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Navigating The Duality of Silver Nanocomposites: Antimicrobial Promise Versus Cytotoxic Risks

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ABSTRACT

Silver nanocomposites (Ag-NCs) have garnered significant attention in recent years owing to their exceptional antimicrobial properties, which make them promising candidates for various biomedical applications. However, concerns regarding their potential toxicity and cellular compatibility persist. This review offers a comprehensive overview of the current status of Ag-NCs, covering their synthesis, characterization, and biological interactions. It examines the effects of Ag-NCs on cellular responses, including cytotoxicity, genotoxicity, and oxidative stress, alongside their potential applications in healthcare systems. The review also underscores the key factors influencing cellular compatibility, such as the size, shape, concentration, and surface chemistry of Ag-NCs. Furthermore, it identifies existing knowledge gaps and suggests future research directions to facilitate the safe and effective utilization of Ag-NCs in biomedical contexts. The literature search was performed using Google Scholar, Web of Science (WoS), and Scopus-indexed repositories. The objective of this review was to advance a comprehensive understanding of the complex interplay between Ag-NCs and biological systems, thereby supporting the development of Ag-NC-based biomaterials with optimal cellular compatibility.

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Introduction

Silver nanocomposites (Ag-NCs) have garnered significant attention in recent years due to their potent antimicrobial activity and versatile applications in biomedicine. These nanostructures, owing to their high surface area-to-volume ratio and unique physicochemical properties, have demonstrated remarkable efficacy in inhibiting the growth of bacteria, fungi, and viruses, positioning them as promising candidates for wound dressings, antimicrobial coatings, and drug delivery platforms (Pan et al., 2025; Wang et al., 2021). Their potential to combat multi-drug resistant pathogens is particularly noteworthy, as conventional antibiotics are increasingly compromised by resistance, highlighting the urgent need for alternative antimicrobial strategies.

Despite their promising antimicrobial properties, the clinical translation of Ag-NCs is limited by concerns regarding their cytotoxicity and cellular compatibility. The interaction of silver nanocomposites with biological systems is highly complex and can elicit adverse cellular responses, including oxidative stress, membrane damage, and apoptosis, which may compromise tissue viability and function (Malik et al., 2025; Sukumaran & Mansour, 2023). Such cytotoxic effects are influenced by multiple factors, including nanoparticle size, morphology, surface charge, concentration, and the presence of surface functional groups (El-Sayied Ali et al., 2024). Hence, a detailed understanding of these parameters is critical to ensure the safe application of Ag-NCs in biomedical contexts.

Balancing antimicrobial efficacy with biocompatibility remains a major challenge in the development of Ag-NC-based therapeutics. Recent research has emphasized strategies to mitigate cytotoxicity while retaining antimicrobial activity, such as surface functionalization with biocompatible polymers, incorporation into targeted delivery systems, and fine-tuning of physicochemical properties (El-Sayied Ali et al., 2024). Moreover, evaluating Ag-NC interactions across a variety of cell types—including epithelial, endothelial, and immune cells—is essential to predict in vivo behavior and optimize therapeutic outcomes.

This review aims to systematically examine the current understanding of the cellular compatibility of Ag-NCs, highlighting key factors that govern their biocompatibility and summarizing strategies employed to enhance their safety profile. By integrating insights from physicochemical characterization, in vitro cytotoxicity assessments, and in vivo studies, this work seeks to provide a comprehensive framework for the rational design of Ag-NCs that maximize therapeutic benefits while minimizing adverse effects. Such an integrative perspective is crucial for the safe and effective implementation of silver nanocomposites in clinical and biomedical applications.

Methods

This study is a review article conducted with the aim of providing a comprehensive overview of the applications, antibacterial properties, cytotoxicity, biocompatibility, and controlled-release potential of silver nanocomposites (Ag-NCs) in biomedical fields.

Search Strategy

A comprehensive and systematic literature search was conducted to capture up-to-date information on the biomedical applications and cellular compatibility of silver nanocomposites (Ag-NCs). Major scientific databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar, were systematically searched for relevant publications from January 2015 to May 2025, ensuring coverage of the most recent advances in the field.

To enhance search precision and comprehensiveness, both controlled vocabulary terms (MeSH) and free-text keywords were used in various Boolean combinations. Key search terms included: “silver nanocomposites,” “AgNPs,” “biomedical applications,” “antimicrobial activity,” “cytotoxicity,” “biocompatibility,” “controlled release,” “hydrogels,” “polymeric matrices,” “tissue engineering,” and “surface functionalization.” Boolean operators such as AND, OR, and NOT were employed to refine the search and reduce irrelevant results.

