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REVIEW ARTICLE

Nanoparticle Based Dressing: The Future of Wound Treatment

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ABSTRACT
Wound healing is an intricate process that requires complex coordination between many cell types and an appropriate extracellular microenvironment. Chronic wounds often suffer from high protease activity, persistent infection, excess inflammation, and hypoxia. While there has been intense investigation to find new methods to improve cutaneous wound care, the management of chronic wounds, burns, and skin wound infection remain challenging clinical problems. Ideally, advanced wound dressings can provide enhanced healing and bridge the gaps in the healing processes that prevent chronic wounds from healing. These technologies have great potential for improving outcomes in patients with poorly healing wounds but face significant barriers in addressing the heterogeneity and clinical complexity of chronic or severe wounds. Active wound dressings aim to enhance the natural healing process and work to counter many aspects that plague poorly healing wounds, including excessive inflammation, ischemia, scarring and wound infection. Nanoparticle-based dressings hold promise as the future of wound treatment. These innovative dressings utilize nanoparticles to enhance wound healing and combat infections, addressing current challenges in wound care. By leveraging the unique properties of nanoparticles, such as their high surface area and tunable properties, these dressings can improve drug delivery, target bacteria, and promote tissue repair. While still in development, nanoparticle-based dressings represent an exciting avenue for more effective and efficient wound treatment in the future.
Keywords: *Biomaterials, Nanoparticles, Nanotherapeutics, Regenerative medicine, Wound healing*

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INTRODUCTION

Wounds, defined as tissue damage, present clinical challenges, particularly in individuals with conditions like diabetes, hypertension, and obesity. Wound healing is a complex process involving cells, soluble substances, and interactions. Infections occur when microbes overpower the body's defenses. Nanotechnology, working at the nano-scale, has revolutionized wound treatment. Nanoparticles, typically 1-100 nm, exhibit unique properties, such as optical effects. Silver, gold, and other nanoparticles show promise in wound healing. They can enhance drug delivery and formulation effectiveness. Advanced wound dressings, utilizing biomaterials and nanoparticles, offer hope for chronic wound management, which affects millions worldwide and poses a substantial financial burden on healthcare systems.

The prevalence of chronic wounds has surged in recent decades, resulting in escalated healthcare costs and patient distress. These wounds, such as venous leg ulcers and pressure ulcers, often involve factors like heightened protease activity, infections, and tissue ischemia. The rise of antibiotic-resistant microbes globally, especially Methicillin-resistant *Staphylococcus aureus* (MRSA), exacerbates the problem of wound infections. Burn injuries also pose challenges, with complications like scarring and functional loss. An ideal advanced wound dressing must create an optimal microenvironment, supporting gaseous exchange, moisture balance, infection prevention, and aiding natural wound healing processes. The wound healing process consists of four phases: hemostasis, inflammation, proliferation, and remodeling, and a delicate balance between inflammation and proliferation is crucial for effective healing [1].

The wound healing process comprises distinct phases, including hemostasis to control bleeding, inflammation mediated by neutrophils and macrophages, proliferation involving various cell types, and the remodeling phase led by fibroblasts. Chronic wounds can be highly inflammatory, requiring anti-inflammatory drugs and antibiotics. Animal models for wound healing are essential, with small mammals like mice and rats providing cost-effective options, but differences from human healing processes exist. Porcine models, with skin similarities to humans, are valuable but costly. Biomaterials have played a vital role in wound care, with liquid adhesive bandages, dextran-based hydrogels, and materials selectively degraded by reactive oxygen species showing promise in enhancing wound closure and tissue regeneration. Artificial dermal constructs and synthetic hydrogels also contribute to improved wound healing outcomes [2].

Despite initial optimism, clinical trials for growth factor-based wound healing treatments have shown limited success, with only recombinant platelet-derived growth factor-BB gaining FDA approval for chronic wounds. Novel engineered growth factors, including those fused with ECM-binding domains, have demonstrated promise in enhancing diabetic wound healing in mouse models. Amniotic fluid-derived stem cells, encapsulated in a photo-crosslinkable hydrogel, improved wound closure and reepithelialization by preserving and delivering paracrine factors. Biomaterial-based wound dressings have also evolved to include skin protectants, sealants, moisture barriers, and keratolytics. These innovations aim to address complex wound healing issues by delivering multiple bioactive components and maintaining temporal control over factor release during different wound healing phases [9].

