

Green-Synthesised Silver Nano-Conjugates in Advanced Topical Hydrogels: Mechanisms of Biofilm Disruption and Accelerated Wound-Healing Kinetics

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Abstract

Chronic, non-healing wounds impose a substantial clinical and economic burden worldwide, and multidrug-resistant bacterial biofilms are a principal driver of their persistence. This review examines whether green-synthesised silver nano-conjugates, delivered using polymeric hydrogel scaffolds, offer a valid route to biofilm control and tissue repair. The peer-reviewed literature on phyto-mediated silver nanoparticle synthesis, hydrogel scaffold design, nanoparticle-biofilm interaction and cutaneous repair was surveyed with emphasis on studies reporting mechanistic or in vivo endpoints. Plant secondary metabolites act as both reductants and capping agents, conferring colloidal stability and an organic corona that moderates the oxidative dissolution of the silver core. Embedding these nano-conjugates in hydrogel networks shifts release from burst dissolution toward swelling and diffusion-controlled processes, and several formulations are capable of stimulus-responsive behaviour. Reported antibiofilm activity is attributed to a combination of matrix penetration, membrane destabilisation, reactive-oxygen-species generation, and interference with quorum sensing and biofilm-regulatory gene expression. In animal models, hydrogel-delivered green silver systems accelerate closure and favour a pro-resolving immune phenotype. The results are preclinically encouraging but show heterogeneity in methodology due to batch-to-batch variability of plant extracts, inconsistent reporting of doses, and the absence of biofilm-specific clinical endpoints being the principal barriers to translation. Standardised extract characterisation and harmonised release and toxicity reporting are mandatory prerequisites for clinical evaluation.

Keywords: green silver nanoparticles; bioactive hydrogels; biofilm disruption; wound-healing kinetics; chronic wounds; nanotoxicology.

1. Introduction

Chronic cutaneous wounds like diabetic foot ulcers, venous stasis ulcers and pressure injuries affect a substantial and rising share of the global population, with chronic lower-limb and diabetic foot wounds estimated to affect up to 2.2% of people worldwide and diabetic foot ulcers alone carrying a lifetime incidence of roughly 19–34% among people with diabetes [1,2]. Their management consumes a disproportionate share of health-system expenditure, and recurrence rates remain high [1] among various populations. A major feature of non-healing lesions is colonisation by opportunistic pathogens that assemble into surface-adherent communities. Within a mature biofilm, bacteria are embedded in a self-produced extracellular polymeric substance (EPS) matrix that resists antimicrobial penetration, supports a metabolically dormant subpopulation that tolerates growth-dependent antibiotics, and facilitates horizontal transfer of resistance determinants [2,3].

Physiological heterogeneity and persister-cell formation contribute drastically to the development of resistance in biofilms.

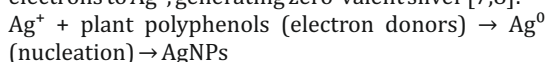
Silver has a long history in wound care. Contemporary silver dressings face critical limitations, including inconsistent ionic release and dose-dependent cytotoxicity toward keratinocytes and dermal fibroblasts. Furthermore, their application on large open wounds can lead to systemic absorption, with documented risks of hepatotoxicity and argyria [4,5]. Particle size is a determinant of mammalian toxicity, as 4.7 nm particles are markedly more toxic to normal human dermal fibroblasts than 42 nm particles at equivalent mass loading, an effect attenuated by antioxidant pre-treatment and therefore at least partly oxidative in origin [6]. Conventional chemical reduction compounds have these concerns as they leave residues of borohydride or comparable reagents on the particle surface [7].

Phyto-mediated or green synthesis offers an alternative in which plant extracts serve simultaneously as reductants and capping agents, yielding biologically coated nano-conjugates with lower reported mammalian toxicity [7,8]. Incorporating these particles into three-dimensional hydrogel networks addresses the second half of the problem, which is delivery, by maintaining a moist wound interface, absorbing exudate and regulating the diffusion of silver toward the biofilm-tissue boundary [9,10]. This review sets out the physicochemical basis of phyto-reduction and capping, the design logic of hydrogel vectors, the molecular mechanisms through which green silver nano-conjugates act on biofilms, and the host pathways implicated in accelerated repair. The review concludes with a critical assessment of the toxicological and manufacturing constraints that currently hinder the clinical use of these materials.

