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Editorial

Therapeutic Potential of Silver Nanoparticles (AgNPs), 2nd Edition

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Silver nanoparticles (AgNPs) have attracted considerable attention across various scientific fields owing to their distinctive physicochemical, optical, and biological properties. Their high surface-area-to-volume ratio, size- and shape-dependent properties, and tunable surface chemistry enable the development of nanostructured systems tailored to specific applications. Moreover, their localized surface plasmon resonance (LSPR) properties enable light–matter interactions that are particularly relevant to optical sensing, imaging, and light-assisted therapeutic strategies [1,2]. The versatility of AgNPs is further enhanced by the availability of diverse synthesis and functionalization approaches, including conventional chemical methods and increasingly explored biological and green synthesis routes [3]. These features have established AgNPs as promising materials for biomedical applications, extending beyond their traditional antimicrobial uses.

The therapeutic interest in AgNPs arises from their ability to interact with biological systems through multiple, often interconnected mechanisms. These include the release of silver ions, the generation of reactive oxygen species (ROS), and interactions with cellular membranes and intracellular components [2,3]. Such effects have motivated investigations into their antibacterial [3–5], anticancer [1,6], anti-inflammatory [7], and antidiabetic potential [8], among other therapeutic applications. Furthermore, the optical properties of silver-based nanostructures enable light-assisted treatments, including photothermal and photodynamic approaches [2]. Nevertheless, the mechanisms underlying their biological activity are strongly influenced by nanoparticle size, morphology, surface chemistry, concentration, and the surrounding biological environment. Importantly, some of the processes responsible for therapeutic activity may also contribute to undesirable cytotoxic effects, emphasizing the need to balance therapeutic efficacy with biological safety.

Comparative studies illustrate the importance of the relationship between the biological activity of AgNPs and their physicochemical characteristics, as well as the conditions under which they interact with biological systems. For instance, Dong et al. [5] investigated AgNPs with approximate diameters of 10, 30, 60, and 90 nm and found that smaller particles exhibited greater antibacterial activity against *Vibrio natriegens*, accompanied by increased oxidative stress and bacterial DNA damage. In another study, Pal et al. [4] reported stronger biocidal activity of truncated triangular nanoplates than that of spherical or rod-shaped particles against *Escherichia coli*, highlighting the potential relevance of exposed crystallographic facets. Beyond size and morphology, Barbalinardo et al. [9] demonstrated that replacing citrate with an oligo(ethylene glycol)-based surface ligand markedly reduced cytotoxicity towards colorectal cancer cells, while neither formulation significantly affected HT-29 cells or primary colonocytes under the conditions tested. Such findings emphasize that biological responses cannot be predicted from a single nanoparticle property.

Light-mediated strategies offer additional opportunities to enhance the therapeutic functionality of silver-based nanostructures, either by associating them with photosensitizers or by integrating them into drug delivery platforms. Raposo et al. [10] demonstrated

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enhanced photodynamic inactivation of *Candida albicans* by combining PVP-coated AgNPs with cationic Zn(II) porphyrins, enabling complete inactivation at submicromolar photosensitizer concentrations under the conditions tested. In a complementary approach, Marta et al. [1] developed injectable chitosan-based lipogels incorporating liposomes loaded with silver nanoprisms and an anticancer drug (5-fluorouracil). The platform provided sustained drug release, which was enhanced by near-infrared irradiation at physiological pH. Together, these studies illustrate distinct ways of exploiting silver-based nanostructures in light-assisted therapeutic strategies, while highlighting opportunities for the development of combined phototherapy and chemotherapy.

Although silver-based nanomaterials are already incorporated into FDA-cleared wound dressings, the safety of emerging AgNP-based formulations must be evaluated based on their composition, intended use, and the route and duration of exposure. The safety assessment of AgNPs should consider tissue retention, local inflammatory responses, and recovery after exposure. Rosário et al. [11] reported greater persistence of silver in several organs following repeated exposure to 5 nm than to 50 nm PVP-coated AgNPs. In a complementary study, Sousa et al. [12] observed intestinal inflammatory changes following oral exposure, despite the absence of significant alterations in body weight or the plasma cytokines assessed. These findings emphasize the importance of evaluating tissue distribution, local biological responses, and potential long-term effects when assessing the safety of silver-based therapeutic systems.