Nanoparticle-based wound therapies

Nanoparticle-based wound therapies have gained significant attention within the context of nanotechnology, an industry with a valuation exceeding $1.5 trillion in 2014. This prominence is closely linked to the widespread adoption of consumer products containing nanoparticles (NPs), a number expected to reach 10,000 by 2020. NPs hold considerable promise as a therapeutic approach due to their ability to precisely target tissues while maintaining low levels of toxicity. With dimensions typically falling within the range of 1 to 100 nanometers, NPs exhibit unique physical and chemical properties in contrast to bulk materials. These distinctive traits encompass variations in melting points, specific surface areas, optical attributes, mechanical strengths, and magnetization properties. Such unique characteristics render NPs highly attractive for a wide array of applications in both industrial and medical domains. Within the realm of regenerative medicine, NPs have evolved into indispensable tools for tasks such as drug delivery, imaging, sensing, and the exploration of intricate biological processes transpiring at the nanoscale.

Metal Nanoparticles

Silver nanoparticles (AgNPs) show potential in enhancing wound healing, with applications in treating full-thickness wounds and impregnated dressings for normal and diabetic mice. They exhibit antimicrobial and anti-inflammatory properties but may induce dose-dependent toxicity in zebrafish embryos. Additionally, other nanoparticles like magnesium fluoride, cerium oxide, copper, and gold NPs have shown promise in wound healing with specific mechanisms of action. Gold and silver NPs stand out as promising options, with silver being antimicrobial and anti-inflammatory, while gold can be tailored for precise drug delivery [3].

Antibiotic-Loaded Nanoparticles

A recent surge in advanced therapeutics involves nanobiotics, where antibiotics are linked to nanoparticles (NPs) to target multidrug-resistant microbes. Various NP-antibiotic conjugates have been developed to enhance antimicrobial activity and reduce toxicity. These include polyacrylate NPs, poly(butyl acrylate-styrene) NPs, gelatin, chitosan, and epigallocatechin gallate NPs, as well as vancomycin-modified NPs and folic acid-tagged chitosan NPs. These innovations address the pressing need to combat antibiotic-resistant bacteria, particularly Gram-negative strains, by improving antibiotic effectiveness in wound care.

Nitric Oxide Releasing Nanoparticles

Nitric oxide (NO) plays a vital role in wound healing, influencing the deposition of ECM proteins, cell proliferation, and endothelial function. Incorporating diazeniumdiolate functional groups into materials enables the controlled release of biologically active NO in aqueous environments. Studies have demonstrated accelerated wound healing with NO delivery. Additionally, NO-releasing silica NPs effectively combat biofilms of various pathogens, including *P. aeruginosa*, *E. coli*, *S. aureus*, *S. epidermidis*, and *Candida albicans*. Intriguingly, endogenous NO can protect bacteria from antibiotics and other microorganisms by chemically modifying toxic compounds and reducing oxidative stress. Targeting bacterial NO synthase may enhance future antimicrobial therapy.

Green Synthesized Nanoparticles

Green synthesis of nanoparticles (NPs) employs plant-based products or extracts, offering a more cost-effective and environmentally friendly alternative to conventional physicochemical methods [2]. Genipin, derived from geniposide using β-glucosidase from Penicillium nigricans, cross-links with chitosan, PEG, and silver NPs to create a wound-healing nanocomposite with strong antimicrobial properties [3]. Similarly, silver NPs produced using Coleus forskohlii root extract effectively healed excision wounds in rats. Silver NPs synthesized with montmorillonite clay and extracts from Homalomena aromatica, combined with hyper-branched epoxy, formed an antimicrobial wound-healing nanocomposite [4].

Lipid Nanoparticles

Lipid-based nanoparticles (NPs) have given rise to the field of lipid nanotechnology, with liposomes serving as versatile drug delivery systems known for protein delivery, biocompatibility, and the ability to modulate size, charge, and surface properties. Growth factor resistance in diabetes can be overcome by delivering co-receptors and growth factors within proteoliposomes, improving diabetic wound healing and ischemic revascularization. Solid lipid nanoparticles (SLNs) are a pharmaceutical delivery system for various bioactive molecules, while cell-produced lipid NPs called exosomes have demonstrated effectiveness in wound healing.

