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Nanotechnology and Drug Delivery Systems in Wound Healing and Scar Reduction

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Abstract

Nanotechnology has emerged as a revolutionary approach in wound healing and scar reduction, offering precise, targeted, and efficient drug delivery systems. This review highlights recent advances in nanotechnology-based solutions, including nanoparticles, nanofibers, hydrogels, and nanoemulsions that address limitations of conventional therapies. These innovations enhance antimicrobial activity, promote angiogenesis, modulate inflammation, and deliver therapeutic agents with remarkable precision. The integration of nanotechnology with scar-reducing agents has transformative potential for collagen remodeling and fibrosis inhibition, improving both functional and esthetic outcomes. Furthermore, smart nanomaterials with biosensing capabilities enable real-time wound monitoring and dynamic treatment adjustments. While these advances are promising, challenges related to biocompatibility, cytotoxicity, and regulatory approval remain critical to address.

This review emphasizes the profound impact of nanotechnology in revolutionizing wound care and provides insights into future directions, including personalized therapies and artificial intelligence-integrated systems for optimized outcomes.

Keywords: nanotechnology, drug delivery systems, wound healing, scar reduction, regenerative medicine

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Нанотехнологии и системы доставки лекарственных средств для заживления ран и уменьшения рубцов

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Резюме

Нанотехнологии – инновационный подход в заживлении ран и уменьшении рубцов, предлагающий системы точной, адресной и эффективной доставки лекарств. В данном обзоре освещаются последние достижения в области нанотехнологий (наночастицы, нановолокна, гидрогели и наноэмульсии), имеющие превосходство над традиционными методами лечения. Данные инновационные разработки повышают антимикробную активность, способствуют ангиогенезу, модулируют воспаление и с прецизионной точностью доставляют терапевтические агенты. Интеграция нанотехнологий с препаратами для уменьшения рубцов открывает революционные возможности для ремоделирования коллагена и подавления фиброза, улучшая как функциональные, так и эстетические результаты лечения. Кроме того, «умные» наноматериалы с биосенсорами позволяют в режиме реального времени отслеживать состояние раны и корректировать лечение. Несмотря на многообещающие результаты, остаются нерешенными вопросы, связанные с биосовместимостью, цитотоксичностью и одобрением регулирующих органов.

В данном обзоре подчеркивается огромное влияние нанотехнологий на прогресс в лечении ран и дается представление о направлениях дальнейших исследований, а именно о персонализированной медицине и системах, интегрированных с искусственным интеллектом, для оптимизации результатов лечения.

Ключевые слова: нанотехнологии, системы доставки лекарств, заживление ран, уменьшение рубцов, регенеративная медицина

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Introduction

Wound healing is a complex physiological process involving a series of coordinated events, including hemostasis, inflammation, proliferation, and remodeling. After tissue injury, the body initiates hemostasis to prevent blood loss, followed by an inflammatory response to combat potential infections.[1] The proliferative phase involves tissue formation and angiogenesis, leading to wound closure. Finally, during the remodeling phase, collagen fibers are reorganized to strengthen the newly formed tissue. However, this process can sometimes result in excessive scar formation, such as hypertrophic scars or keloids, which can impair function and esthetics.[2]

Traditional drug delivery systems in wound management, such as topical creams and systemic medications, often face limitations. These methods may provide inadequate drug concentrations at the wound site, leading to suboptimal therapeutic effects.[3] Additionally, systemic administration can result in off-target effects and increased risk of adverse reactions. Skin's barrier properties further complicate effective drug penetration, making it challenging to achieve desired therapeutic outcomes.[4]

Nanotechnology has emerged as a transformative tool in addressing these challenges in wound healing and scar reduction. Nanoengineering enables to design drug delivery systems that penetrate the skin barrier easier, provide controlled and sustained drug release, and target specific cellular components involved in wound healing.[5] For instance, nanoparticles (NPs) can be engineered to deliver antifibrotic agents directly to fibroblasts, thereby modulating collagen production and reducing scar formation. Recent studies demonstrated the potential of nanomaterials in improving transdermal drug delivery and preventing pathological scar formation.[6] These advancements suggest that nanotechnology-based approaches could overcome the limitations of traditional therapies and offer more effective solutions for wound management.

Methods

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure comprehensive and unbiased reporting.

