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Silver and Copper Nanoparticles in Advanced Wound Dressings for Chronic Venous Leg Ulcers: A Critical Clinical Review of Antibacterial Efficacy and Cytotoxicity

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Abstract:

Background. Chronic venous leg ulcers (CVLUs) are a prevalent and clinically challenging condition, frequently complicated by polymicrobial biofilm infections that impair healing. Silver nanoparticles (AgNPs) and copper nanoparticles (CuNPs) have emerged as promising antimicrobial agents for incorporation into advanced wound dressings.

Aim. This clinical review critically evaluates and compares the antibacterial efficacy and cytotoxic profiles of AgNPs and CuNPs in the context of chronic venous leg ulcer management.

Material and methods. A narrative review of peer-reviewed literature was conducted using PubMed/MEDLINE (2015–2025).

Results. Both AgNPs and CuNPs demonstrate comparable broad-spectrum antibacterial and anti-biofilm activity, including against multidrug-resistant organisms. CuNPs additionally exhibit pro-angiogenic and collagen-stimulating properties. Both nanoparticle types show dose-dependent cytotoxicity toward keratinocytes and fibroblasts, with safety thresholds remaining incompletely defined.

Conclusions. AgNPs and CuNPs represent therapeutically comparable options for chronic venous leg ulcer management. Standardised clinical trials are needed to establish safe concentration ranges and optimal dressing formulations.

Key words: silver nanoparticles; copper nanoparticles; chronic venous leg ulcers; wound dressings; antibacterial activity; cytotoxicity; nanomedicine; wound healing; biofilm; clinical review

1. Introduction

Chronic venous leg ulcers (CVLUs) constitute one of the most prevalent and clinically challenging manifestations of chronic wound pathology, affecting an estimated 1–2% of the adult population in developed countries.^[1,2] Characterised by persistent full-thickness skin loss below the knee, CVLUs arise as a consequence of sustained chronic venous insufficiency, leading to elevated venous pressure, microcirculatory dysfunction, and a pro-inflammatory tissue microenvironment that fundamentally impairs the wound healing cascade.^[3] Recurrence rates exceed 50% within one year of initial healing, resulting in chronic pain, impaired mobility, diminished quality of life, and considerable socioeconomic costs.^[1,4]

A critical factor perpetuating the chronicity of venous leg ulcers is microbial colonisation and infection. The wound bed of CVLUs provides an optimal niche for polymicrobial communities, with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, beta-haemolytic streptococci, and Enterobacteriaceae among the most frequently isolated pathogens.^[5,6] Biofilm-associated infection has been identified in up to 60–80% of chronic wounds and is now widely recognised as a primary driver of healing failure, rendering standard antimicrobial therapies increasingly inadequate in the context of rising antimicrobial resistance.^[5,7]

The escalating global crisis of antimicrobial resistance (AMR) has rendered the development of novel, non-antibiotic antimicrobial strategies an urgent clinical and scientific priority.^[8] Metal-based nanoparticles, characterised by their nanoscale dimensions (typically 1–100 nm), exhibit potent biocidal activity operating through mechanisms that differ fundamentally from those of conventional antibiotics.^[9,10] These properties render them particularly suited for incorporation into advanced wound dressing matrices, where they can exert sustained local antimicrobial effects while minimising the selective pressure that drives resistance development.

Among the metal nanoparticles investigated for wound care applications, silver nanoparticles (AgNPs) have accumulated the most extensive body of evidence.^[11] More recently, copper nanoparticles (CuNPs)

have attracted growing scientific interest, offering comparable broad-spectrum antibacterial and anti-biofilm activity, as well as intrinsic pro-angiogenic properties including stimulation of vascular endothelial growth factor (VEGF) expression.^[12,13] Despite their therapeutic promise, the clinical translation of both AgNPs and CuNPs is complicated by concerns regarding dose-dependent cytotoxicity toward keratinocytes, fibroblasts, and endothelial cells.^[9,14]

In light of these considerations, the present clinical review aims to critically evaluate and compare the antibacterial efficacy and cytotoxic profiles of AgNPs and CuNPs incorporated into modern wound dressings, with specific focus on their applicability in the management of chronic venous leg ulcers.

2. Material and methods

This article constitutes a narrative clinical review based exclusively on previously published data. No ethical approval was required as the study did not involve direct patient participation.