Additionally, reference lists of relevant articles were screened manually to identify further pertinent studies. Only original research articles, reviews, and experimental studies published in English were considered. Studies focusing exclusively on non-biomedical applications or lacking clear evaluation of cytotoxicity or biocompatibility were excluded. This approach ensured that the selected literature provided a robust and current foundation for analyzing both the therapeutic potential and cellular interactions of Ag-NCs in biomedical contexts

Study Selection and Screening Criteria.

Only studies published in English that directly investigated silver nanocomposites (Ag-NCs) within biomedical contexts including medicine, dentistry, tissue engineering, wound healing, implant coatings, and drug delivery systems were considered eligible. Included articles were required to provide experimental, analytical, or high-quality review data on key outcomes, such as antibacterial efficacy, cytotoxicity, biocompatibility, and physiological effects of Ag-NCs. Studies lacking clear evaluation of these parameters or focusing solely on non-biomedical applications were excluded to ensure relevance and reliability of the data.

Conversely, studies focusing solely on industrial or environmental applications, sources lacking scientifically verifiable data, non-peer-reviewed conference papers, and duplicate publications were excluded from the review.

Data Extraction and Analysis

From each selected study, the following core information was extracted: type of matrix (polymeric, ceramic, hydrogel-based, or hybrid), synthesis method of silver nanoparticles, biomedical application area, assessment methods for cytotoxicity and biocompatibility, and major outcomes.

These data were subsequently organized and analyzed using a descriptive and comparative approach to identify scientific trends, advantages, limitations, and current challenges within the field.

Qualitative and Comparative Evaluation

All eligible studies were critically appraised in terms of scientific quality, methodological rigor, model type (cellular or animal), citation impact, and novelty. The synthesized findings were further compared with review papers published between 2019 and 2025 to highlight existing research gaps and emerging directions for future investigation.

Results and Discusion

Positive Aspects and Potential Benefits

The proven antimicrobial properties of silver are often enhanced by incorporating silver nanoparticles (AgNPs) in a composite matrix. This encapsulation strategy improves the stability of AgNPs, enables controlled release of silver ions and ultimately increases antimicrobial efficacy (Azizi-Lalabadi et al., 2021; Isah et al., 2025). This enhanced performance is particularly beneficial in preventing infection and promoting tissue regeneration in various cellular environments (Nqakala et al., 2021), as AgNP-based composites can deliver antimicrobial agents directly to the site of infection or injury while minimizing negative effects on surrounding healthy cells (Barua & Buragohain, 2024; Tripathi & Goshisht, 2022). This targeted delivery approach is critical to achieving effective treatment outcomes and reducing the risks associated with systemic silver exposure.

Encapsulation of AgNPs in polymer, hydrogel or fibre matrices remains a predominant strategy to tune the release kinetics of silver ions and reduce direct particle-cell contact that promotes cytotoxicity; recent reviews and experimental reports show that polymer- and hydrogel-based AgNP composites achieve sustained release while maintaining bactericidal concentrations at wound sites. (Ahmad et al., 2024; Nešović & Mišković-Stanković, 2020). Embedding AgNPs in electrospun fibres, 3D-printed scaffolds or composite films has not only improved the mechanical integrity and handling of dressings, but also enabled spatially controlled release profiles that reduce the maximum silver exposure of host cells — a critical parameter when balancing antimicrobial efficacy and cytotoxicity in mammals (Astaneh & Fereydouni, 2024).

In addition to passive encapsulation, a growing

body of work (2023–2025) is exploring functionalisation and stimulation strategies — pH-, enzyme- or redox-dependent linkers, and PEGylation or biomolecule coatings — to achieve triggered Ag+ delivery to infected or inflamed microenvironments while sparing healthy tissue. These approaches aim to concentrate the antimicrobial effect where it is needed and minimize systemic release that contributes to off-target toxicity (Huang et al., 2022).

There is also growing evidence that compound platforms can synergise modes of action: Combining AgNPs with bioactive polymers, growth factors or other antimicrobial agents both broadens the spectrum against biofilms and modulates the inflammatory milieu to promote regeneration rather than chronic inflammation (Paladini & Pollini, 2019). However, reports vary widely in terms of materials, dosimetry and biological models — therefore claims of 'non-toxicity' or 'safety' need to be verified on a case-by-case basis with standardized dose measurements and relevant in vivo models (Sithole & Singh, 2024).

Finally, greener synthesis routes and biogenic capping agents continue to attract attention as they can alter the surface chemistry and biological interactions of AgNPs (sometimes reducing cytotoxicity), but environmentally friendly methods are not a panacea: physicochemical characterisation and comparative biological testing are still essential to determine the trade-off between safety and efficacy for any AgNP-composite proposed for clinical use (Motaleb et al., 2025).