Polymer Nanoparticles

Wound dressings containing titanium dioxide nanoparticles coated with chitosan and pectin exhibit antimicrobial properties and facilitate effective wound healing. Encapsulation of growth factors within polymer nanoparticles enhances their stability, bioactivity, and controlled release. PDGF-BB, FDA-approved for diabetic foot ulcers, is effectively delivered using hyaluronan-based porous nanoparticles. FGF-2 and EGF have been microencapsulated for applications in tissue engineering, angiogenesis, and wound healing [5].

Silver Nanoparticles

Silver has a long history of use, from ancient Roman times to modern biomedical devices. Silver nanoparticle-based ointments and creams are widely employed for their antimicrobial properties, promoting moist wound care, cosmetic healing, and cytokine modulation. They are suitable for minor cuts, burns, and skin irritations. While the exact mechanisms of silver's antibacterial action are not fully understood, it is known to disrupt bacterial membranes and metabolic activity. Prolonged exposure can result in argyria, causing the skin to turn blue-gray. Silver-based treatments are cost-effective, with low systemic toxicity and effectiveness against infections, although they have limited impact on chronic wound healing.

Biomaterials have a long history in wound healing, but nanoparticles (NPs) have gained prominence in the last two decades. Clinical wound healing products include films, foams, hydrogels, and more, but there are no approved biomaterials for releasing bioactive components. CRISPR-Cas9 technology offers new possibilities for gene editing to enhance wound healing by mimicking fetal regeneration. Wound care poses a significant societal and economic burden, with variability in patient symptoms, necessitating multipronged therapies to address pain, inflammation, infection, slow healing, and rising drug-resistant bacteria. Biomaterials and NPs hold promise for improving wound care.

Medical textiles: Nanofiber-based 'smart' dressings for burn wounds

Burn injuries are a significant global health concern, leading to high mortality and lifelong disabilities. They can result from various sources, including fire, electricity, radiation, and chemicals. Effective wound care is crucial to prevent infections caused by bacteria and fungi, particularly in patients with compromised immunity. Nanofiber-based wound dressings (NFDs) offer advantages such as promoting hemostasis, high absorption, semi-permeability, flexibility, and the ability to incorporate medications. They operate in a moist environment, reducing the need for frequent dressing changes, minimizing pain, and preventing scars, which is especially beneficial for burn victims. Electrospinning is the primary method for producing polymeric nanofibers used in NFDs, and protein nanofibers like tropoelastin show promise for this application.

Recent breakthroughs and R&D activities in the field of NFDs are as follows:

Various nanofiber-based wound dressings (NFDs) have been developed for enhanced wound healing and drug delivery applications. Chitosan-coated poly(vinyl alcohol) nanofibers displayed improved mechanical stability and wound healing acceleration, offering a promising NFD. Hyperbranched polyglycerol (HPGL) NFDs, incorporating Calendula officinalis for anti-inflammatory and wound healing properties, demonstrated potential as drug delivery vehicles. SiO_2 NFDs embedded with silver nanoparticles (Ag NPs) provided a convenient, long-term antibacterial wound cover, with recoverable inorganic components. Collagen blended with zein improved electrospinnability and allowed the regulation of mechanical and degradable properties. Nano-ZnO in sodium alginate/PVA nanofibers

enhanced antibacterial properties, but optimal ZnO concentration requires further study. Composite nanofibers facilitated programmable dual drug release, offering a promising approach for early wound healing.

Chitosan Based Dressings for Wound Care

Biopolymer research has made significant strides in enhancing wound dressing properties, particularly in the last decade, marking a rapidly growing field in biomedical and pharmaceutical sciences. Biopolymers, such as chitosan, offer advantages for various biomedical applications due to their ease of processing into different forms. Chitosan, a well-known natural biopolymer, is valued for its safety, biocompatibility, and biodegradability. This review focuses on chitosan's properties and its biomedical applications, emphasizing its role in anti-inflammatory and wound care management. In the realm of biomedical applications, polymers play a crucial role, with notable advancements in polymeric materials, including composites, blends, and nano-polymeric materials. Several biopolymers, such as starch and carbohydrate polymers from fungi, bacteria, as well as animal-derived biopolymers like chitosan, chitin, gelatin, and collagen, have gained favor for various industrial applications.

