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Comparative Study of Silver, Gold, and Zinc Oxide Nanoparticles for Their Antimicrobial Activity and Cytotoxicity Against Cancer Cell Lines

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Abstract

The rapid advancement of nanotechnology has positioned metallic nanoparticles as promising alternatives to conventional antimicrobial and anticancer agents. This review provides a comprehensive comparative analysis of silver (Ag), gold (Au), and zinc oxide (ZnO) nanoparticles, focusing on their synthesis strategies, physicochemical characteristics, antimicrobial efficacy, and cytotoxic potential against various cancer cell lines. Emphasis is placed on the influence of synthesis routes particularly green synthesis on particle morphology, stability, and biocompatibility, highlighting how phytochemical-mediated approaches enhance therapeutic performance while reducing toxicity. Among the three nanomaterials, Ag nanoparticles demonstrate the

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strongest broad-spectrum antimicrobial activity due to sustained Ag^+ ion release and membrane disruption, while ZnO nanoparticles exhibit potent reactive oxygen species (ROS)-mediated antibacterial effects and notable selective cytotoxicity against cancer cells. Au nanoparticles, although relatively inert in antimicrobial applications, serve as highly effective drug delivery platforms and sensitizing agents in combination therapies. The review further discusses the mechanistic basis of anticancer activity, including oxidative stress induction, mitochondrial dysfunction, DNA damage, and activation of apoptotic signaling pathways such as p53 and caspase cascades. Comparative cytotoxicity data indicate that nanoparticle efficacy is strongly dependent on size, shape, dose, and surface functionalization, with smaller and biogenically synthesized particles generally exhibiting higher biological activity. Additionally, hybrid nanocomposites such as Ag/ZnO and Au/ZnO show synergistic effects, enabling enhanced antimicrobial and anticancer performance at reduced dosages. Despite their promising biomedical applications, challenges such as long-term toxicity, biodistribution concerns, and regulatory limitations remain significant barriers to clinical translation. Overall, this review underscores the potential of Ag, Au, and ZnO nanoparticles particularly in green-synthesized and hybrid forms as next-generation therapeutic agents for addressing multidrug-resistant infections and improving cancer treatment outcomes.

1. Introduction

The rapid evolution of nanotechnology has significantly altered the landscape of modern medicine, particularly in the fields of oncology and infectious disease management. At the nanoscale, materials exhibit physicochemical properties that are fundamentally different from their bulk counterparts, primarily due to their high surface-area-to-volume ratio and quantum confinement effects (Malik et al., 2023). Among the diverse array of nanomaterials investigated for biomedical applications, silver (Ag), gold (Au), and zinc oxide (ZnO) nanoparticles (NPs) have emerged as the most promising

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candidates due to their unique optical, electronic, and biological characteristics (Kadhim et al., 2025). The transition from traditional pharmacological agents to nanoparticle-based therapeutics is driven by the urgent global need to address multidrug resistance (MDR) in bacterial pathogens and the debilitating systemic toxicity associated with conventional cancer chemotherapies (Ahmed et al., 2025). This report provides an exhaustive comparative evaluation of these three nanoparticle types, examining their synthesis methodologies, antimicrobial mechanisms, and cytotoxic efficacy against various cancer cell lines, while articulating the structural and chemical factors that govern their biological performance (Bama et al., 2021).

2. Synthesis Paradigms and Structural Evolution

The biological activity of nanoparticles is inherently dictated by their structural parameters, including crystallite size, morphology, surface charge, and the presence of capping agents. Synthesis strategies are broadly classified into "top-down" physical methods and "bottom-up" chemical and biological methods (Joudeh & Linke, 2022). Physical methods such as laser ablation and arc plasma utilize external energy to disintegrate bulk materials into nanoparticles, offering high purity but requiring significant energy consumption and specialized infrastructure (Jagdeo, 2023). Chemical methods, including the sol-gel process, hydrothermal synthesis, and precipitation, provide precise control over morphological outcomes but often utilize hazardous reducing agents like sodium borohydride or toxic solvents that pose risks to human health and the environment (Bilecka & Niederberger, 2010).

