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Review Article

Long-Term Follow-Up of gold nanoparticle-based therapy for chronic wounds

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Abstract

Background: Gold nanoparticles combine photothermal, antibacterial, and immunomodulatory properties, making them a studied platform for chronic wounds, which affect 6.5 million US patients and cost over \$25 billion annually [1].

Objective: This review synthesizes evidence on gold nanoparticle-based therapy for chronic wounds, emphasizing long-term wound-healing efficacy and systemic biodistribution and safety.

Methods: We synthesized in vitro antibacterial studies, animal wound models, comparative metal nanoparticle reviews, and toxicological studies reporting biodistribution beyond the acute dosing window.

Findings: Gold nanoparticles disrupt bacterial membranes and metabolism [5,6], accelerate closure of infected and diabetic wounds combined with peptides or photothermal activation [13,20], and drive macrophage M2 polarization [21]; rodent studies show organ retention for weeks to months without an alarming toxicity signal [22,23,24].

Conclusions: Gold nanoparticle-based chronic wound therapies rest on a coherent preclinical literature, but genuine long-term follow-up remains the critical gap before mainstream use [3,4].

Keywords: gold nanoparticles; chronic wounds; wound healing; antimicrobial nanomedicine; biodistribution

1. Introduction

Chronic wounds, wounds that fail to progress through the normal stages of healing within an expected time frame, remain an underappreciated burden in contemporary medicine. In the United States alone, chronic wounds affect an estimated 6.5 million patients, and treating them consumes in excess of \$25 billion annually, a figure Sen and colleagues argued was still climbing faster than most other categories of chronic disease spending because of an aging population and rising rates of diabetes and vascular disease [1]. Diabetic foot ulcers, venous leg ulcers, and pressure injuries make up the bulk of this burden and share a common thread: a wound microenvironment locked in persistent inflammation, colonized by biofilm-forming bacteria that systemic antibiotics penetrate poorly, and starved of the angiogenic and re-epithelializing signals that drive normal repair.

Gold nanoparticles (AuNPs) have emerged over roughly the past fifteen years as an unusually versatile candidate for interrupting that cycle. Their appeal rests on properties few other materials combine in one platform: a tunable localized surface plasmon resonance that converts near-infrared light into localized heat for photothermal antibacterial ablation, a large and chemically addressable surface for peptides, antibiotics, growth factors, or polysaccharide coatings, intrinsic antibacterial activity operating through mechanisms distinct from conventional antibiotics, and, in most formulations studied to date, favorable biocompatibility relative to silver or copper nanoparticles [2,3,4]. Reviews of inorganic nanomaterials for wound repair have consistently placed gold among the most actively investigated platforms, citing low intrinsic cytotoxicity, straightforward surface chemistry, and a reported ability to modulate the inflammatory and angiogenic phases of healing directly, not merely to suppress bacterial load [3,4].

What the field has lacked, and what motivates this review,

is a synthesis focused on the long-term evidence: what happens to gold nanoparticle-based wound therapies, and to the animals or patients who receive them, beyond the two-to-three week endpoints that dominate most efficacy studies. This review synthesizes the evidence on gold nanoparticle-based therapy for chronic wounds across three threads: the antimicrobial and antibiofilm mechanisms that make AuNPs attractive for infected, non-healing wounds; the preclinical evidence for accelerated wound closure; and what is known about the long-term biodistribution and safety of gold nanoparticles once introduced into a healing wound bed.

2. Methods

We synthesized peer-reviewed studies addressing gold nanoparticle-based interventions for wound healing, drawing on in vitro antibacterial mechanism studies, animal models of acute, diabetic, and chronic infected wounds, comparative reviews of metal nanoparticles used in wound care, and pharmacokinetic and toxicological studies reporting long-term biodistribution of gold nanoparticles in vivo. Sources were identified through the published nanomedicine and wound-care literature spanning approximately 2009 through 2026, with priority given to studies reporting a defined follow-up period, a quantifiable wound-healing or antibacterial endpoint, or systemic distribution data beyond the acute dosing window. Case reports, non-peer-reviewed preprints, and studies not involving gold as the primary nanomaterial were excluded except where used explicitly as a comparator (silver or copper nanoparticles). Because the literature is heterogeneous in particle size, surface coating, animal model, and follow-up duration, this review is a narrative synthesis rather than a pooled meta-analysis, and outcomes are presented as described in the source study rather than re-derived.