2. Phyto-Synthesis and Capping of Silver Nano-Conjugates

2.1 Phyto-reduction mechanisms

Green synthesis proceeds by a bottom-up route in which aqueous silver nitrate is combined with a crude botanical extract. Plant extracts supply polyphenols, flavonoids, terpenoids and soluble polysaccharides bearing hydroxyl and carbonyl functionalities of sufficiently low reduction potential to donate electrons to Ag^+ , generating zero-valent silver [7,8]:



The reaction proceeds in three stages as given below.

- **Activation /nucleation.** During this first step, reduction of silver ions produces a supersaturated population of free atoms which cluster into stable nuclei.
- **Growth.** In the growth phase, nuclei coalesce and enlarge by the process of Ostwald ripening, consuming the residual ionic silver.
- **Termination /stabilisation.** In the final stage, capping molecules adsorb to growing crystal facets, arresting growth and fixing the final size and habit.

This is affected by factors like reaction temperature, pH, extract concentration and contact time, which regulate nucleation and growth, and thereby the final size distribution of the particle and hence reproducibility is difficult to achieve across botanical batches [9,11].

2.2 Biological capping and interfacial stability

Chemically reduced particles generally require synthetic stabilisers such as polyvinylpyrrolidone to resist precipitation. But green-synthesised particles instead carry an endogenous biomolecular corona. This layer contributes steric hindrance and a strongly negative surface charge with zeta potentials more negative than -30 mV, indicating colloidal stability [7]. Flavonoid amide and carbonyl groups have high affinity for metal ions and can encapsulate the nascent particle, forming a shell that suppresses further aggregation [8]. The corona also mediates the interface with host tissue.

By slowing surface oxidation, it moderates the rate at which free Ag^+ is liberated, and this is the most credible explanation for the lower acute cytotoxicity reported for green versus chemically reduced preparations. Because the capping layer consists of pharmacologically active metabolites, the conjugates frequently retain intrinsic antioxidant and anti-inflammatory activity that may act additively with the silver core [8,12].

3. Architecture and Rheology of Hydrogel Vectors

3.1 Natural and synthetic polymeric scaffolds

Hydrogels suit topical deployment because their high-water content approximates the hydration of the extracellular matrix and sustains a moist wound interface [13]. The type of scaffold chemistries falls into two broad classes as given below.

- **Natural biopolymers.** Chitosan, sodium alginate, hyaluronic acid and collagen offer biocompatibility and biodegradability. Chitosan additionally presents a cationic backbone that interacts electrostatically with anionic bacterial envelopes, contributing intrinsic antimicrobial and haemostatic activity [13].
- **Synthetic polymers.** Polyvinyl alcohol, polyethylene glycol and poly(N-isopropylacrylamide) provide predictable and tunable mechanical strength, mesh size and swelling ratio. Recent practice involves combining the bioactivity of natural matrices with the mechanical reproducibility of synthetic ones like chitosan/poly(vinyl alcohol) and chitosan-alginate systems, which are loaded with green AgNPs [14,15].

3.2 Mechanical properties and exudate management

- **Shear-thinning behaviour.** Viscosity should fall under applied shear so that the gel can be extruded and spread across an irregular, tender wound bed, then recover its elastic modulus to remain *in situ*.
- **Water-vapour transmission rate (WVTR).** A rate of approximately $2000\text{--}2500 \text{ g m}^{-2} \text{ day}^{-1}$ is widely cited as the target range for a full-thickness dressing, balancing dehydration against maceration [14]. But usually reported values for real formulations often fall outside it; for example, AgNP-loaded chitosan/PVA films have been measured at $1389 \text{ g m}^{-2} \text{ day}^{-1}$, against $2778 \text{ g m}^{-2} \text{ day}^{-1}$ for the unloaded control, and chitosan-based systems have been reported between 2000 and $3500 \text{ g m}^{-2} \text{ day}^{-1}$ [13,14]. The range should therefore be treated as a design target rather than a specification met by most published materials. Porosity governs both exudate uptake and gas exchange, and interacts with WVTR: increasing crosslink density to slow silver release tends also to reduce vapour permeability, so the two cannot be optimised independently.

3.3 Controlled silver release kinetics

Unformulated nanoparticles applied directly to a wound are rapidly cleared and dissolve in a burst,

producing transient concentrations that are locally cytotoxic. Within a crosslinked network, release becomes matrix-controlled as water ingress relaxes and expands the polymer chains, opening diffusive pathways for both intact conjugates and liberated Ag^+ . Thus it follows a modest initial release and then a sustained delivery over days, and this is the mechanism by which hydrogels are intended to hold the interfacial silver concentration within a therapeutic window [9,14]. Some designs are stimulus responsive. Photo crosslinked silver/Aloe vera/silk fibroin hydrogels release more silver under the acidic conditions that characterise a chronically infected wound, and carboxymethyl cellulose/Aloe vera/tannic acid networks show tunable pH-dependent release [16,17]. Such systems, in principle, couple dose to infection burden, though no comparative *in vivo* study has yet demonstrated that responsiveness improves outcomes over a well-tuned sustained-release control.