A significant shift toward green synthesis has occurred in the last decade, emphasizing the use of plant extracts, microorganisms, and biopolymers as sustainable alternatives to traditional chemical routes (Hano & Abbasi, 2021). In green synthesis, phytochemicals such as polyphenols, flavonoids, and terpenoids act as dual reducing and stabilizing agents, facilitating the conversion of metal salts into stable nanoparticles (Ovais et al., 2018). This biogenic approach not only reduces toxicity but also results in

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nanoparticles capped with bioactive molecules that enhance their therapeutic potential, often leading to synergistic effects in antimicrobial and anticancer assays (Ghanem et al., 2021).

2.1 Characterization and Structural Comparison

Accurate characterization is the cornerstone of nanomedical research, enabling scientists to correlate physical attributes with biological responses. X-ray diffraction (XRD) is routinely employed to confirm the crystal phase and purity. Zinc oxide nanoparticles typically exhibit a hexagonal wurtzite crystal structure, with characteristic peaks appearing at specific 2θ angles corresponding to orientations such as (100), (002), and (101) (Ghanem et al., 2021). In contrast, noble metal nanoparticles like silver and gold generally exhibit face-centered cubic structures. The Scherrer equation is frequently used to calculate the average crystallite size from XRD data, which for many biogenic ZnO and Ag nanoparticles ranges between 15 nm and 40 nm (Shi et al., 2020).

Microscopic techniques, specifically scanning electron microscopy (SEM) and transmission electron microscopy (TEM), reveal the diverse morphologies achievable through different synthesis methods (Datye & DeLaRiva, 2023). While AgNPs and AuNPs are frequently spherical or quasi-spherical, ZnO nanoparticles exhibit a wider range of shapes, including rods, flowers, flakes, and hexagonal prisms (Ali et al., 2023). The synthesis environment, such as pH and precursor concentration, plays a critical role in defining these shapes; for instance, higher pH values in ZnO-Ag nanocomposite synthesis have been observed to increase crystallinity and alter agglomeration patterns (Saka et al., 2024).

Table 1. Comparison of Synthesis Techniques, Morphologies, and Particle Sizes for Zinc Oxide and Silver Nanoparticles

Synthesis Technique	Material	Shape	Average Size (nm)	Processing Conditions
Hydrother	ZnO	Spherica	33 ± 2	6.5 h,

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mal		l		distilled water
Precipitation	ZnO	Granular	18	6 h, deionized water/acetone
Plant-mediated	Ag/ZnO	Spherical	16	7 h, leaf extract
Microbial	ZnO	Spherical	46	24 h, LAB strains
Arc plasma	ZnO	Hexagonal column	88–103	24 h, dry air
Laser ablation	ZnO	Spherical	Not specified	15–20 min, distilled water
Chemical vapor	ZnO	Nanowires	~100 (diameter)	Several hours, argon gas

The presence of organic molecules on the surface, identified through Fourier transform infrared (FTIR) spectroscopy, confirms the role of plant metabolites in stabilizing the particles. Peaks in the 400–600 cm^{-1} range are diagnostic of Zn–O vibrations, while absorption bands for hydroxyl and amine groups indicate the successful capping by phytochemicals (Pasieczna-Patkowska et al., 2025). Dynamic light scattering (DLS) and zeta potential analysis are further utilized to determine the hydrodynamic size and surface charge, with stable biogenic nanoparticles often exhibiting negative charges (e.g., −16.2 mV) that prevent excessive aggregation in biological media (Rahdar et al., 2019). The major synthesis strategies for metallic nanoparticles, including physical, chemical, and green approaches, are illustrated in Figure 1. This schematic highlights the transformation pathways and key agents involved

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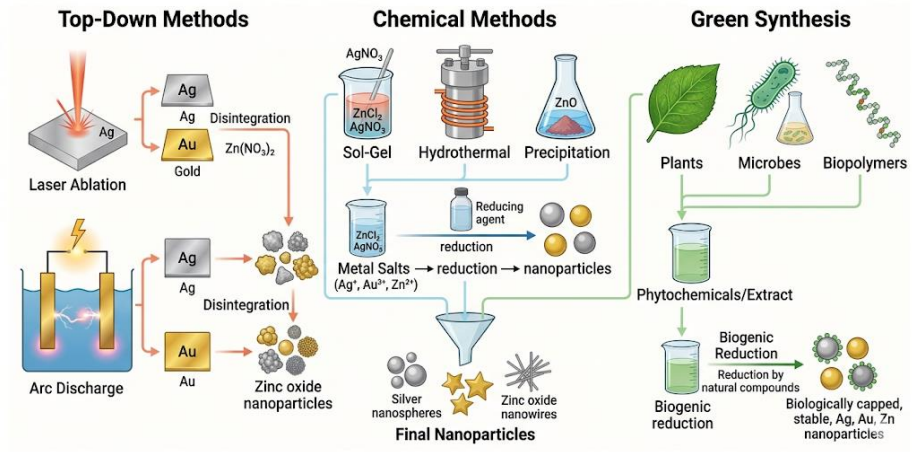
in nanoparticle formation.

