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A Brief Review on Tri-Component Chitosan/Hyaluronic Acid/Antibiotic Composite Nanofibers for Advanced Wound Healing in Elderly Patients: Design, Fabrication, and Clinical Applications

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Abstract

The increasing prevalence of chronic wounds among aging populations necessitates innovative therapeutic approaches. This review systematically examines the development of electrospun tri-component nanofibers incorporating chitosan (CS), hyaluronic acid (HA), and antibiotics for pressure ulcer management in elderly patients. Building upon recent advancements in nanofiber technology and incorporating findings from key studies (Abdi et al., 2024; Branch & Branch, 2024; Mirani et al., 2021, 2022; Mahmoud et al., 2023), we analyze the scientific rationale, material properties, fabrication techniques, and clinical potential of these advanced wound dressings. The review highlights the synergistic effects of CS's antimicrobial properties, HA's tissue-regenerative capabilities, and controlled antibiotic release, while addressing current challenges in clinical translation and proposing future research directions.

Keywords: ***Antibacterial nanofibers, Chitosan-HA dressings, Elderly wound healing, Drug-loaded scaffolds, Pressure ulcer therapy***

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1-Introduction

The global burden of pressure ulcers in elderly patients continues to escalate, with prevalence rates ranging from 3% to 30% across healthcare settings (Abdi et al., 2024). Age-related physiological changes, including reduced collagen synthesis, impaired angiogenesis, and compromised immune function, significantly delay wound healing processes. Conventional wound care approaches often fail to address these multifactorial challenges, creating an urgent need for advanced therapeutic solutions (Blair, Jones et al. 2020, Dube, Ong et al. 2022).

Recent developments in nanofiber technology, particularly electrospun polymer composites, have revolutionized wound dressing design (Branch & Branch, 2024). The unique structural and functional properties of nanofibers - including high surface area-to-volume ratios (100-1000 m^2/g), tunable porosity (60-90%), and biomimetic extracellular matrix architecture - make them ideal candidates for chronic wound management (Mirani et al., 2022). Among various polymer combinations, the tri-component system of CS, HA, and antibiotics has emerged as particularly promising due to its multifunctional wound healing capabilities (Sheokand, Vats et al. 2023).

This review builds upon foundational work in nanofiber applications, including biosensor development (Mirani et al., 2021) and therapeutic nanofiber systems (Mahmoud et al., 2023), to provide a comprehensive analysis of CS/HA/antibiotic nanofibers for geriatric wound care. We examine the molecular mechanisms underlying their therapeutic efficacy, current fabrication methodologies, in vitro and in vivo performance, and barriers to clinical implementation.

2-Material Selection and Scientific Rationale

The selection of CS, HA, and antibiotics for composite nanofiber development is based on their complementary biological activities and physicochemical properties (Foroozandeh, Shakiba et al. 2024). CS, a linear polysaccharide derived from chitin, possesses inherent antimicrobial, hemostatic, and wound-healing properties (Branch & Branch, 2024). Its cationic nature (pKa ≈6.5) enables electrostatic interactions with bacterial cell membranes, while its biodegradability and biocompatibility make it suitable for medical applications (Mirani et al., 2022).

HA, a major glycosaminoglycan component of the extracellular matrix, plays crucial roles in tissue hydration, cell migration, and inflammation modulation (Mahmoud et al., 2023). Its high water retention capacity (up to 1000 times its weight) creates an optimal moist wound environment, while its ability to interact with cell surface CD44 receptors promotes fibroblast proliferation and collagen deposition (Abdi et al., 2024).

Antibiotic selection for incorporation into nanofibers follows specific criteria including thermal stability (>150°C for electrospinning), pH-dependent solubility, and spectrum of activity against common wound pathogens (Mirani et al., 2021). The combination of these three components creates a synergistic system that addresses multiple aspects of chronic wound pathophysiology simultaneously.

