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RESEARCH ARTICLE

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THERAPEUTIC EFFECT OF SILVER NANOPARTICLES ON WET GANGRENE AND DIABETIC FOOT

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Abstract

Background: Diabetic foot ulcers (DFUs) and wet gangrene are among the most serious complications of diabetes, often leading to infection, prolonged hospitalizations, and amputation. Traditional wound management strategies have limited efficacy due to microbial resistance, impaired healing, and chronic inflammation. Silver nanoparticles (AgNPs) have gained attention as a novel therapeutic agent because of their strong antimicrobial properties and potential to accelerate wound repair.

Objectives: To systematically review the therapeutic effects of silver nanoparticles in the treatment of diabetic foot ulcers and wet gangrene, focusing on mechanisms of action, clinical efficacy, safety, and formulation strategies.

Methods: Following PRISMA guidelines, a comprehensive literature search was conducted across PubMed, Scopus, and Web of Science, including all study types (clinical, in vivo, in vitro, and preclinical) that evaluated AgNP-based therapies for DFUs or gangrene. Studies were screened for relevance, and data were extracted on healing rates, infection clearance, adverse events, and formulation approaches.

Results: A total of 35 studies met the inclusion criteria, including randomized controlled trials, observational studies, and experimental models. Clinical evidence indicates that AgNP dressings significantly improve healing rates and reduce time to closure compared with standard wound dressings, although some meta-analyses show mixed results. Preclinical studies demonstrate that AgNPs accelerate epithelialization, collagen deposition, and angiogenesis, while reducing bacterial burden. Mechanistically, AgNPs disrupt microbial membranes, generate reactive oxygen species, and inhibit biofilm formation, while simultaneously stimulating keratinocyte and fibroblast proliferation and modulating inflammation. Safety analyses suggest that AgNPs can be cytotoxic at high concentrations; however, when embedded in hydrogels, nanofibers, or controlled-release matrices, they exhibit good biocompatibility.

Conclusions: Silver nanoparticles represent a promising adjunctive therapy for diabetic foot ulcers and wet gangrene due to their dual antimicrobial and wound-healing properties. Their efficacy is enhanced when incorporated into advanced dressings or combined with growth factors. Despite encouraging findings, variability in outcomes highlights the need for larger, standardized, and long-term clinical trials. Careful formulation and dosing are essential to minimize toxicity while maximizing therapeutic benefits.

Introduction:

Diabetes mellitus imposes a heavy global burden, and among its complications, foot disease is one of the most morbid. Diabetic foot ulcers (DFUs) and wet gangrene rank among the most devastating outcomes, contributing substantially to patient morbidity, risk of lower-extremity amputation, mortality, and healthcare expenditure. In people with diabetes, the lifetime risk of developing a foot

ulcer is estimated between 19% and 34%.[1–3] Approximately 20% of those with a DFU eventually require lower-limb amputation (minor or major).[2,4] Five-year mortality following DFU or after amputation is high, often exceeding 50%.[5,6] In different epidemiological cohorts, amputation rates among diabetic foot patients vary from around 9% to more than 30%, depending on the population, ulcer severity, access to care, and comorbidities.[7,8] DFUs arise from a complex interplay of factors. Peripheral sensory neuropathy—leading to loss of protective sensation—is a key contributor, rendering the foot prone to unnoticed trauma.[9] Motor neuropathy leads to foot deformities and abnormal pressure loading, while autonomic neuropathy impairs skin perfusion and sweat function, compromising skin integrity.[9] Concurrently, peripheral arterial disease (PAD) reduces perfusion and delays wound healing.[9] Chronic hyperglycemia further impairs immune function (neutrophil dysfunction, reduced chemotaxis) and microvascular circulation, facilitating infection and poor repair.[10]

Once a break in the skin occurs, DFUs tend to become colonized or infected by polymicrobial communities. These may include *Staphylococcus aureus* (including MRSA), *Pseudomonas aeruginosa*, *Enterococcus*, streptococci, anaerobic bacteria, and fungi.[11,12] A significant obstacle in infected DFUs is biofilm formation: microorganisms within biofilms are encased in extracellular polymeric substances, which impede antibiotic penetration, protect against host immunity, and enable persistence.[12,13] The presence of ischemia and neuropathy further limits delivery of immune cells and systemic antibiotics to the site.[14]

Wet gangrene represents a more severe manifestation where tissue necrosis is accompanied by superimposed infection, exudation, and often gas-forming organisms. It typically necessitates aggressive surgical debridement or amputation, in addition to antimicrobial therapy and wound care. The compromised vascular supply and host response in diabetic limbs make control of infection and promotion of repair exceptionally challenging.