Figure 1. Schematic Representation of Synthesis Approaches for Silver, Gold, and Zinc Oxide Nanoparticles



3. Antimicrobial Efficacy and Mechanistic Pathways

The antimicrobial prowess of metallic nanoparticles is a multifaceted phenomenon involving physical, chemical, and biological interactions with microbial cells. Unlike traditional antibiotics, which typically target a single cellular function, nanoparticles exert a multi-pronged attack that significantly minimizes the likelihood of developing resistance (Gudepu et al., 2026).

3.1 Comparative Mechanisms of Action

Silver nanoparticles are widely recognized as the most potent antimicrobial agents among the three. Their mechanism involves the continuous release of silver ions (Ag^+), which possess a strong affinity for thiol groups in microbial proteins and enzymes. This interaction disrupts the respiratory chain and enzymatic activity, leading to metabolic collapse (Hamad et al., 2020). Additionally, AgNPs physically adhere to the bacterial cell wall, increasing its porosity and facilitating the internalization of particles that subsequently interact with DNA, causing structural damage and preventing replication (Menichetti et al., 2023).

Zinc oxide nanoparticles operate through distinct but complementary pathways. A primary mechanism is the generation of reactive oxygen species (ROS), such as superoxide radicals and hydrogen peroxide, on the nanoparticle surface. This process is

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often enhanced by UV or visible light irradiation, as ZnO is a wide-band-gap semiconductor (3.3 eV) (Li et al., 2020). ROS induce severe oxidative stress, damaging cellular components like lipids, proteins, and DNA. Furthermore, the release of zinc ions (Zn^{2+}) and direct contact between the abrasive surface of ZnO and the microbial cell wall contribute to membrane disintegration and cell death (Jomova et al., 2025).

Gold nanoparticles, in their pristine form, are often described as having negligible inherent antimicrobial activity (Gold et al., 2018). However, their high surface energy and stability make them ideal as carriers or adjuvants. When functionalized with small molecules or antibiotics, AuNPs can significantly enhance the efficacy of traditional drugs (Amina & Guo, 2020). For example, gold nanoparticles capped with vanillin have demonstrated the ability to inhibit efflux pumps in *Pseudomonas aeruginosa*, drastically reducing the minimum inhibitory concentration (MIC) of antibiotics like trimethoprim and meropenem (Maisch et al., 2022).

3.2 Spectrum of Activity and Synergistic Interactions

The antimicrobial effectiveness of these nanoparticles is highly dependent on the bacterial strain and its cell wall structure. Gram-negative bacteria, such as *Escherichia coli* and *Aeromonas hydrophila*, often show higher sensitivity to nanoparticles due to their thinner peptidoglycan layer compared to Gram-positive strains like *Staphylococcus aureus* (Tavares et al., 2020). However, ZnO has shown specific potency against *S. aureus*, with smaller spherical particles (20 nm) outperforming larger hexagonal or rod-shaped structures (Abdelghafar et al., 2022).

Table 2. Comparative Antimicrobial Activity (MIC) of Metallic Nanoparticles Against Various Pathogens

Pathogen Type	Nanoparticle	MIC Concentration (µg/mL)	Notable Observations
Aeromonas	Ag	17.0	Disruption of

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salmonicida			membrane integrity
Aeromonas salmonicida	ZnO	15.75	Strong inhibition observed
Yersinia ruckeri	ZnO	31.5	Significant activity against fish pathogens
Aphanomyces invadans	ZnO	3.15	Exceptionally high sensitivity
Staphylococcus aureus	ZnO	100.0	Spherical morphology most effective
Pseudomonas aeruginosa	ZnO/Au NC	80% increased activity	Synergistic effect compared to bare ZnO
Staphylococcus aureus	ZnO/Au NC	55% increased activity	Enhanced ROS production and metal ion release