This volume brings together original research and review articles published in the Special Issue "Therapeutic Potential of Silver Nanoparticles (AgNPs), 2nd Edition" of *Pharmaceuticals*. The collection explores complementary approaches to the development and therapeutic application of silver-based nanostructures, covering different aspects of their preparation, physicochemical characteristics, and biological performance. These contributions (Figure 1) highlight the potential of AgNPs in several therapeutic areas, including (i) antibacterial activity, (ii) cancer treatment, (iii) diabetes management, and (iv) bone regeneration. In addition to the original research articles, three reviews provide broader perspectives on recent advances in silver-based nanostructures for cancer treatment, antidiabetic applications, and phototherapy. Together, these contributions illustrate the growing diversification of AgNP-based therapeutic strategies and the importance of integrating materials design with biological evaluation.

The antibacterial potential of AgNPs is particularly relevant in the context of antimicrobial resistance, which continues to represent a major challenge for healthcare systems worldwide. In this regard, Gusso et al. [13] investigated AgNPs synthesized using *Cymbopogon citratus* (lemongrass) essential oil against multidrug-resistant bacteria isolated from surfaces and personal protective equipment in an intensive care unit. The nanoparticles were obtained using different silver nitrate concentrations (3 and 6 mM), with the essential oil acting as a reducing and stabilizing agent. Physicochemical characterization revealed marked differences between the formulations, with AgNPs prepared using 3 mM $AgNO_3$ exhibiting a smaller hydrodynamic diameter (87 nm), a lower polydispersity index (0.14), and a more negative zeta potential (−23 mV), indicating a more homogeneous and colloidally stable dispersion than the formulation prepared using 6 mM $AgNO_3$ (147 nm; polydispersity index of 0.91; zeta potential of −10 mV). Interestingly, despite its less favorable colloidal characteristics, the latter formulation demonstrated greater antimicrobial efficacy against a resistant *Enterococcus* spp. isolate. These findings highlight the potential of plant-mediated AgNP synthesis for developing alternative antimicrobial formulations targeting clinically relevant multidrug-resistant microorganisms. This study provides an in vitro proof of concept for hospital microbial control and illustrates why particle size or colloidal characteristics alone cannot predict antibacterial performance. The demonstrated in vitro activity

also supports further investigation of these formulations for infection-control applications in healthcare environments.