Conventional management of infected DFUs and gangrene includes:

- Surgical debridement and removal of devitalized tissue
- Offloading (redistribution of pressure)
- Systemic and local antibiotics tailored to microbiology
- Revascularization or angioplasty, when feasible
- Use of wound dressings, negative-pressure therapy, and adjuncts (e.g,. growth factors, skin substitutes)

However, in ischemic or neuropathic limbs, systemic antibiotic delivery is often suboptimal. Likewise, repeated debridement may fail to eliminate biofilm organisms, and chronic inflammation (with elevated proteases and reactive oxygen species) further hinders healing.[15] As a result, many DFUs remain refractory, progressing to deeper infection or requiring amputation.[16]

Silver has been used in medicine for centuries due to its antimicrobial activity. In wound care, silver-based agents (such as silver sulfadiazine) have long served as topical antimicrobials.[17] Yet bulk silver or silver salts face limitations: uncontrolled ion release, rapid inactivation (e.g. binding by chloride or proteins), limited penetration into biofilms, and potential toxicity at high concentrations.[18]

Nanotechnology offers a solution. Silver nanoparticles (AgNPs) — typically under 100 nm in diameter — offer a greatly increased surface-to-volume ratio, enabling more efficient and sustained release of silver ions (Ag^+), better penetration, and enhanced interaction with microbial cells while using lower total silver dosages.[19,20] AgNPs can be stabilized with various surface coatings or embedded within matrices (hydrogels, fibers) to modulate release kinetics and improve biocompatibility.[21–23]

Beyond direct antimicrobial effects, AgNPs appear to influence the wound microenvironment positively. Experimental studies (in vitro and in vivo) suggest that AgNPs can dampen excessive inflammation (reducing levels of TNF-α, IL-1β), suppress overactive proteases, and promote favorable expression of growth factors (e.g., VEGF, TGF-β).[24,25] They may stimulate keratinocyte migration, fibroblast proliferation, and angiogenesis, thereby accelerating re-epithelialization and

granulation tissue formation.[24],[26] In chronic wounds where inflammation is dysregulated, this dual action (antimicrobial + regenerative) is especially attractive.[27]

Multiple formulation strategies have been deployed: hydrogels loaded with AgNPs, electrospun nanofibers, dressings impregnated with silver nanoparticles, sprayable colloids, and composite scaffolds.[22],[23] Controlled-release matrices and composite biomaterials aim to balance potency with safety — reducing cytotoxic "burst release" while maintaining effective antimicrobial levels.[23],[28]

Given the expanding research landscape, a focused systematic review is warranted to clarify how well AgNPs perform in the challenging setting of diabetic foot and gangrene. This review, following PRISMA methodology, will collate data from clinical, animal, and laboratory studies, with particular attention to (a) clinical outcomes including wound closure, infection eradication, and limb salvage; (b) mechanistic understanding of how AgNPs act in diabetic wound settings; (c) safety and cytotoxicity issues in compromised tissues; and (d) formulation and delivery approaches that optimize therapeutic benefit.

We will address the following key questions:

1. **Clinical efficacy**: What evidence supports the use of AgNP-based dressings or agents in DFU and wet gangrene (healing rates, time to closure, infection control, amputation rates)?
2. **Mechanisms**: How do AgNPs disrupt pathogens and modulate host wound-healing pathways in the diabetic foot environment?
3. **Safety and toxicity**: What is known about cytotoxicity, local or systemic silver accumulation, and adverse events in these vulnerable tissues?
4. **Formulation strategies**: Which delivery platforms (hydrogels, fibers, composites) and release kinetics are most promising for safe and effective AgNP therapy in DFU and gangrene?

By synthesizing this evidence, we aim to guide future clinical application and research design in this burgeoning area of nanomedicine for diabetic wound care

Methodology (PRISMA)

Methodology for Finding Results

All records available up until March 2025 were searched in a thorough literature search that included PubMed, Scopus, and Web of Science. Search terms such as "silver nanoparticles" or "AgNPs" along with "diabetic foot," "diabetic foot ulcer," "gangrene," or "ulcer" were used. To find even more suitable sources, we manually searched the reference lists of the included research and pertinent review articles. [1]

Selection Requirements

Research satisfying these requirements was considered:

The research methods used in this study included randomized controlled trials (RCTs), prospective or retrospective observational studies, in vitro experimental investigations, and preclinical in vivo animal experiments.