Effective wound dressings necessitate properties such as moisture and nutrient retention, oxygenation, inflammation control, fibroblast proliferation, and epithelialization. Chitosan, with its antimicrobial characteristics, meets these requirements and holds promise for future wound dressings. Unlike many commercial polysaccharides, such as dextran, starch, alginic acid, carrageenan, and heparin, which are either acidic or neutral polymers, chitosan stands out as a basic polymer. Its solubility is pH-dependent, as it is insoluble in neutral or basic pH, while becoming soluble in water under acidic conditions due to protonation of its amino groups. Chitosan's solubility hinges on the distribution of free amino and N-acetyl groups.

Chitosan structure and its origin

Chitosan is a copolymer composed of β-(1→4)-linked 2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose units, typically derived from the alkaline deacetylation of chitin, a prominent component of crustaceans' exoskeletons. Chitin, the second most abundant biopolymer after cellulose, forms the primary structural element in the exoskeletons of animals, including crustaceans, mollusks, and insects. Deacetylation of chitin produces chitosan, which can be obtained in various forms such as powder, paste, film, and fiber. Chitosan exhibits solubility in dilute acids like acetic acid, lactic acid, malic acid, formic acid, and succinic acid. In acidic conditions, chitosan adopts a cationic nature, enabling interactions with negatively charged molecules like proteins, alginate, carrageenan, bile acids, and phospholipids.

Given its biodegradability, biocompatibility, antimicrobial properties, and non-toxic nature, chitosan has garnered substantial attention for biomedical applications. Chitosan promotes hemostasis and expedites tissue regeneration, making it valuable in wound healing management. For biomedical research materials, natural products are preferred due to their enhanced biocompatibility compared to synthetic counterparts. Chitosan is particularly attractive for tissue engineering scaffolds, as it shares structural similarities with glycosaminoglycans and exhibits hydrophilic properties. The monomeric unit of chitosan, N-acetyl glucosamine, plays a crucial role in wound healing.

Enhancing the performance of chitosan can be achieved by modifying its surface properties, facilitating the development of clinically applicable chitosan. Chitosan can be processed into gels, membranes, nanofibers, nanofibrils, beads, microparticles, nanoparticles, scaffolds, and sponge-like forms, rendering it highly versatile in applications like tissue engineering, wound healing, drug delivery, and gene delivery. Crosslinking is another strategy to improve chitosan, with hydrogel crosslinking dependent on factors such as crosslinking density and the nature of the crosslinker, either covalent or ionic bonds, giving rise to various network structures [6].

Chitosan in wound care

Chitosan, with its inherent antimicrobial and anti-inflammatory properties due to its cationic nature, holds great promise in various biomedical applications, particularly in wound healing and as an antimicrobial agent. It's essential to understand that antimicrobials combat microorganisms, while anti-inflammatories reduce inflammation and alleviate pain. Chitosan exhibits a multitude of biomedical applications, serving as a novel material in drug delivery, wound healing, antibacterial treatments, fat binding, hemostasis, and hypocholesterolemic effects, as evidenced by recent studies. Chitosan can reduce inflammatory pain, as seen in the case of intraperitoneal acetic acid administration. Additionally, it possesses strong antimicrobial activity against fungi, algae, and bacteria, with varying effects influenced by factors like chitosan type, degree of polymerization, and environmental conditions. Its application extends to diverse fields, including tissue engineering, drug delivery, gene delivery, and more. For wound healing, effective dressings should maintain moisture, support oxygenation, control inflammation,

promote fibroblast proliferation, and encourage epithelialization. Chitosan-based dressings address these requirements, offering a soothing effect when applied to open wounds. Their pain relief benefits are evident when used in burn injuries, skin abrasions, ulcers, and skin-grafted areas. Moreover, chitosan plays a vital role in addressing hemorrhage and infectious complications following trauma, as these are leading causes of early death and a constant challenge for healthcare providers. Chitosan dressings have been developed to tackle these issues, offering solutions for bacterial control and bleeding management at wound sites. Incorporating silver nanoparticles, known for their antimicrobial properties, enhances the wound healing potential. Plant extracts, when encapsulated within hydrogel films, serve as natural antimicrobial agents, contributing to wound care.