2.1. Literature search strategy

A systematic literature search was performed in the PubMed/MEDLINE electronic database in April 2026. The following Boolean search string was applied: ("silver nanoparticles" OR "AgNPs" OR "copper nanoparticles" OR "CuNPs") AND ("wound dressing" OR "chronic wound" OR "venous leg ulcer" OR "wound healing") AND ("antibacterial" OR "antimicrobial" OR "cytotoxicity" OR "biofilm"). Additionally, reference lists of retrieved articles were manually screened for relevant publications.

2.2. Eligibility criteria

Inclusion criteria: (1) published between 2015 and 2025; (2) written in English or Polish; (3) reporting on AgNPs and/or CuNPs in wound dressings or wound healing models; (4) addressing antibacterial efficacy, anti-biofilm activity, or cytotoxicity; (5) in vitro, in vivo, or clinical study designs; (6) full text available.

Exclusion criteria: (1) publications prior to 2015; (2) studies unrelated to wound care; (3) nanoparticles other than AgNPs or CuNPs as the primary intervention; (4) conference abstracts, editorials, and letters without original data; (5) duplicate publications; (6) full text not accessible.

2.3. Data collection and analysis

Titles and abstracts of all retrieved records were screened against the eligibility criteria. Full texts of potentially relevant articles were subsequently retrieved and assessed for final inclusion. Data were extracted narratively, with attention to nanoparticle type, synthesis method, particle size and concentration, carrier matrix, target microorganisms, antibacterial and anti-biofilm outcomes, and cytotoxicity endpoints. Given the narrative design, formal meta-analytic synthesis was not performed.

3. Mechanisms of action

The antibacterial activity of metal-based nanoparticles emerges from a constellation of interrelated physicochemical and biological processes that act synergistically to disrupt bacterial viability.

3.1. Mechanisms of action of silver nanoparticles (AgNPs)

3.1.1. Ion release and direct membrane interaction. The primary bactericidal mechanism of AgNPs involves the controlled release of silver ions (Ag^+) from the nanoparticle surface.^[1] Ag^+ ions possess a high affinity for sulfhydryl (-SH) groups in bacterial proteins and enzymes, irreversibly inhibiting key metabolic enzymes including those involved in the electron transport chain and ATP synthesis.^[2] Both Ag^+ ions and intact nanoparticles destabilise the bacterial cell envelope, increasing membrane permeability and causing leakage of intracellular contents.^[1,3]

3.1.2. Reactive oxygen species generation. A second major mechanism involves the generation of reactive oxygen species (ROS), including superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals ($\cdot\text{OH}$).^[3] The resulting oxidative burden overwhelms bacterial antioxidant defense systems, leading to lipid peroxidation, oxidative damage to nucleic acids, and protein carbonylation.^[2,3] Importantly, ROS-mediated mechanisms operate independently of classical antibiotic targets, explaining the efficacy of AgNPs against multidrug-resistant organisms including MRSA and carbapenem-resistant *Pseudomonas aeruginosa*.^[4]

3.1.3. Biofilm disruption. AgNPs have been shown to penetrate the extracellular polymeric substance (EPS) matrix, disrupting quorum sensing signalling pathways and inhibiting biofilm formation and maturation — of particular clinical relevance given the high prevalence of biofilm infection in chronic venous leg ulcers.^[5]

3.2. Mechanisms of action of copper nanoparticles (CuNPs)

3.2.1. Ion release and protein inactivation. CuNPs exert antibacterial activity through the release of copper ions (Cu^{2+} and Cu^+), which interact with thiol and amino groups of bacterial proteins, inactivating essential enzymes and disrupting oxidative phosphorylation.^[6,7]

3.2.2. Oxidative stress and membrane disruption. CuNPs are potent inducers of intracellular oxidative stress through Fenton and Haber-Weiss reactions.^[7,8] Membrane disruption proceeds through electrostatic interactions between positively charged Cu^{2+} ions and the negatively charged bacterial surface, followed by pore formation and loss of membrane potential.^[8]

3.2.3. Pro-angiogenic and wound-healing properties. A mechanistically distinct property of CuNPs — not shared by AgNPs — is their capacity to modulate host tissue repair. Copper ions are cofactors for lysyl oxidase, critical for collagen and elastin cross-linking.^[9] Furthermore, Cu^{2+} upregulates VEGF and HIF-1 α expression, promoting neovascularisation in ischaemic wound beds — particularly relevant in the context of microcirculatory dysfunction in chronic venous leg ulcers.^[9,10]

3.3. Comparative overview

Both AgNPs and CuNPs share fundamental antibacterial mechanisms including ion-mediated protein inactivation, ROS generation, membrane disruption, and DNA damage, but differ in relative pathway contributions and interactions with host tissue biology. Both demonstrate multimodal, non-specific mechanisms of action that reduce the likelihood of resistance development — a critical advantage over conventional antibiotics. The additional pro-regenerative properties of CuNPs may confer clinically meaningful benefits in the setting of chronic venous leg ulcer treatment.