Search Strategy

A structured search was performed in the databases PubMed, Scopus, Web of Science, and Google Scholar to identify relevant articles on nanotechnology and drug delivery systems in wound healing and scar reduction. The following keywords and Boolean operators were used: ("Nanotechnology" OR "Nanoparticles") AND ("Drug delivery systems") AND ("Wound healing" OR "Scar reduction") AND ("Regenerative medicine"). Additional manual searches were conducted in the reference lists of key articles to identify any overlooked studies.

Eligibility Criteria

To be included in the review, studies must be

- published in peer-reviewed journals between 2000 and 2025
- written in English
- focused on the application of nanotechnology and drug delivery systems for wound healing and/or scar reduction
- based on experimental or clinical data on the efficacy, biocompatibility, or challenges of nanotechnology-based interventions.

Studies with insufficient data, conference abstracts, or papers unrelated to wound care were excluded.

Study Selection

A total of 132 studies were retrieved. After duplicate removal using EndNote (Clarivate Plc, UK), 111 studies remained. The titles and abstracts were screened, resulting in exclusion of 91 articles that did not meet the eligibility criteria. The full texts of the remaining 64 studies were assessed and finally included in the review.

Data Extraction

Data were extracted using a predefined template with the following variables: study objectives, intervention type, nanotechnology application, outcomes, and limitations and independently verified by 2 reviewers to ensure accuracy and consistency.

Quality Assessment

The Joanna Briggs Institute critical appraisal checklists for experimental and observational studies were used to assess the quality of the included studies. The studies scoring less than 50% were excluded to ensure the reliability of the findings.

Data Synthesis

The findings from the selected studies were synthesized thematically, focusing on the types of nanotechnology-based drug delivery systems, their mechanisms of action, therapeutic benefits, and limitations. The quantitative data were summarized in tables (if applicable) and analyzed to identify recurring themes and trends.

The PRISMA flow diagram (Figure) gives a transparent overview of the study selection process, detailing the number of records identified, screened, and included, along with the reasons for exclusion at each stage.

Discussion

NPs in Wound Healing

NPs have garnered significant attention in wound healing for their unique physicochemical properties, enabling their interaction with biological systems at the molecular level. Various NPs made from silver, gold, zinc oxide, and polymers have been explored for their therapeutic potential in enhancing wound repair processes.[7]

Silver NPs (AgNPs) are among the most extensively studied for wound care applications. Their broad-spectrum antimicrobial activity is well-documented, with