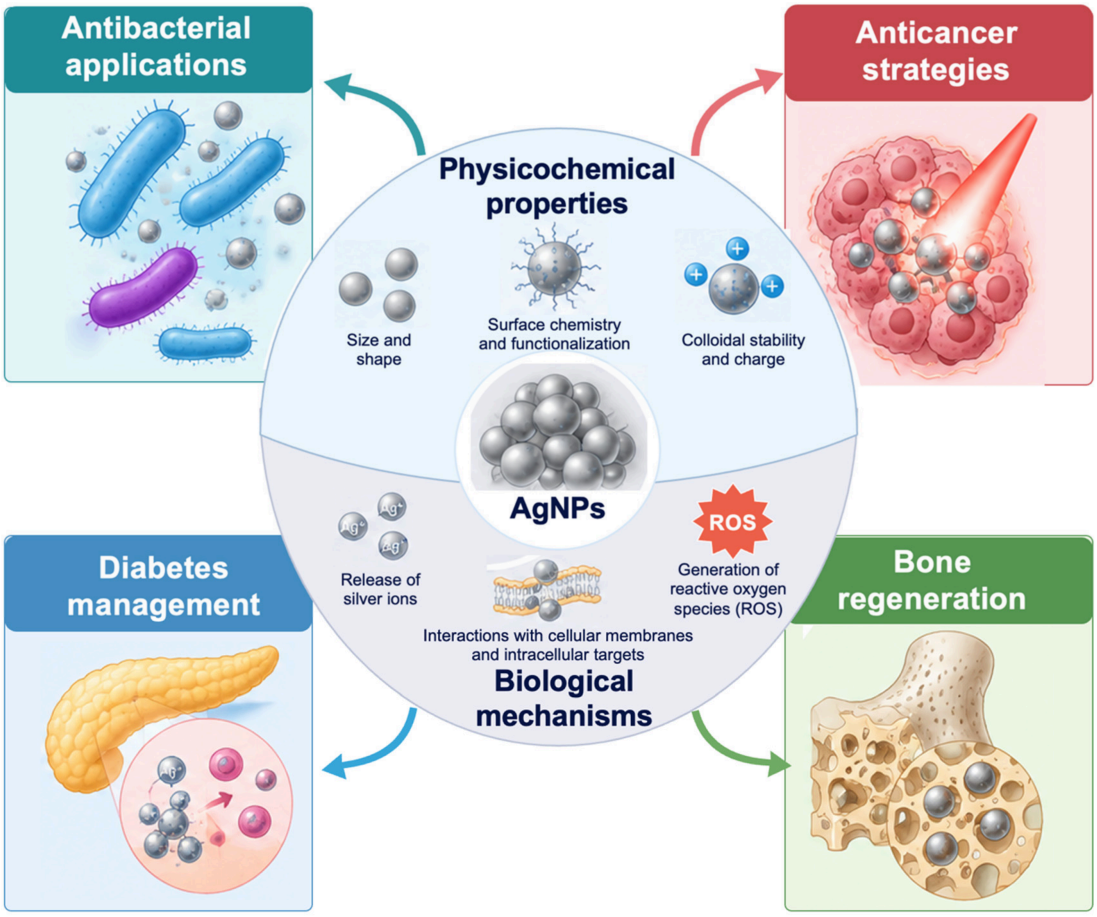


Figure 1. Schematic overview of the physicochemical properties and biological mechanisms of silver nanopartciles (AgNPs), and the applications highlighted in this collection.

Building on this antibacterial functionality, Monte et al. [14] incorporated AgNPs into multifunctional biomaterials for bone-related applications. AgNPs were synthesized in aqueous medium through sodium borohydride-mediated chemical reduction, using either alginate or sodium polyphosphate as stabilizing agents. The resulting AgNPs exhibited predominantly spherical morphology, hydrodynamic diameters ranging from approximately 25 to 143 nm, and negative zeta potentials between −38.7 and −23 mV, evidencing the influence of the capping agent and synthesis conditions on their physicochemical properties. Subsequently, the AgNPs were incorporated into calcium polyphosphate/alginate composite matrices. Importantly, the silver-containing composites demonstrated antibacterial activity against *Staphylococcus aureus* and *Staphylococcus epidermidis*, two clinically relevant microorganisms frequently associated with orthopedic and implant-related infections. The inhibition zones generally increased with composite dosage, and antibacterial activity was achieved with relatively low silver contents. These results support further investigation of the materials as antibacterial biocomposites, while cytocompatibility, silver-release behavior, antibiofilm activity, and osteogenic performance remain to be established.

Beyond antibacterial applications, silver-based nanostructures are also being investigated as components of advanced drug delivery systems for cancer treatment. AlAbdullatif et al. [6] developed halloysite-based nanohybrids functionalized with silver or zinc oxide nanoparticles synthesized through a plant-mediated approach using *Tribulus terrestris* extract. These nanostructured systems were designed as carriers for the chemotherapeutic

agents cisplatin and carboplatin to investigate controlled drug delivery and anticancer activity in cervical cancer models. The study combined structural characterization with drug adsorption, release, and cytotoxicity assays. Drug–carrier interactions and PEG functionalization influenced release behavior, while evaluation in HeLa cervical cancer cells and HFF-1 fibroblasts revealed formulation-, concentration-, and time-dependent responses. Silver-containing systems exhibited substantial cytotoxic activity, but their effects on fibroblasts underscored the need to optimize therapeutic selectivity. The work illustrates both the opportunities offered by hybrid drug delivery platforms and the importance of assessing activity in malignant and non-malignant cells.