4. Antibacterial properties

4.1. In vitro antibacterial activity

4.1.1. Spectrum of activity and minimum inhibitory concentrations. AgNPs inhibit the growth of *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and beta-

haemolytic streptococci at concentrations typically ranging from 1 to 100 µg/mL.^[1,2] CuNPs display a comparable spectrum of antibacterial activity, with reported MIC values generally ranging from 10 to 500 µg/mL.^[3,4] Both nanoparticle types retain bactericidal activity against multidrug-resistant organisms, including MRSA and ESBL-producing Enterobacteriaceae.^[1,3]

4.1.2. Anti-biofilm activity. AgNPs inhibit biofilm formation and disrupt mature biofilms of *S. aureus* and *P. aeruginosa* at sub-MIC concentrations, with reductions in viable biofilm biomass of 70–95% reported in vitro.^[5,6] CuNPs exhibit comparably potent anti-biofilm activity, with complete eradication of *S. aureus* and *P. aeruginosa* biofilms at concentrations of 50–200 µg/mL.^[7,8]

4.2. Efficacy in wound dressing formulations

AgNPs have been incorporated into hydrogels, electrospun nanofibre membranes, collagen matrices, polyurethane foams, and chitosan-based scaffolds, with sustained antibacterial activity demonstrated over 24 hours to 14 days in vitro.^[9,10] CuNP-loaded dressings, including the Cupron® copper oxide-containing fibre technology, have demonstrated sustained antimicrobial activity against a broad panel of wound pathogens.^[11,12]

4.3. In vivo and clinical evidence

AgNP-treated wounds in rodent models consistently demonstrated accelerated bacterial clearance, reduced inflammatory infiltrate, and earlier transition to the proliferative phase of healing.^[9,13] In vivo data for CuNP dressings are supportive of comparable efficacy, additionally showing enhanced granulation tissue formation and collagen deposition.^[11,12] Clinical evidence in chronic venous leg ulcers remains limited for both systems. Silver-containing dressings have demonstrated reductions in wound infection rates in several RCTs, though improvements in healing rates have been less consistently demonstrated.^[10,14] For CuNP-based dressings, clinical data are largely confined to case series, representing an important gap in the evidence base.^[11]

5. Cytotoxicity and safety profile

5.1. Cytotoxicity of silver nanoparticles (AgNPs)

5.1.1. Effects on keratinocytes and fibroblasts. AgNPs induce dose- and size-dependent reductions in cell viability in human HaCaT keratinocytes and dermal fibroblasts, with IC₅₀ values reported in the range of approximately 5–75 µg/mL.^[1,2] The principal cytotoxic mechanisms include intracellular ROS accumulation, mitochondrial membrane depolarisation, and activation of intrinsic apoptotic pathways.^[2,3] Notably, AgNPs impair fibroblast migration and proliferation at concentrations as low as 10 µg/mL.^[3]

5.1.2. Therapeutic window and modulating factors. A narrow but potentially exploitable therapeutic window exists in which AgNPs achieve significant antibacterial activity at concentrations below those producing substantial cytotoxicity.^[4] Surface functionalisation with PVP, citrate, or chitosan demonstrates reduced cytotoxicity relative to uncoated particles.^[4,5] Commercial silver dressings, releasing silver at 1–70 µg/mL into wound fluid, have demonstrated an acceptable clinical safety profile, with argyria reported only with prolonged exposure over large wound surfaces.^[5]

5.2. Cytotoxicity of copper nanoparticles (CuNPs)

5.2.1. Effects on wound-relevant cell populations. CuNPs and CuO NPs induce cytotoxicity in keratinocytes and fibroblasts at concentrations generally ranging from 25 to 200 µg/mL — tending to be higher than equivalent AgNP IC₅₀ values.^[6,7] A critical distinction is the biphasic dose-response of CuNPs: at cytotoxic concentrations Cu²⁺ induces oxidative damage, while at sub-toxic concentrations copper stimulates fibroblast proliferation, collagen synthesis, and VEGF-mediated angiogenesis.^[8,9]

5.2.2. In vivo safety considerations. Murine wound model studies employing CuO NP-containing dressings have reported no significant systemic copper accumulation or organ toxicity at therapeutically relevant doses, with local tissue responses resolving within 72 hours of dressing application.^[9,10]

5.3. Comparative safety assessment and modulating factors

AgNPs appear to exhibit cytotoxicity at lower absolute concentrations than CuNPs, suggesting a narrower therapeutic window; however, the extensive clinical experience with silver dressings indicates this is manageable within appropriately formulated systems.^[5,11] The protein corona effect — biomolecular layer formation around nanoparticles in wound exudate — may substantially attenuate in vitro cytotoxicity, partially explaining the more favourable clinical safety profiles observed in practice.^[11,12] The absence of standardised, clinically validated concentration thresholds defining the boundary between therapeutic efficacy and cytotoxic impairment of wound healing remains the most pressing unmet need in the field.