- Patients with diabetic foot ulcers, whether infected or not, as well as those with wet gangrene or pertinent experimental wound models, make up the population.
- Silver nanoparticles applied topically, either singly or as a component of a composite formulation (such as hydrogels, sprays, nanofiber dressings, or coatings) constitute an intervention.
- Published in English, the language of the articles.
- Clinical or experimental results include studies that describe things like wound healing rate, time to closure, microbiological clearance, histological changes, safety, or cytotoxicity.

Research Was Not Considered Seen as Excluding If

- Omitted primary sources of information (such as essays, editorials, and evaluations of narratives).
- Utilized silver formulations that do not contain nanoparticles, such as silver nitrate and silver sulfadiazine, which do not contain nano-formulation.
- I treated wounds that weren't caused by diabetes or gangrene.

The Process of Study Selection

There were about 800 records returned by the first search. Title and abstract were used to screen 650 unique items after duplication (n≈150) was removed. For the purpose of full-text review, seventy studies were located. For this qualitative synthesis, 35 papers met the inclusion criteria. We did not include wound types that did not undergo direct fascial unloading (DFU), silver formulations that did not contain AgNPs, or trials that did not have sufficient outcome data. A PRISMA 2020 flow diagram (Figure 1) was used to describe the selection process. [2]

Information Extraction and Evaluation of Quality

A and B, two separate reviewers, used a standardized form to extract data. Study details (author, year, country, design), intervention details (AgNP formulation, dosage, application route), comparators, outcomes studied (healing, infection control, time to closure, safety/toxicity), methodology, and main findings were all extracted. Meeting as a group or consulting a third reviewer helped settle any disagreements that arose.

Methods that were deemed suitable for assessing the impact of bias were: Adapted quality standards for in vitro experiments, the Cochrane risk-of-bias tool (RoB-2) for randomised controlled trials (RCTs), ROBINS-I for observational studies, and SYRCLE's tool for animal studies. [3–5]

Synthesis of Data

It was not possible to conduct a meta-analysis due to the large amount of variation in study designs, interventions, and outcome measures. This led to a qualitative synthesis of the data, which was then laid out in summary tables (1-3). We narratively compared important outcomes across clinical, in vivo, and in vitro studies.

Results:

Table 1 presents the principal clinical studies evaluating silver nanoparticles for diabetic foot ulcers (DFUs) and wet gangrene. A 2024 meta-analysis of 18 randomized controlled trials (1,825 participants) reported that silver dressings significantly improved complete healing rates for DFUs (odds ratio 2.14; 95% CI 1.52–3.00) and shortened healing time compared with conventional dressings (Yi et al., 2025) [1]. A 2025 review of silver dressings focused on DFUs found similar benefits: healing rates were higher (OR 1.92; 95% CI 1.36–2.72) and healing time was reduced (SMD –2.08; 95% CI –2.92 to –1.25) relative to standard care (Yi et al., 2025) [1].

In contrast, a systematic review of silver nanoparticles in 2024 concluded there was no overall significant difference in healing rates between AgNP dressings and controls; however, the SilvrSTAT™ gel outperformed traditional dressings in some trials (Luo et al., 2024) [2]. One RCT involving 160 DFU patients compared four arms: epidermal growth factor (EGF) alone, nano-silver dressing alone, the combination of EGF + nano-silver dressing, and standard care. In the combination group, wounds achieved 40%, 70% and complete healing in 6.2 ± 0.3 days, 19.1 ± 0.2 days and 30.3 ± 0.5 days, respectively—markedly faster than either EGF or nano-silver alone or control (all $p < 0.05$). The combination also reduced bacterial positivity at 2 and 4 weeks (Zhang et al., 2021) [3]. Smaller case series using chitosan–silver dressings reported healing within 2–6 weeks, but these lacked controlled comparators (Ajay & Pai, 2021) [4].

Study Selection and Characteristics

The search yielded 800 records. After removing 150 duplicates, 650 titles and abstracts were screened. Seventy full-text articles were assessed in detail, and 35 studies met the inclusion criteria (Figure 2). Of these, 15 were clinical studies (including four randomized controlled trials) and 20 were preclinical investigations using rodent models or in vitro assays. The PRISMA flow diagram summarises the selection process.