Tunable Properties

The tunable properties of Ag-NCs offer a significant advantage for biomedical applications as they allow precise control over parameters such as size, shape, composition and surface functionalization (Dridi et al., 2024; Far et al., 2024). This high degree of customization allows researchers to optimize the material's interactions with cells, enhancing desirable properties such as cell adhesion, proliferation (Slepicka et al., 2015) and antimicrobial activity (Makvandi et al., 2020) while minimizing potentially cytotoxic effects (Harun-Ur-Rashid et al., 2025). By tailoring these parameters, Ag-NCs can be developed for specific applications such as targeted drug delivery (Tiwari et al., 2025), wound healing (Suvetha & Mani, 2024) or coating of implants (Qiu et al., 2025), improving efficacy and safety. The ability to fine-tune these properties ensures that the nanocomposites can be tailored to the unique requirements of different cellular environments and therapeutic targets.

The tunable properties of Ag-NCs have recently been utilised in several experimental platforms. For example, thermosensitive and polymer-based hydrogels loaded with AgNPs have demonstrated accelerated wound closure and potent antibacterial performance in vitro/in vivo: a 2023 collagen-based thermosensitive Ag hydrogel accelerated wound healing in a rat model while maintaining acceptable cytocompatibility, demonstrating how matrix selection and crosslinking influence both release kinetics and biological outcome (Amiri et al., 2023). Similarly, chitosan-g-PVA hydrogels with AgNPs showed broad antibacterial activity (E. coli, S. aureus) and promoted fibroblast responses in vitro as well as improved healing metrics in vivo, indicating the importance of polymer chemistry for cell-material interactions (Aldakheel et al., 2023).

Electrospun fibre membranes and composite films remain a widely used strategy to control AgNP presentation and mechanical properties: Recent experimental reports (2023–2024) show that embedding AgNPs in nanofibrous dressings or scaffold coatings improves handling and provides sustained antibacterial activity while allowing for tunable porosity and mechanical strength, parameters that directly impact cell adhesion and proliferation in wound/implant environments ((Akay & Yaghmur, 2024). For implant coatings, several studies (2023–2024) show that surface functionalisation (AgNP density, bonding chemistry) can significantly reduce bacterial colonisation and early biofilm formation on orthopaedic and dental substrates, although durability and long-term ion release under physiological stress remain open questions (Akay & Yaghmur, 2024).

Systematic studies from 2023–2024 report size-

and shape-dependent differences in cellular uptake, silver ion release and cytotoxicity, emphasising that small changes in synthesis or capping agents cause large changes in biological response. These reports highlight the need to report dose as surface area or Ag+ released (and not just mass) and to use standardized exposure metrics when comparing studies (Öztürk et al., 2024).

All in all, the recent experimental literature supports your assertion that tunability enables application-specific optimisation (drug delivery, wound healing, implant coatings). However — and this is important — many studies use different exposure metrics, models and endpoints (cell lines vs. primary cells; short-term vs. chronic in vivo assays), so claims of "reduced cytotoxicity" or "safety at therapeutic doses" need to be made cautiously and validated with standardized assays and relevant animal models before clinical translation.

Potential for Controlled Release

The composite matrix serves as an effective carrier for the controlled release of silver ions or nanoparticles, which is critical for maintaining sustained antimicrobial activity over time while minimizing toxicity (Ahmad et al., 2024; Dixit & Singh, 2025). This controlled release mechanism allows for a gradual diffusion of the silver species, reducing the risk of rapid bursts of high concentrations that can lead to cytotoxic effects on surrounding healthy tissue (Astaneh & Fereydouni, 2024; Mišković-Stanković & Atanackovic, 2024). Such a strategy not only prolongs antimicrobial efficacy but also improves biocompatibility, making it particularly suitable for biomedical applications such as wound dressings (Bonde et al., 2024), implant coatings (Liu et al., 2024) and scaffolds for tissue engineering (Naghib et al., 2024). Various composite matrices, including polymer (S. Chen et al., 2024), hydrogel and ceramic-based systems (L. Chen et al., 2024), have been explored to effectively modulate the kinetics of silver release (Tessema et al., 2024). It has been shown that tailoring the matrix composition and structure can optimize the balance between antimicrobial efficacy and cytocompatibility (A. B. Singh et al., 2024). This controlled release approach thus offers a promising avenue for the development of safer, more effective antimicrobial materials with long-term therapeutic benefits.