6. Discussion

The most clinically significant finding of this review is that AgNPs and CuNPs demonstrate broadly comparable antibacterial efficacy against the principal pathogens implicated in chronic venous leg ulcer infection, including multidrug-resistant organisms and biofilm-forming bacteria.^[1,2] Both nanoparticle types exert multimodal bactericidal activity through mechanisms fundamentally distinct from those of conventional antibiotics, conferring a critically important resistance-evasion profile.

The perception that AgNPs represent a superior antibacterial agent is not consistently supported by the available evidence; apparent differences in MIC values are largely attributable to heterogeneity in experimental methodology rather than intrinsic differences in bactericidal potency.^[3,4] CuNPs offer a potentially important clinical advantage through their dual antibacterial and pro-regenerative profile, which may be particularly relevant in the impaired healing environment of chronic venous leg ulcers.^[5,6]

With respect to cytotoxicity, both nanoparticle types exhibit dose-dependent toxicity toward wound-relevant cell populations.^[7,8] The biphasic dose-response of CuNPs — pro-regenerative at sub-toxic concentrations — represents a potentially exploitable advantage not shared by AgNPs.^[8,9] The protein corona effect may substantially attenuate cytotoxic effects observed *in vitro*, partially explaining more acceptable clinical safety profiles.^[12]

A recurring limitation of the existing literature is substantial methodological heterogeneity, rendering direct quantitative comparison between studies extremely challenging.^[3,11] The disparity in clinical evidence volume between AgNPs and CuNPs reflects the earlier stage of clinical development of copper nanoparticle technology rather than established inferiority, and should not be interpreted as a basis for preferring silver formulations without further evidence.

6.1. Limitations of this review

Several limitations must be acknowledged: (1) the search was confined to a single database (PubMed/MEDLINE); (2) the narrative design does not permit systematic bias assessment or quantitative synthesis; (3) the 2015–2025 timeframe excludes earlier foundational studies; (4) language restriction to English and Polish may have introduced publication bias.

6.2. Research gaps and future directions

1. Standardised, validated protocols for nanoparticle characterisation and antibacterial/cytotoxicity testing to enable meaningful cross-study comparison.
2. Well-powered randomised controlled trials evaluating AgNP- and CuNP-based dressings specifically in chronic venous leg ulcer populations.
3. Direct head-to-head comparative trials of AgNP versus CuNP dressings under equivalent experimental and clinical conditions.
4. Establishment of clinically validated safe concentration thresholds defining the therapeutic window for both nanoparticle types.

5. Long-term safety studies evaluating systemic nanoparticle accumulation and organ toxicity.
6. Investigation of the pro-angiogenic properties of CuNPs in chronic venous leg ulcer-specific clinical models.

7. Conclusions

1. AgNPs and CuNPs demonstrate broadly comparable broad-spectrum antibacterial and anti-biofilm efficacy against the principal pathogens of chronic venous leg ulcers, operating through multimodal, resistance-evasive mechanisms.
2. CuNPs offer a mechanistically distinct advantage through their dual antibacterial and pro-regenerative properties, including stimulation of angiogenesis and collagen remodelling.
3. Both nanoparticle types exhibit dose-dependent cytotoxicity; however, surface functionalisation, protein corona formation, and precise concentration control offer viable strategies for optimising the therapeutic window.
4. The narrower cytotoxic threshold of AgNPs is offset by a substantially larger body of clinical safety data, whilst the biphasic dose-response of CuNPs represents a potentially exploitable biological property.
5. Current evidence supports the use of both nanoparticle systems as adjunctive antimicrobial strategies; however, the absence of standardised clinical trial data precludes definitive recommendations at this stage.
6. Standardised comparative clinical trials and internationally harmonised nanoparticle characterisation protocols are urgently required to advance the clinical translation of both technologies.

Disclosure

Author Contributions:

Conceptualization: Jan Kabat, Wojciech Nejc

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