A critical development in this field is the synthesis of bimetallic or hybrid nanocomposites, such as Ag-ZnO or Au-ZnO. These materials exhibit synergistic interactions where the presence of noble metals enhances the photocatalytic properties of ZnO by narrowing its band gap and facilitating electron-hole separation (Metals, 2023). In orthodontic applications, brackets coated with a combination of Ag and ZnO nanoparticles have shown the highest reduction in *Streptococcus mutans* and *Lactobacillus acidophilus* counts, significantly outperforming brackets coated with silver or zinc oxide individually (Jose, 2019). This synergy allows for the use of lower material concentrations while achieving superior microbial elimination, promoting sustainability and reducing potential environmental toxicity (Kumar & Singh,

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4. Cytotoxicity and Selective Anticancer Mechanisms

The potential of metallic nanoparticles as anticancer agents stems from their ability to induce selective programmed cell death in malignant tissues while sparing normal cells. This selectivity is often attributed to the unique metabolic environment of tumors, characterized by an acidic microenvironment and higher levels of intracellular oxidative stress (Andleeb et al., 2021).

4.1 Molecular Pathways of Apoptosis

Nanoparticle-mediated cytotoxicity in cancer cell lines, such as HepG2 (liver), MCF-7 (breast), and HeLa (cervical), primarily occurs through the induction of apoptosis (Barabadi et al., 2020). This process is triggered by several interrelated factors.

1. Oxidative Stress Induction: The generation of ROS is the most widely cited mechanism for nanoparticle toxicity. Excess ROS overwhelm the cell's antioxidant capacity, leading to lipid peroxidation and protein denaturation (Samrot et al., 2022).
2. Mitochondrial Membrane Disruption: Nanoparticles such as ZnO cause a reduction in the mitochondrial membrane potential, which triggers the release of cytochrome c into the cytoplasm (Morse et al., 2024).
3. Genotoxicity and DNA Damage: Direct interaction with the nucleus or indirect damage via reactive oxygen species (ROS) leads to DNA fragmentation and chromosomal aberrations. This activates the p53 signaling pathway, which is a master regulator of cell cycle arrest and apoptosis (García-Rodríguez et al., 2018).
4. Caspase Cascade Activation: Quantitative reverse transcription polymerase chain reaction (qRT-PCR) results have demonstrated that exposure to ZnO nanoparticles results in a significant upregulation of pro-apoptotic genes such as *Bax*, *p53*, and *Caspase-3*, while concurrently downregulating the anti-apoptotic gene *Bcl-2* (Othman et al., 2022).

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5. Comparative Cytotoxicity across Cancer Lines: The response of various cancer cell lines to Ag, Au, and ZnO nanoparticles varies based on dose, exposure time, and particle size. Smaller particles typically show higher potency due to easier cellular uptake via endocytosis (Konuk, 2024).

Table 3. Comparative Cytotoxicity (IC_{50}) of Silver, Gold, and Zinc Oxide Nanoparticles Across Human Cancer Cell Lines

Cancer Cell Line	Nanoparticle Type	IC_{50} (µg/mL)	Viability Reduction Details
HepG2 (Liver)	Green ZnO	2.87	26.8% viability at 5 µg/mL after 72 h
HepG2 (Liver)	ZnO (41 nm)	19.94	Green synthesized using Echinops spinosus
MCF-7 (Breast)	Ag	5.18	Meta-analysis results
MCF-7 (Breast)	ZnO	37.0	Meta-analysis results
HeLa (Cervical)	Ag	0.038	Extremely high potency (38.6 ng)
A549 (Lung)	Au	50.0	Induced apoptosis via ROS and caspase activation
HCT116 (Colon)	ZnO	31.42	Biogenic nanoparticles derived from stem extract
MDA-MB-231 (Breast)	ZnO	44.86	Significant activity in triple-negative breast cancer (TNBC)

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MDA-MB-468 (Breast)	ZnO	20.96	Significant activity in triple-negative breast cancer (TNBC)