Composite matrices whether polymeric, hydrogel, ceramic, or hybrid provide an effective means of controlling the release of silver ions or nanoparticles, which is crucial for sustaining antimicrobial activity while avoiding cytotoxic peaks. For example, AgNP/PLGA scaffolds 3D-printed for bone repair showed an initial burst of silver ion release over approximately seven days, followed by a slower, sustained release up to 28 days. Importantly, cell viability (mouse pre-osteoblasts) remained high even in scaffolds with higher AgNP loading, demonstrating that controlled release can maintain antimicrobial efficacy without overt cytotoxicity (F. Chen et al., 2023). Similarly, electrospun polycaprolactone scaffolds doped with silver-modified hydroxyapatite showed substantial bacterial killing (E. coli, S. aureus) over multiple days while preserving mesenchymal stem cell viability and supporting osteogenic differentiation (Paterson et al., 2020). In wound-dressing contexts, injectable hydrogels formed via in situ green reduction of silver ions (e.g., carboxymethyl chitosan/dextran/dextran-aldehyde systems) demonstrated both potent broad-spectrum antimicrobial activity (>85% killing) and good cytocompatibility in vitro, owing to moderated Ag release rather than acute bursts (Zhao et al., 2025). In studies of chitosan-agarose matrices embedded with surface-capped PVA-AgNPs, sustained release in simulated wound fluid, low haemolysis, low cell mortality, and accelerated healing in vivo have also been demonstrated. (Sethuram et al., 2019). These examples collectively support the view that by tailoring matrix composition (polymer type, porosity, hydrophilicity, nanoparticle surface chemistry), one can modulate silver release kinetics to achieve a balance: sufficient release to suppress or kill pathogens over time but limited enough to avoid damage to mammalian cells or tissues. However, as systematic reviews highlight, considerable methodological variability remains (in release

measurement conditions and in model systems for cytotoxicity), which complicates comparisons and underlines the necessity for rigorous quantification of release under physiologically relevant conditions, along with correlated cytocompatibility assessments (Sánchez-Gálvez et al., 2024).

Enhanced Mechanical Properties

Certain composite materials can significantly improve the mechanical strength and stability of the final product compared to pure AgNPs, extending their suitability for structural applications in cellular environments (Abbas et al., 2024). The incorporation of silver nanoparticles into biocompatible matrices such as polymers, ceramics or hydrogels not only preserves or improves their antimicrobial properties, but also confers superior mechanical properties, including increased tensile strength, elasticity and durability (Mamidi et al., 2025; Roy et al., 2025). This reinforcement is particularly important for applications such as tissue scaffolds, implant coatings and wound dressings, where mechanical stability is critical for maintaining structural integrity under physiological conditions. By embedding silver nanoparticles in these composite scaffolds, it is possible to create materials that can withstand mechanical stress while exhibiting sustained antimicrobial activity, reducing the risk of material failure or degradation over time (Monte et al., 2023). Consequently, the development of such composite materials offers a promising strategy to combine antimicrobial efficacy with the mechanical robustness required for load-bearing or dynamic cellular environments, thereby expanding their potential biomedical applications.

Composite materials embedding silver nanoparticles (AgNPs) in biocompatible matrices (polymers, ceramics, hydrogels, or hybrid systems) have consistently been shown to enhance the mechanical strength and stability of the resulting constructs compared with unsupported AgNPs, thereby extending their suitability for mechanically demanding biomedical applications such as tissue scaffolds, implant coatings, and advanced wound dressings. Multiple recent reviews and experimental studies report that the inclusion of AgNPs particularly when combined with matrix-level design strategies such as double-network architectures, nanofiller reinforcement, or polymer-ceramic hybrids can increase tensile strength, toughness, and fatigue resistance while preserving or improving antimicrobial performance. Examples include AgNP-reinforced hydrogels and polymeric scaffolds that display higher fracture toughness and resilience under cyclic loading compared with Ag-free controls (Wang et al., 2024). Mechanistically, improvements result from (i) nanoparticle–matrix interfacial interactions that transfer and dissipate stress, (ii) filler-induced restriction of polymer chain mobility that increases modulus and yield strength, and (iii) hierarchical composite architectures (e.g., bioglass/AgNPs or β-TCP/gelatin composites) that combine bioactivity with structural support—findings supported by recent studies on bioactive glass/AgNP and gelatin/β-TCP/AgNP scaffolds developed for bone repair (I. Singh et al., 2025). Importantly, several reports demonstrate that matrix selection and processing (crosslink density, porosity, nanoparticle surface chemistry, and dispersion method) critically determine whether mechanical gains are achieved without sacrificing cytocompatibility or controlled silver release. Indeed, while some AgNP-containing films and hydrogels show simultaneous increases in tensile strength and acceptable cell viability, other studies reveal trade-offs (e.g., local stiffness increases that impair cell infiltration or heterogeneous particle agglomeration that creates stress concentrators), indicating that mechanical and biological endpoints must be co-optimised. (Feng et al., 2023). Finally, although the literature provides encouraging proof-of-concept studies for mechanically robust, antibacterial composites—including promising demonstrations using 3D printing and advanced hybrid hydrogels—reviews emphasise persistent gaps in standardised mechanical testing under physiologically relevant dynamic loads and in longitudinal in vivo evaluations of durability and host response. Addressing these gaps will be essential before such composites can be reliably deployed in load-bearing or long-term clinical applications (Astaneh & Fereydouni, 2024).