4. Molecular Mechanisms of Biofilm Disruption

Hydrogel-mediated delivery assists green silver nano-conjugates in overcoming three successive barriers, namely the matrix, the envelope and the regulatory circuitry of the resident population.

4.1 Penetration of the EPS matrix

The EPS matrix comprises exopolysaccharides, proteins and extracellular DNA and these sequester antimicrobials [3]. Transport of nanoparticles through it is governed by size-dependent steric filtering, electrostatic interaction with the predominantly anionic matrix, and specific chemical interactions, nanoparticle size, surface charge, shape and hydrophobicity, etc and therefore they all determine the penetration [3]. The biological corona of green AgNPs is relevant here because colloidal stability determines whether particles reach the matrix as individual objects or as aggregates too large to enter. Aggregation at the biofilm surface is a recognised failure mode for poorly stabilised preparations. Small, well-dispersed particles diffuse through the aqueous channels of the matrix and can reach the deep, metabolically quiescent persister population that underlies recurrent infection [3,18].

4.2 Antimicrobial cascade and intracellular damage

On reaching the cell envelope, the conjugates initiate a multi-target cascade [8,18,19]:

- **Membrane destabilisation.** Electrostatic association with lipopolysaccharide in Gram-negative organisms and teichoic acids in Gram-positive organisms alters membrane potential, producing structural deformation, pitting and leakage of cytoplasmic contents.
- **Oxidative stress.** Intracellular Ag^+ inactivates respiratory-chain enzymes and drives overproduction of reactive oxygen species, including superoxide and hydroxyl radicals, initiating lipid peroxidation and compounding envelope damage [18,20].

- **Protein and nucleic acid damage.** Silver ions bind avidly to sulfhydryl groups on metabolic enzymes, causing misfolding and inactivation, and interact with phosphate moieties in bacterial DNA, condensing the nucleoid and impeding replication and transcription [12,18].

These pathways interact in such a way that oxidative damage to the cell envelope increases ion influx, which further raises intracellular oxidative stress. Whether toxicity is primarily driven by the nanoparticle itself or its released ions remains debated, and this balance likely depends on particle size, surface capping, and the surrounding medium.

4.3 Quorum sensing and biofilm gene regulation

Beyond direct bactericidal action, green AgNPs interfere with quorum sensing, the density-dependent signalling that coordinates matrix production and virulence. In *Pseudomonas aeruginosa*, sub-inhibitory concentrations of biosynthesised AgNPs suppressed biofilm formation by 78% and reduced expression of *algC*, *pslA* and *pelA* by 77%, 83% and 68% respectively, with attenuation of quorum-regulated phenotypes including elastase, protease and pyocyanin production [21]. Glutathione-stabilised green AgNPs likewise modulate *lasI* and *lasR* expression [22].

In *Staphylococcus*, the *icaADBC* operon encodes the machinery for polysaccharide intercellular adhesin, the principal structural component of biofilm matrix. Swolana et al. [23] reported that nanosilver reduced viability at $5 \mu\text{g mL}^{-1}$ and biofilm formation at $3 \mu\text{g mL}^{-1}$ in *Staphylococcus epidermidis*, but that expression of *icaADBC* and its repressor *icaR* varied with both strain and dose as low concentrations in some cases associated with increased biofilm production showing sub-therapeutic silver at the biofilm interface may promote rather than suppress matrix synthesis.

5. Wound-Healing Kinetics

5.1 Modulation of the inflammatory phase

Chronic wounds are characteristically arrested in a prolonged inflammatory state marked by elevated tumour necrosis factor- α and interleukin-6 and by excess matrix metalloproteinase (MMP) activity. Whereas ionic silver can aggravate local irritation, the antioxidant phytochemicals retained in the capping layer act as radical scavengers and reduce oxidative load in the wound bed [8,12]. Lower oxidative stress is associated with attenuated NF- κB signalling and a shift in macrophage phenotype from pro-inflammatory M1 toward reparative M2. The silver/Aloe vera/silk fibroin hydrogels produced an early M2-dominant profile in full-thickness rat wounds [16]. The specific attribution to NF- κB , however, is inferential in most AgNP studies and warrants direct pathway analysis.