In a comprehensive meta-analysis of MCF-7 breast cancer cells, AgNPs and AuNPs were found to exhibit superior cytotoxic effects at lower concentrations compared to ZnO nanoparticles (Rao et al., 2007). Specifically, at concentrations exceeding 60 µg/mL, silver nanoparticles reduced cell viability to between 9% and 45%, while ZnO nanoparticles-maintained viability between 20% and 40%. However, ZnO nanoparticles often demonstrate a higher therapeutic index. For instance, while AgNPs were three-fold more toxic to normal kidney cells (HEK-293) than to HeLa cancer cells, ZnO nanoparticles have been shown to be 28 to 35 times more toxic to cancer cells than to normal cells (Gurunathan et al., 2019). This selective toxicity is a crucial advantage for ZnO, suggesting it as a safer candidate for clinical translation where minimizing damage to healthy tissues is paramount (Jain & Bhise, 2025). A comparative overview of the biological performance of the three nanoparticles is presented in Figure 2. This comparison highlights the relative strengths and limitations of each nanoparticle type in biomedical applications.

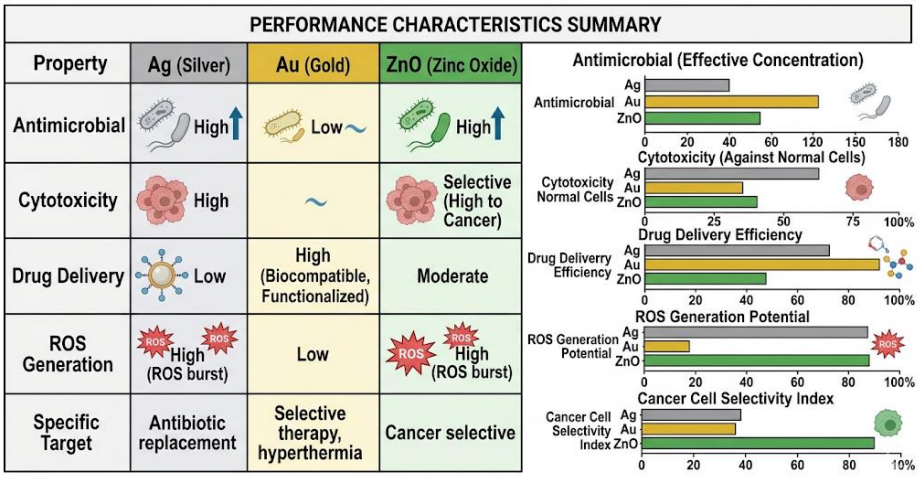

Figure 2. Comparative Performance of Ag, Au, and ZnO Nanoparticles in Antimicrobial and Anticancer Applications

5. The Role of Particle Morphology and Doping

The interaction between nanoparticles and biological membranes is profoundly

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influenced by the particle's physical shape and surface chemistry. For zinc oxide, the influence of morphology on both antimicrobial and anticancer activity has been a subject of intense investigation (Sirelkhatim et al., 2015). Spherical ZnO nanoparticles have consistently shown higher efficacy against S. aureus and HeLa cells compared to hexagonal and rod-shaped particles of similar volume. This is primarily attributed to their smaller size and larger effective surface area, which facilitates higher rates of cellular internalization and reactive oxygen species (ROS) generation (Mendes et al., 2024).

5.1 Surface Modifications and Doping

Doping nanoparticles with secondary metals or incorporating them into polymeric matrices is a widely used strategy to tailor and enhance their physicochemical and biological properties (Avnir, 2014). In this context, silver-doped zinc oxide (Ag–ZnO) nanostructures have demonstrated markedly enhanced cytotoxic effects against human breast cancer cell lines, including MCF-7 and MDA-MB-231, when compared with pristine ZnO nanoparticles. For instance, incorporation of 2% Ag into ZnO nanoparticles has been reported to reduce MCF-7 cell viability to approximately 20%, whereas undoped ZnO maintains a comparatively higher viability of about 35% (Shubha et al., 2024). The functional performance of these nanoparticles can be further improved through embedding in biopolymer matrices. Cellulose Acetate (CA)-based nanocomposites reinforced with Ag/ZnO have shown enhanced thermal stability, improved mechanical integrity, and strong antimicrobial activity (Alahmadi & Hussein, 2023). In particular, the CA@Ag(0.1)/ZnO membrane has demonstrated significant efficacy in inducing apoptosis and cell death in breast cancer assays, indicating its potential applicability in biomedical fields such as therapeutic implants and wound dressings (Xie et al., 2022).