Challenges and Considerations

Cytotoxicity

Cytotoxicity remains a major concern with Ag-NCs, as silver ions can disrupt vital cellular processes, leading to oxidative stress, DNA damage and cell death (Yang et al., 2025). Factors influencing their cytotoxic effect include nanoparticle size, concentration, silver ion release rate, surface chemistry and the type of cells exposed. Smaller nanoparticles tend to penetrate cells more easily, increasing the risk of toxicity, while higher concentrations of silver can exacerbate cellular damage (Tripathy et al., 2025). In addition, the presence of reactive oxygen species (ROS) generated by silver ions can impair cell function (Cao et al., 2025). Therefore, optimization of silver content, control of release kinetics and surface modifications are essential strategies to minimize cytotoxicity while maintaining antimicrobial efficacy. Factors that influence cytotoxicity include:

Silver Nanoparticle Size and Shape

AgNPs size and shape critically influence their reactivity, biological interactions, and potential toxicity. Smaller nanoparticles, typically less than 10 nm, possess a larger surface area-to-volume ratio, which enhances their reactivity and antimicrobial efficacy but also increases their propensity to generate reactive oxygen species (ROS) and penetrate cellular membranes, thereby elevating toxicity risks(Cao et al., 2025; Nayef et al., 2025). Conversely, larger particles tend to be less reactive and exhibit reduced toxicity but may be less effective in biomedical applications (Roszkowski & Durczynska, 2025). The shape of AgNPs such as spherical, rod-shaped, or triangular also impacts their biological activity (Shahzadi et al., 2025); for example, triangular AgNPs have demonstrated higher antimicrobial activity due to their increased surface energy (Casals et al., 2025). In addition, anisotropic forms can affect cellular uptake and interaction with microbial membranes, affecting both efficacy and toxicity profile (Das et al., 2025; Eker et al., 2024). Therefore, careful control of the size and shape of nanoparticles is essential to optimize their biomedical benefits while minimizing adverse effects.

Concentration and Exposure Time

The cytotoxicity of Ag-NCs is generally dose- and time-dependent, meaning that higher concentrations and longer exposure increase the risk of cell damage (Zhu et al., 2025). At lower doses and shorter exposure duration, Ag-NCs can effectively target pathogens without damaging host cells, demonstrating the importance of optimizing concentration and exposure duration (Shi et al., 2024). Excessive or prolonged exposure can induce oxidative stress, DNA damage and apoptosis in healthy cells (Ghosh et al., 2024; Orta-García et al., 2015). Therefore, careful calibration of dosing and exposure duration is critical to maximize therapeutic benefits such as antimicrobial activity while minimizing cytotoxic effects. Establishing safe concentration thresholds and exposure limits is crucial for the clinical use of Ag-NCs.

Composite Matrix Composition

The composition of the composite matrix plays a crucial role in modulating the release of silver ions and nanoparticles, which has a direct impact on cell tolerance and therapeutic efficacy (Azizi-Lalabadi et al., 2021). Different matrix materials differ in their ability to control silver release. For example, biocompatible polymers such as chitosan, alginate (Wathoni et al., 2024) and collagen (Smola-Dmochowska et al., 2023) are often preferred because they provide sustained and controlled release and reduce cytotoxicity while maintaining antimicrobial activity. These polymers also promote cell adhesion and proliferation, thus improving biocompatibility. The chemical properties of the matrix, degradation rate and porosity influence silver ion diffusion, which must be carefully tuned to balance antimicrobial efficacy and minimise adverse effects on host tissue (Agarwalla et al., 2023). Table 1 below, outlined some of the frequently used matrices for incorporation of silver ions or AgNPs for the formulation of nanocomposites and how such composites are used for biomedical purposes.