3. Results

Antimicrobial and antibiofilm mechanisms of gold nanoparticles



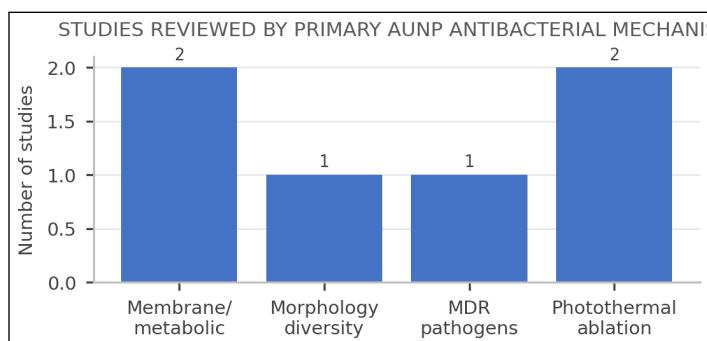


Figure 1: Number of studies reviewed here by primary gold nanoparticle antibacterial mechanism against wound-relevant pathogens, spanning direct membrane/metabolic disruption, engineered nanostructure morphology, activity against multidrug-resistant organisms, and near-infrared photothermal ablation [5,6,7,8,9,10].

Unlike silver, whose antibacterial activity is driven substantially by sustained release of Ag⁺ ions, gold nanoparticles act mainly through direct physicochemical interaction with the bacterial cell envelope and intracellular machinery, an important distinction for a material intended to sit in a wound bed for an extended period. Ortiz-Benítez and colleagues characterized this directly in *Streptococcus pneumoniae*, showing that gold nanoparticle exposure disrupted membrane integrity and altered central metabolic pathways distinct from conventional antibiotics, supporting AuNPs as a strategy less likely to select for cross-resistance with existing antimicrobial classes [5]. A metabolomic analysis by Gong and colleagues mapped the specific bacterial metabolic pathways disrupted by gold nanoparticle exposure at the molecular level, reinforcing that the antibacterial effect operates independently of the membrane-permeabilization mechanisms most antibiotics rely on [6]. Broader surveys of gold-based nanostructures have catalogued engineered morphologies, rods, stars, cages, and clusters, each tuned for a balance of antibacterial activity and biofilm penetration [7], and a review focused on multidrug-resistant pathogens concluded that gold and silver nanoparticles remain among the few platforms with reproducible activity against resistant Gram-positive and Gram-negative organisms without inducing the resistance

mechanisms that limit small-molecule antibiotics [8] (Figure 1).

Photothermal activation adds a physically orthogonal mechanism particularly relevant to biofilm-associated infection, since biofilm matrices are notoriously difficult for antibiotics or ion-release-based antimicrobials to penetrate. Hajfathalian and colleagues showed that theranostic gold-in-gold cage nanoparticles, activated with near-infrared light, achieved photothermal ablation of established bacterial biofilms while simultaneously enabling photoacoustic imaging of the treated site [9]. Xu and colleagues functionalized gold nanorods with an antimicrobial peptide and coupled that chemistry to near-infrared photothermal therapy, reporting more effective wound healing than either component alone in an infected wound model [10]. Taken together, this work supports gold nanoparticles as a multimodal antibacterial platform, tunable toward direct contact killing, photothermal ablation, or both, which matters for chronic wounds where the causative organism and biofilm burden are rarely known in advance (Figure 1).

Accelerating wound closure: preclinical and translational evidence

The largest body of gold nanoparticle wound-healing evidence comes from animal models of impaired, infected, or diabetic wounds, deliberately compromised to mimic the clinical chronic-wound population. Mendes and colleagues, using a chronic wound model induced with the TLR7/8 agonist resiquimod to reproduce the persistent inflammatory phenotype of non-healing human wounds, found that green-synthesized gold nanoparticles accelerated closure and reduced oxidative-stress markers relative to untreated controls, one of relatively few studies using a genuinely chronic rather than acute wound model [11]. The same group had earlier reported that combining photobiomodulation with hyaluronic acid-linked gold nanoparticles produced a healing benefit greater than either intervention alone,

suggesting AuNPs can act as an adjuvant that potentiates already-established wound therapies rather than only as a stand-alone agent [12].

Diabetic wound models, combining impaired angiogenesis, chronic inflammation, and polymicrobial infection, have been a particularly active area. Wang and colleagues engineered gold nanoparticles carrying an antimicrobial peptide and a gene-delivery payload, reporting accelerated closure of infected diabetic wounds from the combined bactericidal and pro-regenerative effect [13]. Zheng and colleagues used chirality-engineered gold nanoparticles to modulate immunometabolic crosstalk in the diabetic wound microenvironment, reporting improved healing linked to a shift in local immune cell metabolism [14]. Salama and colleagues combined curcumin with gold nanoparticles and reported enhanced antibacterial efficacy alongside improved healing metrics in diabetic rats compared with either component alone [15], and Meng and colleagues showed that chitosan-modified gold nanoparticle hydrogels achieved significant efficacy against diabetic wounds infected with antibiotic-resistant bacteria [16].