In addition, surface modification strategies such as PEGylation play a crucial role in improving in vivo performance. Polyethylene Glycol (PEG) coatings can significantly prolong nanoparticle circulation time in the bloodstream and reduce macrophage-

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mediated uptake by approximately 60–75%, thereby enhancing tumor-targeting efficiency and overall therapeutic effectiveness (Fam et al., 2020).

6. Clinical Challenges and Regulatory Frameworks

Despite the promising in vitro data, the successful translation of Ag, Au, and ZnO nanoparticles into clinical therapies faces significant hurdles. As of 2024–2025, the number of metal-based nanoparticle systems approved for clinical use remains small compared to the volume of research being conducted (Almajidi et al., 2025).

6.1 Toxicological and Regulatory Obstacles

A major challenge is the inherent toxicity and potential bioaccumulation of metallic nanoparticles in vital organs like the liver and kidneys. Long-term studies have reported that repeated administration of certain metal-based compounds over 28 days can lead to marked metabolic disturbances, oxidative stress, and lipid peroxidation (Waris et al., 2024). Furthermore, standard regulatory tests for genotoxicity and mutagenicity may not be fully applicable to nanomaterials. The Ames test, for instance, has been criticized for producing false negatives because nanoparticles may fail to penetrate the specific bacteria used in the assay (Sundar et al., 2018).

The regulatory landscape is slowly evolving to address these unique properties. Guidelines like ISO/TR 22293:2021 provide a framework for evaluating the toxicological risks of nanomaterials, but uncertainties in biological interactions continue to delay approvals and increase the cost of commercialization (Pfohl et al., 2022). In 2024, the FDA's Center for Drug Evaluation and Research (CDER) approved 17 novel oncology drugs, including several antibody-drug conjugates and monoclonal antibodies, but direct metal nanoparticle therapies were noticeably absent from the list of original medical entities (Sangwan et al., 2024).

6.2 Future Horizons in Nanomedicine

The future of the field is increasingly focused on "smart" nanoplatforms that combine diagnostic and therapeutic functions (theranostics). The integration of gold

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and zinc oxide into core-shell structures or multi-metallic nanocomposites represents a frontier (Omidian & Gill, 2025). where the unique properties of each metal the stability and SPR of gold, the antimicrobial potency of silver, and the selective cytotoxicity of zinc oxide are harnessed simultaneously (Kadhim et al., 2025). Green synthesis remains the preferred route for developing these materials, as it aligns with global sustainability goals and yields biocompatible products that are less likely to cause adverse immune responses (Kirubakaran et al., 2026).

Table 4. Summary of Primary Applications and Future Research Directions for Metallic Nanoparticles and Hybrids

Nanoparticle/Composite	Primary Application	Key Future Focus
Silver (Ag)	Wound Healing, Water Disinfection	Minimizing long-term bioaccumulation
Gold (Au)	Bio-imaging, Adjuvant Therapy	Enhancing deep tumor penetration
Zinc Oxide (ZnO)	Targeted Drug Delivery, Oncology	Optimizing selective therapeutic indices
Ag/ZnO Hybrid	Antimicrobial Coatings	Sustainability in large-scale production
Au/ZnO Hybrid	Theranostics, Catalysis	Clinical safety trials and regulatory approval

Conclusion

Silver, gold, and zinc oxide nanoparticles represent highly promising platforms in nanomedicine due to their distinct yet complementary biological activities. AgNPs and ZnO NPs demonstrate robust antimicrobial effects against both Gram-positive and

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Gram-negative bacteria, often surpassing conventional antibiotics, while AuNPs excel as versatile carriers for targeted delivery and combination therapies. In oncology, these nanoparticles effectively induce selective apoptosis in multiple cancer cell lines through ROS-mediated oxidative stress, mitochondrial disruption, and modulation of key apoptotic pathways, with hybrid systems (e.g., Ag/ZnO or Au/ZnO) showing enhanced efficacy and reduced required doses. Green synthesis routes further improve biocompatibility and sustainability, making these materials attractive for clinical development.

However, concerns regarding long-term cytotoxicity, organ accumulation, and regulatory approval remain significant barriers. Future research should prioritize rigorous in vivo studies, optimization of therapeutic indices, development of smart theranostic platforms, and standardized safety protocols. With continued advancements in surface engineering and hybrid nanocomposites, Ag, Au, and ZnO nanoparticles hold substantial potential to address multidrug-resistant infections and improve cancer treatment outcomes with minimized side effects on healthy tissues.

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