Surface Functionalization

Surface modification of Ag-NCs with biocompatible molecules such as proteins or polymers can improve cellular interactions and reduce adverse effects. Coating Ag-NCs with biocompatible agents such as PEG (polyethylene glycol), collagen or albumin improves cellular adhesion and proliferation by creating a favourable interface (Bharatiya et al., 2023; Pan et al., 2025). In addition, such modifications can decrease non-specific protein adsorption and reduce cytotoxicity by stabilizing silver release and preventing aggregation (Abdelkawi et al., 2023). These surface modifications help to strike a balance between antimicrobial activity and biocompatibility, making Ag-NCs safer for biomedical applications.

Cell Type

Different cell types have different sensitivities to silver ions and nanoparticles, primarily due to differences in their membrane properties, metabolic activity and defense mechanisms. Mammalian fibroblasts, for example, are generally more tolerant to silver exposure compared to sensitive cell types such as keratinocytes or immune cells such as macrophages, which are more susceptible to silver-induced cytotoxicity (González-Fernández et al., 2025; Shrestha et al., 2021). This variability emphasizes the importance of selecting appropriate cell models for in vitro studies, especially in the development of biomedical applications such as wound dressings or implants targeting specific tissues. Considering silver concentrations and release profiles to the cell types relevant to the intended application can optimize antimicrobial efficacy while minimizing cytotoxic effects (Sánchez-Gálvez et al., 2024). Comprehensive testing on relevant cell lines is therefore essential to predict biocompatibility and ensure safety in clinical contexts.

Table1. Literature summary of some silver-based nanocomposites for biomedical applications

Matrix	Title	Application	Reference
Hydrogel	Silver nanoparticle-infused hydrogels for biomedical applications: A comprehensive review	Wound healing, drug delivery, antimicrobial coatings	(Albao et al., 2025)
Chitosan-Agarose	Effects and formulation of silver nanoscaffolds on cytotoxicity dependent ion release kinetics towards enhanced excision wound healing patterns in Wistar albino rats	Wound healing	(Sethuram et al., 2019)
Guar Gum	New Guar Biopolymer Silver Nanocomposites for Wound Healing Applications	Wound healing	(Ghosh Auddy et al., 2013)
Nanocellulose	Silver-Incorporated Nanocellulose Fibers for Antibacterial Hydrogels	Antibacterial hydrogels	(Shin et al., 2018)
Polymeric Scaffold	Synthesis and Characterization of Silver-Coated Polymeric Scaffolds for Bone Tissue Engineering: Antibacterial and In Vitro Evaluation of Cytotoxicity and Biocompatibility	Bone tissue engineering	(Khan et al., 2021)
Extracellular Matrix	Silver nanoparticles–decorated extracellular matrix graft: fabrication and tendon reconstruction performance	Tendon reconstruction	(S. Chen et al., 2023)
Mesoporous Silica	Mesoporous silica nanoparticles containing silver as novel antimycobacterial agents against Mycobacterium tuberculosis	Antimycobacterial therapy	(Montalvo-Quirós et al., 2021)

Mechanism of Toxicity

Understanding the mechanisms of toxicity of Ag-NCs is crucial for the development of strategies to reduce adverse effects. Current research suggests that silver induces oxidative stress, disrupts cell membranes and impairs mitochondrial function (Batir-Marin et al., 2025; Piao et al., 2024). However, the complex interactions between Ag-NCs and cellular metabolic pathways are not yet fully understood (Huang et al., 2025). Further studies are needed to clarify these mechanisms and to develop safer and more effective biomedical applications.

Long-Term Effects

While many studies focus on the immediate or short-term cytotoxic effects of Ag-NCs on cells, there is a significant gap in understanding their long-term effects. The potential for chronic toxicity, accumulation in tissues and possible delayed adverse effects remains largely unexplored. Such effects could have serious consequences for biomedical applications, especially with repeated or prolonged exposure. Therefore, comprehensive longitudinal studies are essential to evaluate the safety of Ag-NCs over longer periods of time, assess bioaccumulation risks and determine the potential for chronic health problems (Priya et al., 2025). These studies will help to ensure the safe development and use of Ag-NC-based materials in medical and consumer products.

Strategies To Enhance Cellular Compatibility

Biocompatible Matrix Materials

The use of biocompatible polymers or other suitable materials as a composite matrix is essential in the development of Ag-NCs. These materials serve as a protective barrier around the AgNPs, preventing premature release and reducing potential toxicity (Martínez-Cisterna et al., 2025). In addition, they help control the release rate of silver ions, which is important to maintain antimicrobial efficacy while minimizing adverse effects (Xiong et al., 2025). Similarly, the matrix can improve cellular adhesion and compatibility and promote better integration into biological tissues (Zahedah & Dinç, 2025). Overall, the selection of appropriate biocompatible materials improves the safety, efficacy and functionality of Ag-NCs in biomedical applications.