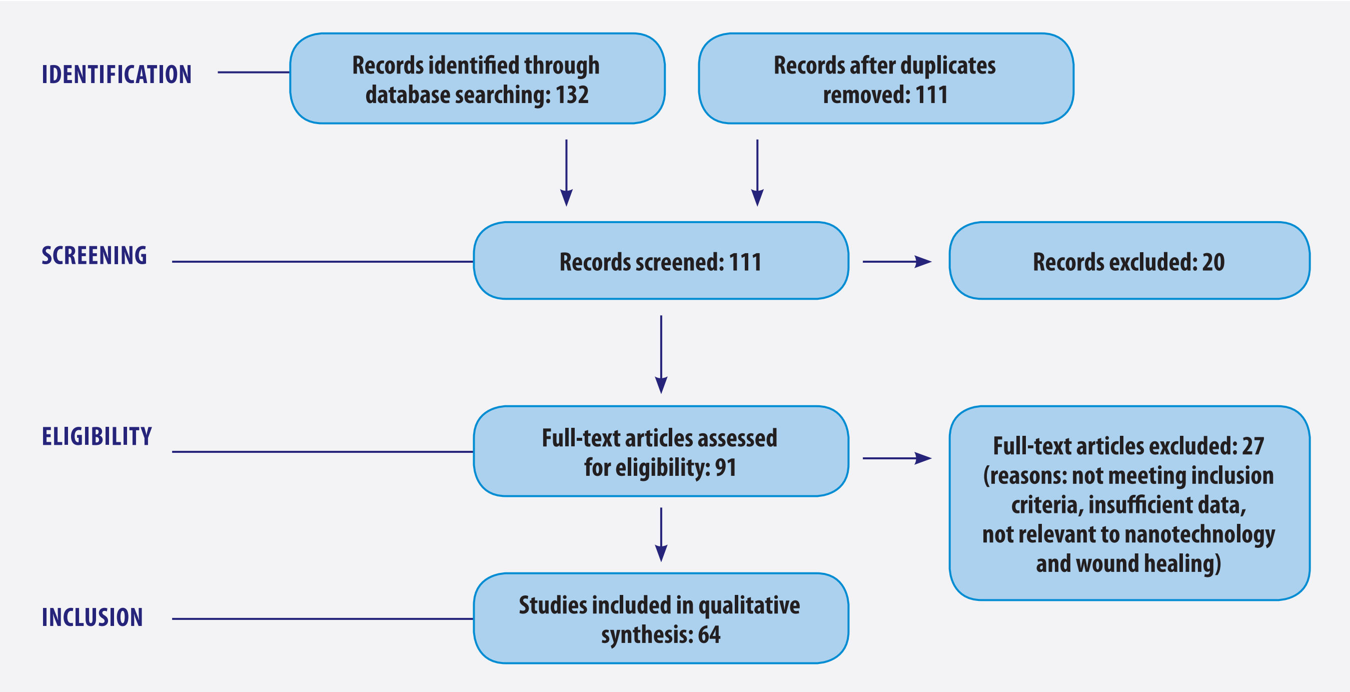

Figure. PRIMSA flow diagram
Рисунок. Блок-схема PRISMA

mechanisms involving the bacterial cell membrane disruption, generation of reactive oxygen species, and interference with microbial DNA replication.[8] AgNPs have been shown to promote keratinocyte proliferation, thereby facilitating reepithelialization and reducing scar formation. Clinical applications include their incorporation into wound dressings, which demonstrated efficacy in inhibiting bacterial colonization and accelerating healing of burn wounds and diabetic foot ulcers.[9] However, concerns over their potential cytotoxicity and development of bacterial resistance to AgNPs require careful consideration of their clinical use.

Gold NPs (AuNPs) have also been investigated for their role in wound healing. At low concentrations, AuNPs promote keratinocyte growth and exhibit antimicrobial properties, which are beneficial in preventing wound infections.[10] Additionally, AuNPs have been found to possess anti-inflammatory and antioxidant properties, contributing to an improved wound healing environment. Their ability to modulate cellular responses and promote tissue regeneration makes them promising candidates for therapeutic interventions.[11]

Zinc oxide NPs (ZnO NPs) are recognized for their potent antimicrobial activity and their role in promoting angiogenesis and reepithelialization. ZnO NPs generate reactive oxygen species, which exhibit bactericidal effects, and have been incorporated into hydrogel-based dressings to enhance wound healing outcomes.[12] These NPs not only prevent infection but also support angiogenesis and tissue regeneration, which are critical for effective wound repair.

Polymeric NPs, such as those made from poly(lactic-co-glycolic acid) (PLGA), have been utilized as carriers for various therapeutic agents in wound healing. Growth factors, antimicrobial peptides, and other bioactive molecules can be encapsulated in PLGA NPs, providing controlled and sustained drug release at the wound site.[13] This targeted delivery system enhances the local therapeutic effect while minimizing systemic side effects. Studies have shown that PLGA NPs can promote granulation tissue formation, angiogenesis, and collagen deposition, leading to improved wound healing outcomes.[14]

Nanotechnology-Enhanced Drug Delivery Systems

Nanotechnology has significantly advanced drug delivery systems in wound healing, offering innovative platforms, such as nanoemulsions, nanofibers, hydrogels, and nanocapsules. These systems enhance the controlled and targeted drug release, addressing limitations of traditional treatments.[15]

Nanoemulsions are fine oil-in-water or water-in-oil dispersions stabilized by surfactants, with droplet sizes typically ranging from 20 to 200 nm. Their small size allows for enhanced skin penetration, making them effective carriers for hydrophobic drugs.[16] In wound care, nanoemulsions have been utilized to deliver antimicrobial agents directly to the wound site, reducing bacterial load and promoting healing. For instance, a study demonstrated that a nanoemulsion-based delivery system effectively transported the antimicrobial peptide LL-37 into biofilms, resulting in significant bacterial reduction.[17]

Electrospun nanofibers create a fibrous mat that mimics the extracellular matrix, providing a conducive environment for cell attachment and proliferation. These structures can be loaded with various therapeutic agents, including growth factors and antibiotics, allowing for sustained and localized drug release.[18] Electrospun nanofibers loaded with basic fibroblast growth factors (bFGF) have been shown to significantly enhance skin regeneration in diabetic rats, indicating their potential in chronic wound management.[19]

Hydrogels are 3-dimensional, hydrophilic polymer networks capable of absorbing substantial amounts of water. Their biocompatibility and tunability make them suitable for wound healing applications. Incorporation of NPs into hydrogels can create composite systems that offer both structural support and controlled drug delivery.[20] For example, an AgNP-embedded hydrogel scaffold exhibited enhanced antimicrobial activity and promoted wound healing in a rat model.[21]