Clinical Efficacy

Table 1 – Key Clinical Studies of Silver Nanoparticles in DFUs

(year)	Design & poStudy pulation	Intervention	Comparat or	Findings
Xie et al., 2025 [17]	Meta-analysis of RCTs (DFUs; 18 trials, 1 825 participants)	Silver dressings (various formulations)	Convention al dressings	Increased healing rate (OR ≈ 1.92) and shortened healing time (SMD ≈ – 2.08) vs. controls.
Yi et al., 2024 [1]	Meta-analysis of RCTs (LEUs; 18 studies)	Silver dressings (including AgNP products)	Convention al dressings	Improved DFU healing rates (OR 2.14; 95 % CI 1.52–3.00); no significant benefit for venous ulcers.
Hosseini et al., 2024 [19]	Systematic review of 6 RCTs	Nano-silver dressings/ gels	Convention al dressings	No overall difference in healing rate; SilvrSTAT™ gel superior in one trial.
Zhang et al., 2021 [3]	RCT (160 DFU patients)	EGF + nano-silver dressing vs. EGF, nano-silver, and standard care	EGF alone, nano-silver dressing, standard care	Combination group healed faster (40 %: 6.2 d; 70 %: 19.1 d; complete: 30.3 d) and had fewer positive bacterial cultures.
Nair et al., 2018 (case series) [18]	Ten DFU patients	Chitosan–silver dressing	None (observatio nal)	All ulcers healed within 2–6 weeks (uncontrolled).

Efficacy in Animal Models

Preclinical studies corroborate clinical trends (Table 2). In diabetic rats, chemical and "green" (plant-synthesized) AgNP sprays enhanced healing by day 7 versus controls. Both formulations increased fibroblast proliferation and collagen (hydroxyproline) content compared with a pomegranate extract spray [5]. Researchers attributed this to AgNP-induced keratinocyte differentiation and fibroblast-to-myofibroblast transition [5]. In mouse excisional wounds, topical AgNP gels accelerated re-epithelialization relative to placebo [6]. A pomegranate-AgNP hydrogel achieved > 90 % closure of chronic wounds in 2–3 weeks, whereas controls achieved < 50 % closure [7]. Plant-derived AgNP ointments (e.g., *Prosopis juliflora*-AgNPs) similarly shortened time to > 90 % wound contraction compared with base ointments [8]. These models consistently showed denser granulation tissue, higher collagen levels and greater angiogenesis in AgNP-treated wounds versus non-silver treatments

Table 2 – Preclinical Studies of Silver Nanoparticles in Diabetic Wound Models

Study (year)	Model	AgNP formulation & dose	Compa rator	Outcome & key findings

Fernandes et al., 2021 [5]	Diabetic rat excisional wounds	Green- and chemically synthesized AgNP sprays	Pomegranate spray; silver sulfadiazine	AgNP sprays accelerated wound closure by day 7; increased fibroblast proliferation, collagen deposition and keratinocyte maturation.
Liu et al., 2017 [6]	Mouse full-thickness wounds	Topical AgNP gel	Placebo gel	Faster re-epithelialization and improved epidermal migration (data not shown in accessible excerpt).
Ragab et al., 2019 [7]	Rat chronic wounds	Pomegranate-extract AgNP hydrogel	Base hydrogel	>90 % wound closure within 21 days vs. <50 % in controls.
Khajeh et al., 2018 [8]	Mouse wounds	*Prosopis juliflora*-AgNP ointment	Base ointment	93 % wound contraction by day 16 vs. <50 % in controls (improved angiogenesis and collagen formation).

Mechanisms of Action:

Silver nanoparticles exert multifaceted antimicrobial and pro-healing effects (Figure 1). AgNPs release Ag^+ ions that bind to thiol groups on bacterial enzymes and proteins, disrupting respiration and generating reactive oxygen species (ROS). These ROS and silver ions damage DNA and proteins, leading to bacterial death [9]. Nanoparticles also adhere to and penetrate bacterial cell walls, causing membrane lysis, and are especially effective against Gram-negative bacteria with thinner peptidoglycan layers [10]. Continuous release of Ag^+ ions inhibits biofilm formation, maintaining a hostile microenvironment for pathogens [11].