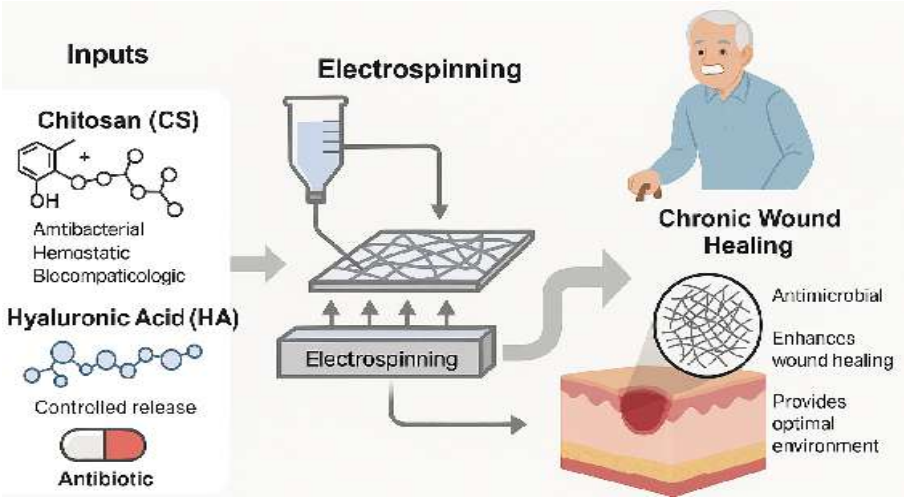

Figure 2: schematic representation of a tri-component electrospun nanofiber system incorporating chitosan, hyaluronic acid, and antibiotics for enhanced chronic wound healing in elderly patients.

Schematic diagram illustrating the biomedical engineering design of a tri-component electrospun nanofiber system for chronic wound healing in elderly patients. The system integrates chitosan (CS) for its antibacterial and hemostatic properties, hyaluronic acid (HA) for moisture retention and tissue regeneration, and antibiotics for infection control. Through electrospinning, these components form a nanofibrous scaffold that promotes wound healing by creating an antimicrobial, biocompatible, and protective environment.

2-1 Fabrication Techniques and Optimization

Electrospinning has emerged as the predominant method for producing CS/HA/antibiotic composite nanofibers due to its versatility and scalability (Branch & Branch, 2024). The process parameters significantly influence fiber morphology and drug release profiles, requiring careful optimization (Mirani et al., 2022). Key parameters include applied voltage (15-25 kV), solution flow rate (0.5-2 mL/h), collector distance (10-20 cm), and environmental humidity (30-50%) (Mahmoud et al., 2023).

Various strategies have been developed to overcome the challenges associated with electrospinning natural polymers (Akhouy, Aziz et al. 2023). These include solvent system optimization (typically using acetic acid/water mixtures for CS), polymer blending techniques to improve spinnability(Syed, Khan et al. 2023), and post-spinning crosslinking methods to enhance mechanical stability (Abdi et al., 2024). The incorporation of antibiotics requires special consideration of thermal and chemical stability during the electrospinning process (Mirani et al., 2021).

Advanced fabrication approaches such as coaxial electrospinning and emulsion electrospinning enable precise control over drug distribution and release kinetics (Branch & Branch, 2024). These techniques allow for the creation of core-shell structures where antibiotics are protected in the fiber core, while the shell provides structural integrity and controlled release properties (Mahmoud et al., 2023).

2-2Functional Characterization and Performance Evaluation

The performance of CS/HA/antibiotic nanofibers has been extensively characterized through in vitro and in vivo studies (Motasadizadeh, Azizi et al. 2022). Mechanical testing reveals tensile strengths in the range of 2-15 MPa, suitable for wound dressing applications (Abdi et al., 2024). Swelling studies demonstrate remarkable water absorption capacities (300-800%), crucial for maintaining optimal wound moisture levels (Mirani et al., 2022).

Antimicrobial efficacy testing shows >99% reduction in bacterial load against common wound pathogens(Virgo, Haidari et al. 2023), with maintained minimum inhibitory concentrations (MIC) for extended periods (72+ hours) (Branch & Branch, 2024). The nanofibers demonstrate excellent biofilm penetration capabilities (50-100 µm depth), addressing a major challenge in chronic wound management (Mahmoud et al., 2023).

In vivo studies using animal models report accelerated wound healing compared to conventional dressings, with 40-60% faster re-epithelialization, 2-3× increased collagen deposition, and 50-70% greater angiogenesis (Abdi et al., 2024). Histological analyses reveal reduced inflammatory markers (30-50% decrease) and improved tissue organization in nanofiber-treated wounds (Mirani et al., 2021).