Formulation strategies have converged on hydrogel and dressing platforms combining a gold nanostructure with a second functional material. Wu and colleagues built a photothermal hydrogel with gold nanoparticles and an N-halamine polymer, reporting effective closure of infected skin wounds under near-infrared activation [17]. Zhao and colleagues combined gold-decorated halloysite nanotubes with a chitin hydrogel, reporting antibacterial and hemostatic activity for wounds with active bleeding [18], and Cai and colleagues developed a gold nanocluster-complexed dressing reporting near-instant closure of infected wounds [19]. Dar and colleagues cloaked cytokine-functionalized gold nanoparticles in an erythrocyte membrane coating to create a localized, controlled inflammatory stimulus that accelerated closure without the systemic response free cytokine delivery

would risk [20].

Immunomodulatory effects: macrophage polarization and inflammation resolution

A chronic wound is, in large part, a wound stuck in the pro-inflammatory M1 macrophage phase, unable to transition to the pro-resolving, tissue-remodeling M2 phenotype that normal healing requires. Several of the studies above attribute part of the observed healing benefit to gold nanoparticles' effect on this transition rather than to antibacterial killing alone. Peilin and colleagues showed this directly, reporting that gold nanoparticles of a defined size promoted M2 macrophage polarization while simultaneously enhancing intracellular clearance of *Staphylococcus aureus*, coupling an immunomodulatory and an antibacterial mechanism within the same particle and cell population [21] (Figure 2). This dual action is mechanistically coherent with the erythrocyte-membrane-cloaked cytokine nanoparticle work above, where a controlled, localized inflammatory signal, rather than its wholesale suppression, was the therapeutic strategy [20], and with the chirality-engineered nanoparticle work in diabetic wounds, where benefit was attributed to a shift in immune cell metabolic state [14]. Broader reviews of nanomaterial-based wound therapeutics have highlighted this immunomodulatory axis as an increasingly central mechanism distinguishing next-generation nanoparticle dressings from earlier formulations built around antibacterial activity alone [4,3] (Figure 2).

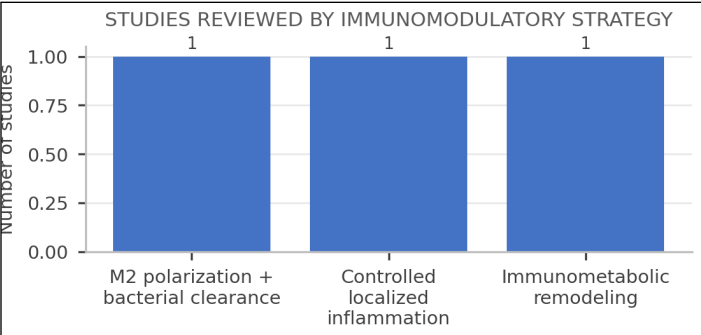


Figure 2: Number of studies reviewed here reporting each distinct immunomodulatory strategy by which gold nanoparticle formulations shift the chronic wound microenvironment away from a stalled pro-inflammatory state [21,20,14].

Long-term safety, biodistribution and persistence

What happens to gold nanoparticles after they have done their antimicrobial or pro-healing work, whether they are cleared, sequestered locally, or redistributed systemically, is the piece of the literature most directly relevant to genuine long-term follow-up, and it is markedly thinner than the efficacy literature reviewed above. Fraga and colleagues followed rats after a single intravenous dose of gold nanoparticles and reported that particles distributed predominantly to the liver and spleen, with concentrations declining only slowly, indicating meaningful retention in reticuloendothelial organs rather than rapid clearance [22]. Jakic and colleagues extended this to long-term accumulation, reporting that bovine serum albumin-coated gold nanoparticles remained detectable and produced measurable, generally modest, biological effects in the liver, spleen, and kidneys of mice well beyond the acute dosing window, underscoring that surface coating chemistry shapes both magnitude and duration of retention [23]. Xia and colleagues, examining cellular uptake and in vivo distribution across particle sizes and cell types, found both strongly size- and cell-type dependent, a finding relevant to wound formulations since smaller particles optimized for tissue penetration may also be most prone to systemic distribution and longer-term organ retention [24] (Table 1).