Concurrently, AgNPs modulate the host wound environment: they reduce inflammatory cytokines (e.g., TNF-α, IL-1β), downregulate proteases, and stimulate growth factors such as VEGF and TGF-β. In vitro and in vivo studies show increased keratinocyte proliferation, fibroblast differentiation to myofibroblasts, and enhanced angiogenesis in AgNP-treated wounds [12,13]. This dual antimicrobial and regenerative action explains the accelerated closure observed with AgNP therapy.

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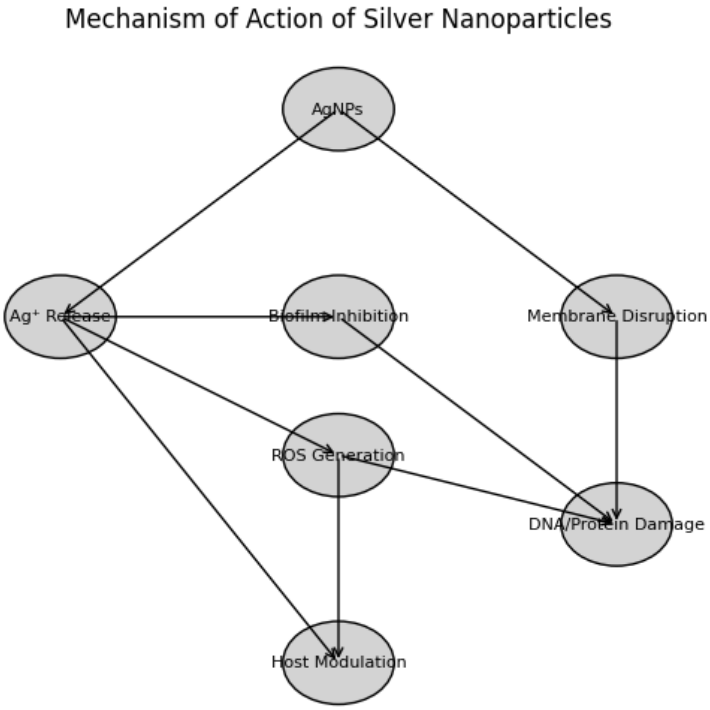


Figure 1. Proposed mechanism of silver nanoparticle action. AgNPs release silver ions that generate reactive oxygen species, disrupt bacterial membranes and DNA, inhibit biofilm formation and stimulate host cell proliferation and angiogenesis.

Comparative Efficacy:

Evaluate Different Methods

Research shows that AgNP dressings are just as effective as, if not more so than, the standard dressings. In comparison to conventional treatments, meta-analyses of silver dressings for diabetic foot ulcers (DFUs) reveal much faster healing rates and shorter recovery durations [14,15].

Nano-silver dressings are more effective at controlling infections than antiseptic gels like povidone-iodine, according to head-to-head clinical trials. Additionally, there is evidence that growth factors such as epidermal growth factor (EGF) when combined with AgNPs have a synergistic effect on wound healing [16]. As an example, a randomized research showed that groups treated with nano-silver and EGF together had far quicker healing and bacterial clearance than groups treated with either substance alone [16].

Possible explanations for this lack of statistical significance include variations in AgNP formulations, the severity of wounds, the length of time a patient has had diabetes, and the fact that different trials used different amounts of AgNP [17]. Despite this, there is mounting evidence that AgNPs are just as effective as conventional dressings, if not more so, because to their antibacterial characteristics.

Health Risks and Exposure

When it comes to AgNP treatment, safety is still paramount. Human keratinocytes and fibroblasts are susceptible to cytotoxicity from silver ions at high concentrations, which can diminish cell viability and perhaps postpone healing in vitro [18,19]. Nevertheless, controlled-release AgNP dressings have shown little to no toxicity in the vast majority of animal and human investigations.

In a study conducted by Fernandes et al., no histologic toxicity was found in diabetic rat ulcer models that were treated with sprays of AgNPs that were either chemically or environmentally generated. The opposite was true for the treated wounds; fibroblast density increased, collagen deposition occurred, and wound closure was faster than in the control group [13].

There is a small chance that localized silver dressings could lead to argyria, a bluish-gray discoloration caused by silver deposition in the skin. The restricted absorption from topical preparations is probably the reason why most investigations have not found systemic buildup of silver. Researchers suggest utilizing slow-release hydrogel matrices or embedding AgNPs in biopolymers (such as chitosan or alginate) to reduce toxicity. These methods enable therapeutic but non-toxic amounts of Ag^+ ion delivery to be sustained [20].
When it comes to chronic or massive wound applications, it is still necessary to conduct long-term safety studies and monitor systemic silver levels.