Aloe vera and other materials added to chitosan-based membranes improve their antimicrobial effectiveness, making them promising wound dressings. With their intrinsic antimicrobial, biocompatible, and biodegradable properties, chitosan-based materials find applications in diverse biomedical fields, with a focus on wound healing and anti-inflammatory effects. Their ability to interact with growth factors, exhibit antibacterial activity, biocompatibility, and versatility in form, positions them as ideal candidates for scaffold materials in wound dressings. Effective wound dressings must be tailored to specific wound types, offering optimized characteristics at a reasonable cost and minimal patient inconvenience. Future research should explore the potential of various chitosan-based dressings for effective wound healing [7].

Nanoparticle-based strategies for controlling biofilm infections

Recent advances in nanoparticle-based technology provide new and promising opportunities for effectively defending wound infection associated with biofilms. Over the last decade, nanoparticle-based approaches against biofilm infection have been directed towards designing nanoparticles to exhibit specific chemical and physical properties towards anti-biofilm activities.

Nanoparticles as an intrinsic antimicrobial agent

Traditional antibiotic therapies face limitations due to toxicity and drug resistance. Metal nanoparticles, especially silver and zinc oxide nanoparticles, have shown promise in managing wound biofilm infections. Silver nanoparticles disrupt biofilms by releasing silver ions and can be effective when used in combination with antibiotics. Zinc oxide nanoparticles exhibit antibacterial activity but may have cytotoxic effects on human cells. Balancing their benefits and risks is essential for clinical translation [8].

Nanoparticles for controlled delivery of antimicrobial agents

The primary challenge in treating biofilm infections in chronic non-healing wounds using conventional antibiotics is inadequate drug delivery. The complex biofilm matrix and avascular nature of chronic wounds limit the effectiveness of systemically or topically administered drugs and can lead to drug resistance. To address this, nanoparticle-based drug delivery systems have been developed to provide controlled, sustained release of antimicrobials, protect drugs from enzymatic inactivation, and enable targeted delivery to the infection site, offering enhanced antimicrobial efficacy.

Controlled release of antibiotics

Encapsulating antibiotics within nanoparticles enhances their ability to penetrate biofilm matrix and target bacterial cells effectively. Liposomes, composed of a lipid bilayer, have been used to deliver antibiotics, offering advantages such as mimicking cell membranes and protecting antibiotics from degradation. Polymeric nanoparticles, particularly poly(lactic-co-glycolic acid) (PLGA), provide biocompatibility and controllable drug release kinetics. Hybrid lipid-polymer nanoparticles combine biocompatibility with structural stability. While nanoparticle-based antibiotic delivery shows great promise for treating biofilm infections, challenges like stability and drug leakage need addressing for wider clinical use. Increasing antibiotic encapsulation efficiency and developing infection-sensitive nanoparticles can improve nanoparticle-based treatments.

Controlled release of nitric oxide

Nitric oxide (NO) displays broad-spectrum antimicrobial properties and can disrupt biofilm formation. Using nanoparticles as carriers for controlled NO release has shown promise in treating wound infections, including MRSA and Candida albicans, in animal models. NO-releasing nanoparticles not only combat bacteria but also promote wound healing. Precise control of NO release kinetics is crucial to avoid hindering the wound healing process.

Controlled delivery of photosensitizer

Photodynamic therapy (PDT) combines light and photosensitizers (PS) to combat infections. PDT has gained interest for localized infections, including wound infections. PDT generates cytotoxic reactive oxygen species (ROS) when PS is activated by light. While effective against planktonic bacteria, PDT's efficacy in biofilms is reduced due to poor PS penetration. Encapsulating PS in nanoparticles can enhance delivery, but selectivity to target bacteria without harming host cells is crucial for successful clinical use.

Responsive nanoparticles for anti-bacterial hyperthermia treatment

New antimicrobial treatments involve using external energy sources to activate energy-absorbing nanoparticles and cause irreversible thermal damage to bacterial cells. When nanoparticles are exposed to near-infrared (NIR) light or high-frequency alternating magnetic fields (AMF), they quickly convert this energy into heat, raising the temperature on their surface. With effective targeting, this nanoparticle-based hyperthermia offers a non-invasive, tissue-specific method for precisely localized heating to eliminate pathogens [9].