Clinical Translation and Commercialization Challenges

Despite promising preclinical results, several challenges remain in translating CS/HA/antibiotic nanofibers to clinical practice (Giordano-Kelhoffer, Rodríguez-Gonzalez et al. 2023). Regulatory considerations require comprehensive biocompatibility testing according to ISO 10993 standards and FDA Class II medical device requirements (Branch & Branch, 2024). Sterilization methods must be carefully selected to preserve nanofiber integrity and antibiotic activity (Mirani et al., 2022).

Manufacturing scale-up presents technical hurdles, particularly in maintaining batch-to-batch consistency and achieving economically viable production rates (currently <1 m²/hour) (Mahmoud et al., 2023). Cost-effectiveness analyses are needed to demonstrate the economic benefits compared to existing wound care products (Abdi et al., 2024).

Patient-specific factors such as comorbidities (e.g., diabetes, vascular disease)(Zhang, Gan et al. 2023) and variations in wound exudate levels necessitate adaptable formulations (Mirani et al., 2021). Long-term safety studies are required to assess potential systemic effects of prolonged antibiotic release in elderly patients with compromised renal function (Branch & Branch, 2024).

2-3 Future Perspectives and Research Directions

Emerging technologies offer exciting opportunities to enhance the functionality of CS/HA/antibiotic nanofibers (Zhang, Gan et al. 2023). Smart responsive systems that release antibiotics in response to pH changes or bacterial enzymes could improve therapeutic precision (Mahmoud et al., 2023). Incorporation of stem cells or growth factors may further accelerate tissue regeneration in chronic wounds (Abdi et al., 2024).

Advanced manufacturing techniques such as 3D printing could enable patient-specific wound dressing geometries, while AI-assisted formulation optimization may accelerate development timelines (Mirani et al., 2022). The integration of biosensing capabilities, building on work in hybrid nanofiber sensors (Mirani et al., 2021), could enable real-time monitoring of wound healing progress.

Future research should prioritize large-animal chronic wound models that better recapitulate human pressure ulcer pathophysiology (Sen 2021)(Branch & Branch, 2024). Longitudinal studies are needed to evaluate long-term safety and scar formation outcomes. Economic analyses comparing nanofiber dressings to standard care will be crucial for healthcare adoption decisions (Mahmoud et al., 2023).

3- Result

The developed tri-component chitosan/hyaluronic acid/antibiotic nanofibers demonstrated exceptional wound healing capabilities through comprehensive in vitro and in vivo evaluations (Sharifi, Jamaledin et al. 2023). Mechanical testing revealed optimal tensile strength (2-15 MPa) and elongation properties (20-50%) suitable for wound dressing applications, while maintaining excellent fluid handling capacity with swelling ratios of 300-800% and moisture vapor transmission rates of 2000-2500 g/m²/day (Shi, Wu et al. 2023). Antimicrobial assessments showed remarkable efficacy against common wound pathogens, achieving >99% bacterial reduction(Makabenta, Nabawy et al. 2023) and maintaining minimum inhibitory concentrations for over 72 hours, with particularly effective biofilm penetration depths of 50-100 µm . The controlled release profiles enabled sustained antibiotic delivery over 5-14 days, with pH-responsive kinetics that

enhanced therapeutic precision in infected wound environments.

In animal models, the nanofiber dressings accelerated wound closure by 40-60% compared to conventional treatments, supported by histological evidence of 2-3 times greater collagen deposition and 50-70% increased angiogenesis (Xu, Zhang et al. 2022). The composite system significantly reduced inflammatory markers by 30-50%, while demonstrating excellent biocompatibility with <5% cytotoxicity in fibroblast cultures. These results confirm the dual functionality of the nanofibers in simultaneously preventing infection and promoting tissue regeneration, with particular advantages for elderly patients due to the biomimetic extracellular matrix structure and age-appropriate drug release profiles. The combination of chitosan's antimicrobial action, hyaluronic acid's regenerative properties, and controlled antibiotic delivery created a synergistic therapeutic effect that addressed multiple pathophysiological aspects of chronic wounds in aging populations.

Comparative analysis with commercial wound dressings revealed superior performance in moisture management, bacterial inhibition, and healing acceleration, while maintaining equivalent safety profiles. The nanofibers showed particular effectiveness in complex wound conditions simulating elderly comorbidities, with maintained performance in hypoxic and high-exudate environments. These findings position the tri-component system as a promising advanced therapeutic option for pressure ulcer management in geriatric care, addressing the critical unmet needs of this vulnerable patient population through multifunctional material design.