Surface Functionalization

Modifying the surface of Ag-NCs with biocompatible molecules such as proteins, peptides or polymers enhances their interaction with cells by increasing biocompatibility and promoting cellular uptake, which can improve their therapeutic or antimicrobial efficacy (de Oliveira et al., 2024; Pan et al., 2025; Suvetha & Mani, 2024). In addition, such surface modifications can form a protective layer around the nanoparticles, which reduces direct contact with cellular components and thus reduces toxicity (Haque et al., 2024). This approach not only helps to minimize unwanted biological reactions but also enables the targeted delivery and controlled release of silver ions, making Ag-NCs safer and more effective for biomedical applications.

Controlled Release Strategies

Controlling the release rate of silver ions or nanoparticles from the composite matrix is a crucial strategy to minimize cytotoxicity while maintaining antimicrobial efficacy. Rapid release of silver can lead to high local concentrations that are toxic to mammalian cells and cause adverse effects such as inflammation or cell death (Pletts & Burrell, 2025). Techniques such as incorporating silver into biodegradable polymers, encapsulating nanoparticles in layered or core-shell structures or modifying the surface chemistry of AgNPs can help to regulate the release profile (Harun-Ur-Rashid et al., 2025). For example, embedding AgNPs in a polymer matrix such as chitosan or PLGA allows a sustained and gradual release of silver ions over time, reducing peak concentrations that could be harmful to cells (Harun-Ur-Rashid et al., 2025). By fine-tuning these release mechanisms, it is possible to achieve a balance where antimicrobial activity is maintained without exposing tissue to cytotoxic levels of silver, thereby improving the safety and efficacy of silver-based biomaterials (Frippiat et al., 2025).

Optimization of Nanoparticle Properties

Careful control of the size, shape and concentration of AgNPs is crucial as these factors directly influence their cellular compatibility and biological interactions. Smaller AgNPs tend to have a higher surface area to volume ratio, which can enhance antimicrobial activity, but can also increase cytotoxicity if not properly regulated (Luo et al., 2024). Similarly, the shape of AgNPs affects their cellular uptake and reactivity. For example, spherical nanoparticles are generally more biocompatible than rod-shaped or triangular ones, which can induce more cellular stress (Duman et al., 2024). In addition, maintaining appropriate concentrations of nanoparticles is crucial. Higher concentrations can lead to increased release of silver ions, resulting in increased toxicity to human cells (Saker et al., 2024). Optimizing these parameters therefore ensures that AgNPs are effective against pathogens while minimizing adverse effects on healthy cells, enhancing their potential for biomedical applications (Sati et al., 2025).

Thorough In Vitro and In Vivo Testing

Rigorous testing with appropriate cell and animal models is a crucial step in evaluating the biocompatibility of Ag-NCs before they enter clinical use. In vitro cell studies allow researchers to evaluate cytotoxicity, cellular uptake, inflammatory responses and possible mechanisms

of toxicity at the cellular level. For example, human cell lines such as fibroblasts, keratinocytes and macrophages are commonly used to evaluate the cytocompatibility of Ag-NCs, providing insights into how these materials interact with different tissue types (Rosli et al., 2021; Zamel et al., 2023). These studies help to identify safe concentration ranges and surface modifications that minimize adverse cellular effects.

However, in vitro assessments alone cannot fully predict biological responses in living organisms. Therefore, in vivo animal models are essential for the evaluation of systemic toxicity, biodistribution, clearance, immunogenicity and long-term effects of Ag-NCs. Rodent models, such as mice and rats, are commonly used due to their cost-effectiveness and genetic similarity to humans. These models can be used to determine whether Ag-NCs cause inflammation, organ toxicity or other adverse reactions when administered systemically (Al Aamri et al., 2024; Stensberg et al., 2011). In addition, animal studies can reveal potential risks associated with accumulation or prolonged exposure that are not apparent in cell cultures (Pyambri et al., 2025).

Prior to clinical application, comprehensive biocompatibility assessments should be performed according to standardized guidelines such as ISO 10993, which include tests for cytotoxicity, sensitization, irritation, systemic toxicity and genotoxicity (Rosa et al., 2024). These rigorous tests ensure that Ag-NCs are safe, effective and suitable for human use, reducing the risk of unforeseen adverse effects and facilitating approval. Ultimately, such thorough preclinical evaluation is essential to bridge the gap between laboratory research and safe, effective clinical applications of Ag-NCs.