Nanocapsules are vesicular systems with drugs confined within their cavities and surrounded by polymeric membranes. This structure protects encapsulated agents and provides controlled release.[22] In wound healing, nanocapsules have been explored for delivering anti-inflammatory agents to favorably modulate the wound environment. Curcumin-loaded nanocapsules were reported to effectively reduce inflammation and accelerate healing in a mouse model of cutaneous wounds.[23]

The benefits of these nanotechnology-enhanced drug delivery systems are multifaceted. Controlled and targeted drug release ensures that therapeutic agents are delivered at optimal concentrations directly to the wound site, minimizing systemic exposure and potential side effects.[24] This targeted approach enhances the therapeutic efficacy, particularly in managing infections and modulating inflammation. Furthermore, the sustained release profiles of these systems reduce the frequency of dressing changes, thereby decreasing discomfort and the risk of secondary infections.[25]

Various therapeutic agents have been effectively delivered using nanotechnology-based systems in wound care. Growth factors, such as bFGF and vascular endothelial growth factor, have been incorporated into nanofibers and hydrogels to promote angiogenesis and tissue regeneration.[26] Antibiotics, such as ciprofloxacin and gentamicin, have been loaded into nanoemulsions and nanocapsules to combat wound infections effectively. Anti-inflammatory agents, including curcumin and dexamethasone, have been delivered via nanocarriers to modulate the inflammatory response, which is crucial for optimal healing.[27]

Applications in Scar Reduction

Nanotechnology is a promising option for scar reduction as it facilitates collagen remodeling and inhibits fibrosis. The application of nanomaterials can modulate wound healing, leading to improved esthetic and functional outcomes.[28]

One significant application of nanotechnology in scar management involves the delivery of therapeutic agents that modulate collagen synthesis and deposition. For instance, retinoids, known for their ability to regulate epithelial cell growth and collagen production, have been effectively delivered using lipid-based nanocarriers.[29] Semisolid formulations enriched with retinol-loaded lipid NPs were shown to enhance skin penetration and reduce adverse effects commonly associated with retinoid therapy, thereby improving scar appearance.[30]

Silicone-based treatments are widely recognized for their efficacy in scar management, primarily due to their occlusive properties, leading to stratum corneum hydration and fibroblast activity modulation. The integration of silicone into nanostructured systems has been explored to enhance its therapeutic effects.[31] For example, silicone-based nanofibers have been developed to provide a breathable barrier that maintains optimal hydration levels, which helps regulate collagen production and flatten scars.[32]

Enzymatic therapies targeting excessive collagen deposition have also benefited from nanotechnology. Collagenase, an enzyme that breaks down collagen, has been encapsulated within polymeric nanocapsules for controlled and sustained release.[33] Such approach ensures a localized effect, reducing the risk of systemic side effects and enhancing the aberrant collagen degradation in fibrotic scars. Collagenase-loaded nanocapsules were found to effectively decrease collagen accumulation in fibrotic tissues, showing their potential to reduce scars.[34]

Beyond drug delivery, nanotechnology contributes to improved esthetic and functional outcomes in healed wounds. Nanomaterials can be engineered to create scaffolds that mimic the extracellular matrix, providing structural support and promoting organized tissue regeneration.[35] These scaffolds facilitate uniform collagen deposition and reduce the formation of disorganized fibrotic tissue, leading to less noticeable and more flexible scars. Additionally, the controlled release of anti-inflammatory agents from nanocarriers can modulate the wound environment, preventing excessive inflammation that often leads to hypertrophic scarring.[36]

Nanotechnology and Biocompatibility

Nanotechnology integration into wound care presents significant opportunities for enhancing healing processes and outcomes. However, developing biocompatible nanomaterials suitable for clinical applications poses several challenges, particularly concerning cytotoxicity and overall safety.[37]

Potential cytotoxic effects are a primary concern. Certain NPs, such as AgNPs, are renowned for their antimicrobial properties but can exhibit cytotoxicity toward human cells.[38] One of the strategies to mitigate these adverse effects is to coat AgNPs with biomolecules and incorporate them into hydrogel-based wound dressings. These approaches aim to enhance antibacterial efficacy while minimizing cytotoxicity, thereby improving biosafety and treatment outcomes.[39]

