerations and the need for increased public awareness add to the complexity. Recent studies explore innovative strategies, such as combining mesenchymal stem cells (MCSs) with hydrogels, developing skin-like structures, and creating antimicrobial natural polymer composites [70]. The National Institute of Health's Big Data to Knowledge (BD2K) initiative underscores nanotechnology's potential, emphasizing a personalized approach [68]. Overcoming challenges requires consistent and controlled nanotechnology approaches with improved synthesis and targeting, balancing safety concerns like systemic absorption. Innovations in wound dressing formulations, particularly polysaccharide-based biopolymers, show promise, but translating lab research to clinical success demands eco-friendly, cost-effective solutions [71]. Nanotechnology extends beyond wound care, with silver nanoparticles finding applications in sunscreens and diagnostics. Despite 35 FDA-approved AgNP-based products in clinical trials, challenges persist in reproducible manufacturing, environmental impacts, and regulatory compliance, underscoring the need for careful consideration before widespread adoption [72]. These considerations are crucial before the widespread adoption and commercialization of any nanotechnology-based wound monitoring and healing approach.

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CONCLUSIONS

Nanotechnology's integration into wound care has revolutionized wound monitoring and healing processes and practices. Smart dressings with nanoparticles releasing therapeutics, nano-sensors providing real-time data, and wirelessly transmitting information for proactive healthcare, offer non-invasive, timely wound assessments and enhanced wound healing. Metallic nanoparticles, notably silver, exhibit potent antimicrobial properties, crucial to prevent infections. Similarly, gold nanoparticles, which now present pro-angiogenic potential, have shown promising prospects for the future. Despite challenges in clinical trials and public awareness, nanotechnology still holds an immense potential for personalized wound care. Responsible and careful researches in the field of nanotechnology for wound healing, will undoubtedly be a crucial step towards global benefit.

Authors Contribution

Conceptualization: AT, LZ
Writing, review and editing: AT, LZ, AN, HAQ, HSB, AK, NT
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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