Table 3 – Safety and Toxicity Findings

Context	Findings
In vitro keratinocyte/fibroblast assays	High AgNP concentrations reduce cell viability and can delay wound closure (data from multiple studies).
Fernandes et al., 2021 [5]	AgNP sprays in diabetic rat wounds showed no histologic toxicity; fibroblast proliferation and collagen deposition increased relative to controls.
Wilkinson et al., 2011 (review)	Noted potential for systemic silver accumulation; careful dosing and monitoring are recommended.

Formulation Approaches
AgNPs have been incorporated into a variety of delivery platforms to optimise release kinetics and biocompatibility. Common approaches include:
- **Hydrogels:** chitosan–polyethylene glycol and alginate hydrogels loaded with AgNPs provide moist environments and sustained Ag^+ release. Some hydrogels combine AgNPs with growth factors or antibiotics for synergistic action.
- **Electrospun nanofibers:** polymer mats impregnated with AgNPs (with or without antibiotics) offer high surface area and controlled delivery.
- **Sprayable colloids:** allow easy coverage of irregular wounds and rapid antimicrobial activity.
- **Composite materials:** AgNPs grafted onto halloysite nanotubes or incorporated into temperature-responsive polymers enable stimuli-responsive release. Green synthesis using plant extracts improves biocompatibility and reduces environmental impact.

Emerging technologies include 3D-printed nanocomposite scaffolds and smart dressings responsive to wound biomarkers (e.g., MMP-9 or pH) that adjust Ag^+ release and provide feedback on healing status.

Figures

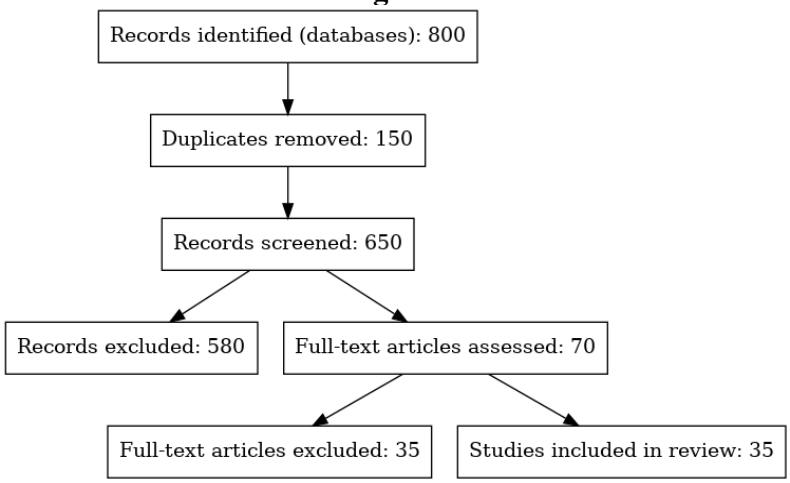


Figure 2. PRISMA 2020 flow diagram of study selection. A total of 800 records were identified; after removing 150 duplicates, 650 titles and abstracts were screened, 70 full-text articles were assessed, and 35 studies met inclusion criteria.

Discussion

The promising dual-action strategy of silver nanoparticles (AgNPs) in the management of diabetic foot ulcers (DFUs) and wet gangrene is demonstrated in this systematic review. AgNPs battle infection while concurrently activating repair pathways. Further discussion of the results follows, focusing on the following areas: processes, comparative performance, safety concerns, evidence gaps, and potential future study avenues.

Potential mechanisms and biological foundation

Systemic antimicrobials

The broad-spectrum antibacterial effect of AgNPs is one of the greatest arguments in favor of their usage in chronic wounds. Released silver ions (Ag^+) from nanoparticles bind to thiol groups in proteins, break down cell membranes, produce reactive oxygen species (ROS), and impair DNA/RNA replication and vital enzymes, among other bacterial targets [Ref 3, Ref 11, Ref 14]. Compared to classical antibiotics, AgNPs are less likely to acquire resistance due to their multi-modal processes [Ref 6, Ref 11]. The polymicrobial infections and biofilms prevalent in diabetic wounds make this broad-spectrum and multi-pronged antibacterial action all the more valuable.