Another challenge is the potential of nanomaterials to induce oxidative stress, leading to cellular damage. For instance, although effective as antibacterial agents, copper-based NPs have faced challenges due to their toxicity to cells and tissues.[40] To address this, researchers have explored biocompatible and biodegradable nanomaterials, such as cerium oxide NPs (CeO_2 NPs), with antioxidant properties. Encapsulating CeO_2 NPs in biocompatible polymers has been shown to reduce cytotoxicity and improve cell survival, offering a promising strategy for enhancing wound healing.[41]

The size, shape, and surface charge of NPs also significantly affect their biocompatibility. Optimizing these parameters is crucial to minimize adverse interactions with biological systems: eg, modifying the surface properties of NPs can reduce protein adsorption and prevent unintended immune responses.[42] Also, utilizing natural polymers, such as chitosan and silk fibroin, in nanomaterial fabrication can enhance biocompatibility. Such materials not only support cell proliferation and tissue regeneration but also exhibit inherent antimicrobial properties, making them suitable for wound healing applications.[43]

Incorporating nanomaterials into existing wound dressing materials, such as cotton bandages, has also been explored to enhance their functionality. For instance, decorating commercial cotton bandages with nanomaterials that have drug-releasing and antibacterial properties can minimize local pain and postdressing infections at a wound site. This approach offers a practical solution to improve wound care by enhancing the properties of widely used dressing materials.[9,44]

Smart Nanomaterials for Wound Monitoring

The integration of smart nanomaterials into wound care has significantly advanced wound healing monitoring and management. These innovative materials enable real-time detection of critical parameters, such as infection, pH levels, and moisture content, facilitating dynamic treatment adjustments and improving patient outcomes.[45]

One of the primary applications of nanotechnology in wound monitoring is the development of intelligent dressings capable of early infection detection. Traditional methods often fail to provide timely information, delaying treatment and potentially exacerbating wound conditions. To address this, researchers designed soft intelligent dressings with pH and temperature sensors.[46] For instance, Zhang et al (2022)[47] developed a flexible wound infection monitoring system using a polyaniline-based pH sensor and a commercial temperature sensor integrated onto a styrene-ethylene-butylene-styrene elastomer film. This system demonstrated a pH measurement range of 4-10 with a response time of less than 6 seconds and accurately monitored temperature changes between 30 and 40 °C. In vitro tests and a rat model of *Staphylococcus aureus* infection confirmed the system's ability to detect early-stage infection by monitoring pH and temperature variations.

Furthermore, smart nanomaterials have been utilized to monitor wound pH levels, indicative of the healing process. Normal skin maintains an acidic pH between 4 and 6; however, upon wounding, the pH becomes neutral or slightly alkaline. Increased pH can signal bacterial colonization and infection.[48] To exploit this, Qiao et al (2020)[49] developed a smart hydrogel-based wound dressing capable of monitoring bacterial infection via a pH-responsive fluorescence resonance energy transfer (FRET) system. The hydrogel, composed of polyvinyl alcohol and an ultraviolet-cleavable polyprodrug, was loaded with silica NPs modified with fluorescent dyes. Changes in the pH induced a FRET transition visually indicating the presence of bacterial infection. Furthermore, the hydrogel facilitated near-infrared light-triggered antibiotic release, offering on-demand treatment.

Moisture management is another critical aspect of wound care, as maintaining an optimal moisture level promotes healing and prevents desiccation or maceration. Smart nanotechnology-based dressings have been designed to monitor and regulate moisture levels in real time.[50] Such dressings often employ hydrogel matrices embedded with nanosensors that can detect changes in moisture content and respond accordingly. For example, certain hydrogels can swell or contract in response to moisture variations, providing both a protective barrier and a means to signal the need for dressing changes or an additional intervention.[51]

The real-time data collection enabled by these smart nanomaterials allows for dynamic treatment adjustments. Continuous monitoring of wound parameters ensures that any deviations from the normal healing trajectory are promptly identified, and appropriate therapeutic measures can be promptly implemented. This proactive approach minimizes complications, reduces healing times, and improves overall patient care.[29]

Despite these advances, widespread clinical adoption of smart nanomaterial-based wound monitoring systems remains a challenge: biocompatibility, production scalability, and eco-friendliness are critical factors to be addressed. Moreover, integrating these systems into existing medical infrastructure and ensuring data security and privacy are essential considerations for future development.[52]

Regulatory and Ethical Considerations

The integration of nanotechnology into wound care introduces complex regulatory and ethical considerations that must be meticulously addressed to ensure patient safety and public trust. The US Food and Drug Administration (FDA) regulates nanotechnology products under existing statutory frameworks, evaluating them based on their intended use and specific attributes.[53] The FDA emphasizes that nanotechnology products can exhibit unique properties, necessitating thorough safety and efficacy assessments. Consequently, selection of a regulatory pathway for a nanotechnology-based wound care product depends on its classification as a drug, device, biological product, or combination product and must adhere to the pertinent regulatory requirements.[54]