NIR light-triggered hyperthermia

Nanoparticles made of materials like gold, iron oxide, and graphene respond to near-infrared (NIR) light, and they have been explored as photothermal agents to kill bacteria. These nanoparticles can raise temperatures when exposed to NIR light and effectively inhibit bacterial growth. However, their potential to harm host cells due to off-target thermal effects requires careful targeting. Combining photothermal therapy with other antimicrobial approaches, such as controlled antibiotic release, can enhance pathogen eradication and reduce the risk of non-specific damage to host cells. A recent study combined NIR light-triggered hyperthermia with antibiotic delivery using hybrid microspheres, resulting in a synergistic effect for eradicating bacteria in wound abscesses.

AMF-triggered hyperthermia

Recent developments in using magnetic nanoparticles (MNPs) with high heating efficiency have advanced the potential of hyperthermia treatment against pathogens. This approach involves MNPs combined with a high-frequency alternating magnetic field (AMF) to generate localized heat effectively. While this technology has been extensively explored for cancer treatment, its application in antimicrobial therapy has received less attention. Studies have demonstrated that magnetic fluid hyperthermia can successfully destroy bacteria, including biofilms, in vitro and in vivo. This method was effective in disrupting Staphylococcus aureus biofilms, with the extent of inactivation depending on MNP concentration and AMF parameters. In a mouse model of S. aureus cutaneous wound infection, MNP hyperthermia enhanced bacterial inactivation, particularly when anti-S. aureus antibody-conjugated MNPs were used.

The strategy for magnetic nanoparticle (MNP) hyperthermia involves targeted heating of pathogen cells in a wound to eradicate infections. While this method can rapidly increase temperature at the MNP surface, it carries the risk of overheating and tissue damage. Safe application requires precise customization of MNP and alternating magnetic field (AMF) parameters.

Nanoparticles for efficient penetration to the biofilm matrix

Overcoming the hindrance posed by the extracellular polymeric substance (EPS) matrix within biofilms to the diffusion of antibiotics and therapeutic drugs is crucial for effective anti-biofilm strategies. Nanoparticles can penetrate biofilms via diffusion, and their size and surface chemistry play a significant role in this process. Smaller nanoparticles with the same surface chemistry tend to be more efficient in penetrating biofilms. For instance, smaller NO-releasing silica nanoparticles demonstrated higher efficacy against *P. aeruginosa* and *S. aureus* biofilms, associated with increased penetration depth. Additionally, designing nanoparticles to target the EPS matrix can synergize with various anti-biofilm approaches, such as combining silver nanoparticles with biofilm-dispersing enzymes to inhibit biofilm-embedded pathogens [10].

FUTURE PERSPECTIVES

Chronic wound infections associated with biofilms pose a persistent challenge despite advances in antimicrobial treatments. Nanoparticles with unique physical and chemical properties offer a promising alternative to conventional antibiotics. However, several crucial issues must be addressed for successful clinical application. Chronic wound infections often involve polymicrobial biofilms, demanding strategies to target multiple bacterial species. Evaluating how nanoparticles interact with biofilms and their ability to penetrate these structures is essential. Concerns about the health impact of engineered nanoparticles and their interactions with host cells, especially phagocytes, need careful consideration. While challenges remain, ongoing research in nanoparticle-based therapeutics may provide a vital tool for treating antibiotic-resistant chronic wound infections, offering a novel approach to patient care.

CONCLUSION

Biomaterials have made strides in aiding wound healing with approved products such as films, foams, hydrogels, and hemostatics. Conversely, there's currently no approval for biomaterials that release bioactive components influencing the wound healing process directly. However, nanoparticle therapies have shown promise in animal models. Wound healing is a substantial economic and social burden, necessitating a multifaceted approach due to the variation in symptoms among patients. Challenges

include pain, inflammation, infection from resistant bacteria, delayed healing, and the associated healthcare costs. The surge in multidrug-resistant bacteria is a global concern. Emerging therapies utilizing biomaterials or nanoparticles to target multiple aspects offer hope for advancing wound care in the face of these challenges.

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