5.2 Proliferation and re-epithelialisation

During proliferation, the hydrogel supplies a moist, compliant substrate that supports keratinocyte and fibroblast migration. Green AgNPs have been reported to promote fibroblast proliferation and migration *in vitro* and to increase collagen deposition *in vivo* [16,24].

Upregulation of vascular endothelial growth factor and fibroblast growth factor, and consequent capillary ingrowth, is the mechanism usually invoked for improved granulation; revascularisation was directly observed in the silver/Aloe vera/silk fibroin model [16]. The concentration remains as a decisive factor as the same particles that stimulate fibroblasts at low dose can be cytotoxic at higher dose [5,6].

5.3 Remodelling and scar mitigation

The final phase requires organised deposition and maturation of the new matrix. Unregulated healing yields disordered, hyper-dense collagen and a rigid scar. By influencing the balance between MMPs and their tissue inhibitors, silver-containing hydrogels have been associated with more orderly conversion of type III to type I collagen and with fibre alignment parallel to the epidermal plane, improving tensile properties and limiting scar formation as reported for the photo-crosslinked silver/Aloe vera/silk fibroin system [16]. Franková et al. [5] showed that AgNPs alter interleukin, growth-factor and MMP secretion by human fibroblasts and keratinocytes in an *in vitro* wound model, providing a cellular basis for these observations, though the direction of effect was dependent on both the dose and the cell-type.

6. Toxicology, Biocompatibility and Translational Obstacles

6.1 The therapeutic window

In every product with human applications, the major question is regarding its safety. Green synthesis lowers but does not abolish toxicity, which is in turn dependent on dose, size and coating [4,6]. The reported adverse effects vary significantly across cell lines, ranging from approximately 3 to 144 ppm in a single comparative series [25] and therefore defining a universal safety threshold is inappropriate. Instead, an effective formulation must maintain an interfacial concentration that exceeds the minimum biofilm eradication concentration for target organisms while remaining below the cytotoxic threshold for keratinocytes and fibroblasts. Finally, because systemic absorption from large open wounds can cause hepatic and renal accumulation, formulations must be designed to explicitly prevent systemic exposure [25].

6.2 Scale-up, standardisation and regulatory readiness

The principal obstacle to commercial green synthesis is batch-to-batch variability. Phytochemical composition varies with species, provenance, season, growth conditions and extraction protocol, and this propagates directly into nanoparticle size, capping density and release kinetics; reproducibility, purity and scalability are consistently identified as the limiting factors [7,9]. The problem is not unique to green routes as a multi-laboratory study of forty-six batches of OECD priority nanomaterials found substantial variability even in conventionally synthesised particles, and traced much of the divergence in reported biological effect to impurities and agglomeration rather than to intrinsic particle properties [26]. This finding emphasizes the importance of carrying out physicochemical characterisation irrespective of route or method of synthesis. Regulatory approval will require standardised botanical sourcing with documented chemotype, validated analytical control using high-performance liquid chromatography for extract fingerprinting, dynamic light scattering and electron microscopy for size and dispersity, inductively coupled plasma methods for total silver and demonstrated consistency of release kinetics across production runs.

6.3 Limitations of the current evidence base

Three limitations recur across the literature summarised in Tables 1 and 2. First, dose metrics are inconsistent as results are variously expressed as total silver, nanoparticle mass or extract equivalent, which impedes cross-study comparison. Second, most *in vivo* models use acute excision or burn wounds in healthy animals, which recapitulate neither the microbial complexity nor the impaired host physiology of a chronic human ulcer, diabetic and biofilm-inoculated models are used far less often. Third, clinical evidence is essentially absent as no randomised trial of a green-synthesised silver hydrogel with biofilm-specific endpoints has been reported, and the diabetic foot ulcer literature identifies the lack of biofilm-specific endpoints and validated bedside biofilm diagnostics as a general gap [2].

7. Comparative Analysis

Tables 1 and 2 summarise representative matrix designs and biological outcomes.