Extending the scope to metabolic disorders, González-Garibay et al. [8] investigated the antidiabetic potential of AgNPs biosynthesized using an aqueous extract of *Stenocereus queretaroensis* flowers. Phytochemical analysis of the extract identified several phenolic and flavonoid compounds, which may contribute to nanoparticle formation and stabilization. The resulting AgNPs exhibited a predominantly spherical morphology with a rough surface and an average hydrodynamic diameter of approximately 99.5 nm. The biological evaluation focused on the inhibition of α-amylase and α-glucosidase, two enzymes involved in carbohydrate digestion and postprandial glucose regulation. The biosynthesized nanoparticles exhibited inhibitory activity against both enzymes, with IC_{50} values of 4.92 and 0.68 µg/mL, respectively. In addition, oral administration of the nanoparticles at 100 mg/kg significantly reduced postprandial blood glucose levels in healthy mice subjected to a carbohydrate challenge. These findings support further investigation of the formulation for postprandial glucose management.

Although the preceding contributions demonstrate the diversity of potential therapeutic applications of silver-based nanostructures, their biomedical development must be accompanied by rigorous evaluation of biological safety. Addressing this essential aspect, Bonatto et al. [15] investigated the acute toxicological effects of AgNPs obtained through a green synthesis route using an aqueous extract of *Caryocar brasiliense*. The plant-derived compounds were employed to reduce and stabilize AgNPs, providing a biologically mediated alternative to conventional chemical synthesis. The study combined hemolysis testing with hematological, biochemical, and histological evaluations in mice 24 h after intravenous administration. The results revealed no statistically significant alterations in most hematological or biochemical indicators compared with the control group. In addition, the AgNPs exhibited very low hemolytic activity, with more than 98% of red blood cells remaining intact even at the highest concentration tested. Histological analyses generally indicated preserved tissue architecture, although small inflammatory infiltrates were observed in the liver, indicating that localized biological responses cannot be entirely excluded. Interestingly, free silver ions produced certain hematological alterations that were not observed with the AgNPs formulation. Taken together, these findings indicate limited acute toxicity associated with the AgNPs under the experimental conditions investigated. Nevertheless, the results should not be extrapolated to long-term exposure or other routes of administration, reinforcing the importance of dose-dependent, biodistribution, and chronic toxicity studies in the development of silver-based therapeutic systems.

Taken together, the contributions presented in this volume demonstrate the versatility of silver-based nanostructures and their potential across a range of therapeutic applications. From antibacterial formulations and multifunctional biomaterials to anticancer drug delivery systems and antidiabetic strategies, the studies illustrate how different synthesis approaches, surface modifications, and composite formulations can be explored to tailor the biological performance of AgNP-based systems. At the same time, the findings highlight the complexity of the relationships between physicochemical characteristics, biological activity, and therapeutic efficacy. In particular, the observed differences in antimicrobial

performance, cellular selectivity, and toxicological responses reinforce the importance of evaluating each formulation within its intended biological and therapeutic context.

Despite these promising advances, important challenges remain before the therapeutic potential of AgNPs can be translated into safe and effective clinical applications. Future investigations should prioritize reproducible synthesis, standardized physicochemical characterization, a more comprehensive understanding of biological mechanisms, and rigorous evaluation of biocompatibility and long-term safety. Particular attention should also be given to nanoparticle stability in biological environments, silver ion release, biodistribution, and the establishment of appropriate dose–response relationships. Moreover, the transition from preliminary in vitro investigations to more representative preclinical models will be essential to determine therapeutic selectivity and establish the clinical relevance of these systems.

Overall, this collection reflects the expanding scope of AgNP research and highlights the importance of integrating nanomaterial design with mechanistic understanding and biological evaluation. By bringing together experimental advances and critical reviews, the volume aims to contribute to a more comprehensive understanding of the opportunities and limitations associated with silver-based nanostructures, supporting the continued development of more effective, selective, and safer therapeutic strategies.

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