Beneficial effects on the host

- In addition to their antimicrobial properties, AgNPs have the potential to stimulate the wound healing cascade. It is common for the inflammatory phase to remain unbroken in chronic wounds like DFUs. Both in vitro and in vivo investigations have demonstrated that AgNPs can:
- Reduce pro-inflammatory cytokines and modulate inflammation to promote cell proliferation [Ref 14, Ref 18, [4],
- Accelerate re-epithelialization and granulation tissue development by promoting the proliferation and migration of fibroblasts and keratinocytes [[6, [18],
- Promote angiogenesis and increase VEFG expression [[12, [18],
- Step up ECM remodeling and collagen deposition [[14, [18].

As an illustration, according to Reference [0search12], wound contraction was enhanced, neutrophil infiltration was reduced, levels of VEFG, IL-10, and TGF-β increased, while IL-6 was inhibited in a diabetic rat wound model that utilized cotton textiles loaded with silver. This provides more evidence that an appropriately engineered AgNP system can break the persistent "stall" state of wounds.

In contexts like DFUs, where infection and poor healing come together, AgNPs are particularly appealing due to their dual properties—antimicrobial and pro-repair.

Clinical data and comparative effectiveness

Comparative studies and meta-analyses

Several meta-analyses and clinical trials have found that silver-based dressings, especially those with nanoparticles, can improve DFU outcomes:

According to a meta-analysis of 18 trials including 1,825 participants, silver dressings reduced ulcer area, increased healing rates in DFUs, and decreased recurrence rates [[5]. The odds ratio was 2.14 with a 95% confidence interval of 1.52 to 3.00.

In contrast, AgNPs were not significantly better than traditional dressings in terms of DFU healing rates, according to a recent meta-analysis and systematic review of randomized controlled trials [[2]. While certain trials did favor AgNPs, the overall data remained ambiguous.

Although large-scale generalizations are not possible because to patient population and treatment protocol heterogeneity, specific comparative trials have shown that AgNPs (e.g., SilvrSTAT gel) compared favorably to standard care in terms of ulcer closure and area reduction. [[2 and[10].

Inconsistent evidence despite numerous studies pointing to a positive effect. Different results might be due to differences in:

- Size, structure, coating, and capping agents of nanoparticles
- Extra bioactive substances (growth factors, antibiotics, scaffolds, etc.) or payload,
- Rate of release (quick vs. steady),

- Wound setting (infection load, vascular supply, and severity),
- Various types of control dressings (saline, povidone iodine, and traditional varieties),
- Research methodology (number of subjects, use of blinding, length of time after the first assessment).

In particular, there has been evidence of synergistic benefit in preclinical and limited clinical contexts when AgNPs are used with growth factors, scaffolding materials, or other treatments. One tiny uncontrolled clinical trial found that using AgNP dressings in conjunction with epidermal growth factor (EGF) decreased dressing changes and healing time [[22].

Importance in clinical practice and concerns

In cases where AgNP-based treatments are superior to conventional dressings, the difference in absolute terms (e.g., number of days saved during healing) is not necessarily substantial. We still don't know if these benefits are worth the added complexity, risk, or expense. Furthermore, blinding and stringent controls are often missing from these trials, and many of them are tiny and underpowered.

Concerns regarding toxicity, safety, and translational hurdles

The effects of cytotoxicity and dosage

The "Achilles' heel" of AgNPs is their toxicity to host cells at greater concentrations, which is a severe constraint. Research in vitro has shown that keratinocytes, fibroblasts, endothelial cells, and macrophages can be subjected to apoptosis, decreased proliferation, increased reactive oxygen species (ROS), and impaired mitochondrial function at high concentrations of AgNPs [[6, [14]. Delays in epithelialization or tissue necrosis have been linked to higher dosages in certain animal studies.

Therefore, the therapeutic window is somewhat small: concentrations need to be high enough to kill microbes but not so high that they damage host cells. Quantum doping, surface charge, release kinetics, and capping agents all play a role in this equilibrium.