Table 1: Representative polymeric hydrogel matrices for green silver nanoparticle delivery

Matrix composition	Crosslinking / fabrication	Reported release or physical behaviour	Reported biological outcome	Reference
Pluronic F127 hydrogel with <i>Azadirachta indica</i> -AgNPs	Thermoresponsive sol-gel	Topically retained gel depot; sustained antibacterial and antioxidant effect relative to leaf extract alone	Improved wound contraction in mice; no signs of skin irritation	[24]
Chitosan / polyvinyl alcohol film with green-synthesised AgNPs	Solvent casting	Gradual AgNP release with plateau; WVTR 1389 g m ⁻² day ⁻¹ for AgNP films vs 2778 g m ⁻² day ⁻¹ for control	Activity against <i>E. coli</i> and <i>S. aureus</i> ; ~82% viability for Aloe vera-AgNP films	[14]
Chitosan-alginate hydrogel with green AgNPs	Ionic / polyelectrolyte complexation	Matrix-retained nanoparticles for topical delivery	Antibacterial activity proposed for wound-healing application	[15]
Carboxymethyl cellulose / Aloe vera / tannic acid with green AgNPs	Chemical crosslinking	pH-responsive release of tannic acid; storage modulus up to 4555 kPa	Non-cytotoxic to human fibroblasts	[17]
Silk fibroin / Aloe vera composite with AgNPs	Photocrosslinking	pH-responsive release; greater AgNP release under simulated chronic-infection conditions	Antibacterial, cytocompatible, pro-migratory <i>in vitro</i>	[16]
Polyacrylamide and related synthetic networks with green AgNPs	Various	Release governed by nanoparticle size and matrix crosslink density	Broad antibacterial activity without loss of keratinocyte viability	[9]

Table 2: Representative green-synthesised silver nanoparticle systems- sources, models and reported antibiofilm or wound-healing outcomes

Biological source	Model / test system	Target organisms	Reported outcome	Reference
<i>Azadirachta indica</i> (neem) leaf	Mouse excision wound; PF127 hydrogel	Gram-positive and Gram-negative isolates	Improved wound contraction rate; no skin irritation; no significant developmental toxicity in the <i>Drosophila</i> feed assay	[24]
<i>Aloe vera</i> + silk fibroin	Full-thickness cutaneous wound, rat	Common wound pathogens	97.0% closure at day 21, exceeding silver sulfadiazine cream; early M2 macrophage shift, revascularisation and reduced scarring	[16]
<i>Nepeta cataria</i> (catnip)	Excision wound model, rat	<i>E. coli</i> , <i>S. aureus</i> , <i>E. fecalis</i>	Faster closure and improved histological scores versus untreated controls	[27]
<i>Camellia sinensis</i> (green tea)	Clinical isolates; CLSM biofilm assay	Bacterial and fungal clinical isolates	MIC 31.25–62.5 $\mu\text{g mL}^{-1}$ (bacteria) and 125–250 $\mu\text{g mL}^{-1}$ (fungi); confirmed antibiofilm activity	[28]
<i>Eucalyptus globulus</i> leaf	Clinical isolates; <i>in vitro</i> biofilm	MDR clinical isolates	Antibacterial and antibiofilm activity of microwave-assisted green AgNPs	[29]
<i>Desertifilum</i> sp. (cyanobacterium)	<i>In vitro</i> , molecular and morphological analysis	Methicillin-resistant <i>S. aureus</i>	ROS-mediated suppression of biofilm formation and virulence gene activity	[20]
<i>Teucrium polium</i>	Sub-MIC exposure; RT-qPCR	<i>P. aeruginosa</i> PAO1	78% biofilm suppression at 50 $\mu\text{g mL}^{-1}$; <i>algC</i> , <i>pslA</i> and <i>pelA</i> downregulated by 77%, 83% and 68%	[21]

8. Conclusion and Future Perspectives

Integrating green-synthesised silver nano-conjugates into polymeric hydrogels is a promising therapeutic for two distinct problems, which are the tolerance of wound biofilms to conventional antimicrobials, and the narrow therapeutic window of ionic silver. The phytochemical component contributes to colloidal stability, moderated dissolution and residual antioxidant activity, whereas the hydrogel contributes to moisture control, exudate management and diffusion-limited release. Although preclinical results are consistent with both propositions, the gap between preclinical and clinical use needs to be addressed furthermore. First, stimulus-responsive networks that couple silver release to a wound-derived signal like local pH shift, bacterial enzyme activity or reactive oxygen species have to be aligned with well-tuned sustained-release controls. Second, dose–response reporting must extend across a concentration range wide enough to capture the paradoxical stimulation of biofilm synthesis observed at sub-therapeutic silver [23]. Third, efficacy should be evaluated in biofilm-inoculated wounds in impaired-healing models, with biofilm-specific endpoints, before clinical trials are contemplated.

Declarations

Ethics approval. Not applicable. This article is a review of previously published literature and does not report new studies involving human participants or animals performed by any of the authors.

Consent. Not applicable.

Conflict of interest. The author declares that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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