The approval of medical devices, including those incorporating nanotechnology, typically involves several stages: product design and development, preclinical testing, clinical evaluation, and regulatory submission. This process takes an average of 18 to 24 months, with approximately 12 to 18 months for product design and development followed by additional 3 to 6 months for regulatory approval.[55]

Ethical considerations are paramount in nanotechnology deployment in wound care. Key ethical principles include nonmaleficence (doing no harm), autonomy (respecting patient self-determination), justice (fair distribution of risks and benefits), and privacy (protection of personal health information).[56] Ensuring informed consent, particularly concerning novel aspects of nanotechnology, is crucial. Patients must be adequately informed about potential risks and benefits associated with nanotechnology-based treatments to make autonomous decisions regarding their care.[57]

Nanomaterial-specific safety concerns arise from unique physicochemical properties, which may lead to unforeseen interactions within biological systems. Potential risks include cytotoxicity, unforeseen immune responses, and long-term environmental impacts. Comprehensive preclinical studies are essential to assess these risks, and continuous postmarket surveillance is necessary to monitor adverse events and ensure ongoing safety.[58]

Environmental considerations also play a significant role in the ethical discourse surrounding nanotechnology. The life cycle of nanomaterials from production to disposal must be managed to prevent environmental contamination and associated health risks. Implementing sustainable manufacturing practices and establishing guidelines for safe disposal of nanomaterials are critical steps in mitigating environmental impacts.[53]

Future Perspectives

Nanotechnology is at the forefront of transformative advances in regenerative medicine, offering innovative solutions for tissue repair and wound healing. Recent developments have showcased various applications of nanomaterials, including diagnostics, disease treatment, and gene therapy. In wound care, nanotechnology has been utilized to develop targeted drug delivery systems and antimicrobial dressings, enhancing treatment efficacy and reducing healing times.[59]

A significant breakthrough in regenerative medicine involves the use of iron nanowires that respond to magnetic fields. Researchers at the King Abdullah University of Science and Technology (Thuwal, Saudi Arabia) developed a nanotechnology platform for culturing bone-forming stem cells on a mesh of these nanowires. The application of a low-frequency magnetic field causes the nanowires to bend, providing mechanical stimulation to the cells and accelerating osteogenic differentiation. Thus, efficient bone formation is achieved in a matter of days compared with weeks in conventional settings.[60] This innovation holds promise for treating degenerative bone diseases and enhancing tissue regeneration.

The emergence of personalized medicine has further propelled the application of nanotechnology in wound care. By tailoring treatments to individual patient needs, personalized approaches aim to optimize therapeutic outcomes.[61] Nanotechnology facilitates this by enabling the development of customized wound care solutions, such as patient-specific drug delivery systems and scaffolds that promote tissue regeneration. These innovations allow for more precise interventions, improving the healing process and reducing the risk of complications.[62]

The integration of artificial intelligence (AI) and machine learning with nanotechnology is an emerging trend that holds significant promise for optimizing wound care. AI and machine learning algorithms can analyze complex medical data to identify patterns and predict wound healing trajectories, thereby informing treatment decisions.[63] For instance, AI has been applied to wound assessment, enabling the prediction of healing outcomes and the customization of treatment plans. Additionally, AI can assist in the design of nanomaterials by predicting their interactions with biological systems, resulting in safer and more effective therapeutic agents.[64]

Conclusions

Nanotechnology has emerged as a transformative force in wound healing and scar reduction, offering innovative solutions through NPs, enhanced drug delivery systems, and smart nanomaterials. This review highlights significant advances, including the development of biocompatible nanomaterials, targeted therapies, and real-time wound monitoring technologies. These innovations have improved therapeutic outcomes by addressing limitations of traditional approaches and enabling personalized care. However, challenges, such as regulatory complexities, potential cytotoxicity, and ethical considerations, remain significant hurdles. Future opportunities lie in integrating nanotechnology with AI, machine learning, and personalized medicine, which promise to revolutionize wound care and unlock new frontiers in regenerative medicine. Continued interdisciplinary research and collaboration are crucial to overcome existing challenges and realize the full potential of nanotechnology in improving patient outcomes.

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Конфликт интересов

Автор заявляет об отсутствии конфликта интересов.