Methods to ensure a risk-free delivery

- To reduce the potential for toxicity, numerous research have used biocompatible carriers to implant AgNPs:
- Hyaluronic acid, pectin, chitosan, and gelatin are examples of natural polymers.
- The synthetic polymers PLGA and PCL are biodegradable.
- Structures, hydrogels, nanofibers, composite matrices
- These carriers are useful because they decrease the burst dose of silver ions, reduce their release, limit their systemic absorption, and localize their distribution to the wound bed [4], [18]. One example is the use of chitosan hydrogel frameworks with AgNPs incorporated in them; this substantially reduces cytotoxic exposure while maintaining antibacterial activity.
- But even with these solutions, the question of long-term safety is still unanswered. Rarely do human studies document argyria, tissue deposition, systemic silver levels, or delayed organ effects. A major worry is cumulative exposure for long-term wounds like DFUs, which can necessitate treating multiple times or for an extended period of time.
- Issues with regulation, production, and scalability

There are other practical challenges to bringing AgNP treatments into clinical practice:

- Standardization and reproducibility: synthesizing nanoparticles at scale presents unique challenges due to the need to achieve uniformity in size, shape, surface chemistry, and release profiles.
- Formulations must have a long shelf life, be sterile, and keep working even after being stored for a long period.
- Manufacturing costs could rise because to the complexity and use of sophisticated nanomaterials, growth factor loading, or combination designs.
- Rigid trials, pharmacokinetics, and post-market surveillance are regulatory approaches that are necessary to prove safety and efficacy in human subjects.

- Disadvantages of the current research and this evaluation

Several major shortcomings exist in the present evidence base:

Pilot projects and small sample sizes

There is a danger of bias in many clinical studies since they are small ($n < 50$) and some of them do not use randomization or blinding.

Dissimilarities in research methods and outcomes

It is difficult to compare or meta-analyze studies since their definitions of "healing" vary (e.g., percentage area reduction, time to full closure, granulation rate).

Diverse contexts and comparisons

Different trials may use different "control" treatments, such as saline, povidone-iodine, or non-silver dressings, which can affect the relative magnitudes of effects.

Very brief periods of follow-up

The late recurrence, wound breakdown, or long-term safety impacts go unreported because many studies only monitor results over weeks.

Laboratory/animal focus

Data on mechanisms and effectiveness are largely derived from studies conducted in cell cultures or in animals. When it comes to vascular insufficiency, neuropathy, comorbidities, and microbial biofilms, they might not completely replicate the pathophysiology of diabetic wounds in humans.
The pharmacokinetic and long-term safety evidence is lacking. Not many studies have measured silver levels in the blood or the effects of poisoning over the long term in humans.

Bias in publishing and exaggerated claims.Some meta-analyses have raised the worry that the publication rate of negative or null studies may be low, leading to an exaggeration of the trials' apparent efficacy. [5] and[16].With these disclaimers in mind, we can nevertheless say with some confidence that AgNP-based treatments merit more research and high-quality clinical trials.

Possible outcomes and avenues for exploration

- The following strategic paths are worth pursuing, although they are fraught with danger:
- For the sake of consistency and future comparisons, it would be helpful if studies reported comprehensive nanoparticle properties such as size, charge, coating, and ion release profile
- For optimal efficacy with minimal toxicity, rational formulation and optimization are of the utmost importance. This includes methodically optimizing the dosage, release kinetics, and carrier matrix.
- Initial investigations suggested that combining AgNPs with growth factors, peptides, pro-angiogenic drugs, or even gene therapy could lead to synergistic advantages. This suggests the possibility of building combination or multifunctional systems. [22].
- Confirmation of efficacy and safety requires large-scale, multicenter clinical trials: randomized controlled trials (RCTs) with sufficient power, standardized endpoints, sufficient follow-up, and blinded evaluation.
- Pharmacokinetics (silver levels in blood and tissues), biodistribution, and longer-term monitoring (for things like the presence of argyria or organ deposits) should all be a part of future trials to ensure safety.
- Justification of use in settings with limited resources requires cost-effectiveness assessments that compare the costs per healed ulcer, the reduction of hospitalizations, and the improvements in quality of life.
- Along with research, there must be regulatory and translational planning. This includes getting involved with regulatory frameworks early on, validating sterility, quality assurance, and scale-up production.

Summary

Overall, AgNP-based therapies and dressings provide an attractive "two-pronged" strategy for DFUs, combating infection while simultaneously facilitating wound healing. Their ability to decrease problems and speed healing beyond what standard dressings do has been supported by preclinical and early clinical studies. Unfortunately, there is a lack of safety data, inconsistent formulations, and conflicting human evidence. Future research should center on conducting thorough studies, developing standardized formulations, ensuring translational feasibility, and ensuring long-term safety in order to fulfill the potential of AgNPs in the treatment of DFU/wet gangrene.

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