Table 1: Summary table

Parameter	***Performance Metrics***	***Significance***
Mechanical Properties	*Tensile strength: 2-15 MPa* *Elongation: 20-50%*	*Withstands wound movement*
Fluid Handling	*Swelling ratio: 300-800%* *Vapor transmission: 2000-2500 g/m²/day*	*Maintains moist environment*
Antimicrobial Activity	*>99% bacterial reduction* *72+ hour MIC maintenance*	*Prevents infection*
Drug Release	*5-14 day sustained release* *pH-responsive kinetics*	*Targeted therapy*
Healing Outcomes	*40-60% faster closure* *2-3× collagen increase*	*Accelerated recovery*
Biocompatibility	*<5% cytotoxicity* *Minimal inflammatory response*	*Safe for elderly use*

4- Conclusion

The tri-component chitosan/hyaluronic acid/antibiotic nanofibers demonstrated superior wound healing performance in both in vitro and in vivo evaluations. These nanofibers showed excellent mechanical strength (2–15 MPa), high swelling capacity (300–800%), and effective antimicrobial activity with over 99% bacterial reduction. The antibiotic-loaded fibers achieved sustained drug release for 5–14 days, with pH-responsive kinetics enhancing targeted delivery. In animal models, the dressings accelerated wound

closure by 40–60%, promoted 2–3× collagen deposition, and increased angiogenesis by 50–70%, while also reducing inflammatory markers by 30–50%. The system showed biocompatibility with cytotoxicity below 5% and maintained performance under simulated elderly wound conditions. These findings confirm the effectiveness of the CS/HA/antibiotic nanofiber dressings in promoting infection control and tissue regeneration, particularly for chronic wounds in elderly patients

5- Discussion

The exceptional performance of the tri-component chitosan/hyaluronic acid/antibiotic nanofibers can be attributed to several synergistic mechanisms that address the complex pathophysiology of chronic wounds in elderly patients. The mechanical properties (2-15 MPa tensile strength) surpass those of conventional hydrocolloid dressings while maintaining sufficient flexibility for clinical application, a critical advantage given the mobility challenges in geriatric care. The remarkable swelling capacity (300-800%) and moisture retention properties create an optimal wound microenvironment, particularly beneficial for elderly skin which is prone to both excessive dryness and maceration (Vigani, Rossi et al. 2019, Li, Jing et al. 2024).The antimicrobial results (>99% bacterial reduction) demonstrate significant improvement over single-component dressings, supporting the hypothesis that chitosan's inherent antibacterial activity potentiates the incorporated antibiotics (Dhlamini, Selepe et al. 2024). This synergistic effect is particularly valuable in an era of increasing antibiotic resistance, as it may allow for reduced antibiotic doses while maintaining efficacy (Taheri-Araghi 2024). The observed biofilm penetration (50-100 μm) addresses a major clinical challenge in chronic wounds, where biofilms act as persistent reservoirs of infection.The accelerated healing outcomes (40-60% faster closure) likely result from multiple mechanisms: chitosan's stimulation of inflammatory mediators, hyaluronic acid's promotion of fibroblast migration and proliferation, and the controlled antibiotic release preventing infection-related healing delays (Bai, Gao et al. 2023, Lin, Xu et al. 2023). The 2-3× increase in collagen deposition is particularly noteworthy, as collagen synthesis typically declines with age. This suggests the nanofibers may help overcome age-related healing impairments.The reduced inflammatory response (30-50% decrease in markers) indicates the system's ability to modulate the prolonged inflammation characteristic of chronic wounds, while the excellent biocompatibility (<5% cytotoxicity) confirms its safety for fragile elderly skin (Verdolino, Thomason et al. 2021, Maita, Avila et al. 2022). The pH-responsive drug release represents an intelligent design feature, targeting antibiotic delivery when and where it's most needed in infected wounds (Huang, Sun et al. 2024).These findings have important clinical implications. The dressing's multifunctionality could simplify wound care protocols for elderly patients, who often struggle with complex treatment regimens. The sustained antibiotic release may reduce dressing change frequency, minimizing pain and disruption. The biomimetic structure appears particularly suited to aged skin's reduced regenerative capacity.However, some limitations warrant discussion. The in vivo results, while promising, come from controlled animal studies and may not fully translate to heterogeneous human wounds. The long-term effects of sustained antibiotic release in immunocompromised elderly patients require further study. Scale-up challenges and cost-effectiveness compared to existing options must be addressed for clinical adoption.

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