Table 1: Rodent studies of gold nanoparticle biodistribution and retention beyond the acute dosing window, summarizing formulation, principal organs of retention, and reported observation window [22,23,24].				
Study	Model / dosing route	AuNP formulation	Principal retention organs	Reported observation window
[22]	Rat, single intravenous dose	Citrate-stabilized AuNP	Liver, spleen	Short- and long-term (weeks to months)
[23]	Mouse, systemic dosing	BSA-coated AuNP	Liver, spleen, kidneys	Long-term, beyond acute dosing window
[24]	Multiple cell types, in vivo	AuNP across a size range	Size- and cell-type dependent distribution	Uptake through systemic distribution

Placed against the other metal nanoparticles proposed for the same indication, silver carries a well-documented risk of ion-release-driven cytotoxicity and argyria-like discoloration with prolonged use [25], and copper its own dose-dependent cytotoxicity that limits dosing [26]; the gold nanoparticle biodistribution literature, though limited in studies extending beyond a few months, has not reported an analogous toxicity signature at wound-formulation doses.

4. Discussion

The evidence assembled here supports a consistent, biologically coherent case for gold nanoparticles as a multifunctional chronic-wound therapeutic: they kill bacteria and disrupt biofilm through mechanisms distinct from conventional antibiotics, they can be engineered to shift the local immune environment from a stalled pro-inflammatory state toward a pro-resolving one, and, combined with a second modality such as photothermal activation or a peptide, they consistently outperform either component alone across the models reviewed here [13,20,10,17]. What the evidence does not yet support is a genuine long-term human follow-up literature: nearly every efficacy study identified reports outcomes measured in days to a small number of weeks, and almost none extend observation into the months-to-years timeframe

over which chronic wounds actually recur.

The biodistribution literature partially fills that gap but does not close it. Studies in rodents consistently find gold nanoparticles retained in the liver and spleen for weeks to months after systemic administration, with degree and duration of retention shaped strongly by particle size and surface coating [22,23,24]. That is reassuring in that no study reviewed here reported a toxicity signal severe enough to halt development, but it is a different question from whether a formulation applied topically and repeatedly to an open chronic wound over months of treatment, the realistic clinical use case, behaves the same way as a single intravenous dose; topical application, repeated dosing, and an already-compromised skin barrier could plausibly alter systemic uptake relative to the studies that dominate the current literature, and this is, in our view, the most important open question before gold nanoparticle dressings can be positioned for the extended, real-world chronic wound management that conditions like diabetic foot ulceration actually require. Because silver dressings have been in clinical use long enough to generate a well-characterized long-term signal, cytotoxicity, argyria, systemic accumulation [25], the relative reassurance from the gold nanoparticle biodistribution data reviewed here should be read as an absence of an alarming early signal rather than confirmation of safety at that same standard; the mechanistic diversity gold nanoparticles offer over single-mechanism metal nanoparticle dressings is a genuine advantage, but translating it into practice will require exactly the extended follow-up the literature has not yet produced at scale.

5. Conclusion

Gold nanoparticle-based therapies for chronic wounds are supported by a substantial and mechanistically coherent preclinical literature spanning direct antibacterial and antibiofilm activity, photothermal ablation of infected tissue, and immunomodulation of the stalled

inflammatory state characteristic of non-healing wounds. Formulations combining gold nanoparticles with a second functional element, a peptide, a photothermal trigger, a polysaccharide matrix, or a cytokine payload, consistently outperform single-mechanism controls across the models reviewed here. The evidence gap that remains, and that any credible long-term follow-up program must address, is genuine extended observation: rodent biodistribution studies suggest gold nanoparticles are retained in reticuloendothelial organs for weeks to months without an alarming toxicity signal at the doses studied, but almost no study reviewed followed a treated chronic wound, or its bearer, beyond a matter of weeks. Closing that gap with standardized, multi-month to multi-year follow-up protocols, tracking wound recurrence, scar quality, and systemic nanoparticle fate together, is the next necessary step before gold nanoparticle dressings can be positioned as a mainstream option for the millions of patients currently living with a chronic wound.

6. Acknowledgements

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8. Conflict of Interest

The authors declare no conflict of interest relevant to the content of this review.

9. Author Contributions

YH conceived the review and drafted the manuscript. JZ performed the literature synthesis on antimicrobial mechanisms and wound-closure evidence. FH contributed the analysis of long-term biodistribution and safety data and critically revised the manuscript. All authors read and approved the final version.

10. Ethics Statement

This article is a narrative literature review of previously published studies and did not involve new data collection from human or animal subjects; institutional ethics approval was therefore not required.

11. Data Availability

No new data were generated for this review. All findings discussed are drawn from the cited, publicly available published literature.

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