Contribution of Review Articles on Silver Nanocomposites for Biomedical Applications

The graph in Fig. 1, shows the annual trend of published and cited review articles as a contribution to the research of Ag-NCs to biomedical applications, based on data from the Web of Science as at 2nd May 2025. From 2004 to around 2010, both publication and citation rates were minimal, reflecting the early stage of research interest in this area. From around 2011, however, a steady increase in publications began, which accelerated significantly from 2015 and peaked in 2022 with almost 90 review articles. Citations followed a similar trend, rising steadily and reaching a peak of over 5,000 in 2024, indicating a growing recognition and impact of research in this area. Despite a high number of citations in 2024, the number of publications has decreased slightly compared to 2022, and there is a sharp decrease for 2025, possibly due to incomplete data for the current year. Overall, the data shows a strong and growing interest in silver nanocomposites for biomedical applications, with review articles playing a crucial role in consolidating and disseminating knowledge in this rapidly advancing interdisciplinary field.

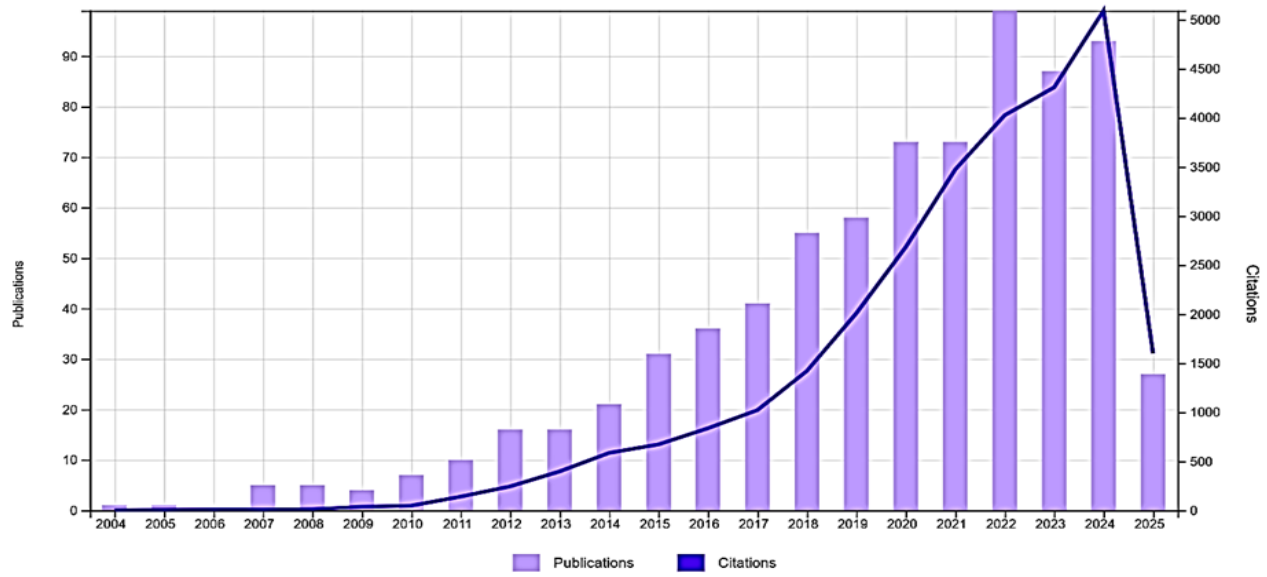

Figure 1. Trends in number of publications and citations on silver nanocomposites for biomedical applications (2004–2025).

Conclusion

The Ag-NCs are very promising for various biomedical applications due to their antimicrobial activity and tunable properties. However, careful testing of their cell compatibility is crucial for safe and effective application. Further research is needed to fully understand the mechanisms of Ag-NCs' toxicity and to develop strategies to mitigate potential adverse effects. By optimizing material composition, surface properties and release kinetics, it is possible to harness the benefits of Ag-NCs while minimizing their cytotoxicity, paving the way for wider use in biomedical applications. Similarly, the review articles play pivotal roles in finding research gaps and help to bridge the existing gaps. Future research should focus on long-term biocompatibility studies and the development of personalized Ag-NCs tailored to specific cellular environments.

Declarations

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the literature reported in this paper.

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Authors' contributions

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Ethical considerations

Ethical issues (including plagiarism, misconduct, data fabrication, falsification, double publication or submission, redundancy) have been completely observed by the authors. As non-native speakers, we have utilized ChatGPT-4.0 and Instatext to enhance the writing and readability of this manuscript. The content has been carefully reviewed and edited where necessary, and we take full responsibility for its accuracy and integrity.

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