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Review Article

Synergistic Effects of Metal Oxide Nanoparticles and Antibiotics: A Systematic Review of Mechanisms and Resistance Patterns

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ABSTRACT

The global rise of multidrug-resistant (MDR) pathogens has eroded the clinical utility of conventional antibiotics, and the World Health Organization has repeatedly identified antimicrobial resistance as one of the most serious threats to public health. Metal oxide nanoparticles (MONPs) — notably ZnO, CuO, MgO, TiO_2, and related oxides — have emerged as adjunctive antimicrobial agents whose physicochemical modes of action differ fundamentally from those of molecular antibiotics. This systematic review synthesizes the current evidence on the synergistic interactions between MONPs and conventional antibiotics and characterizes the mechanisms and resistance patterns that govern these interactions. Following PRISMA-guided screening of publications indexed in Web of Science, PubMed, and Google Scholar, peer-reviewed studies reporting quantitative synergy outcomes between MONPs and antibiotics were identified and synthesized. Synergy was assessed primarily through the Fractional Inhibitory Concentration Index (FICI) derived from checkerboard assays, supported by time-kill kinetics and microscopy-based evidence (SEM/TEM). The literature converges on four mutually reinforcing mechanisms of synergy: (i) ROS-mediated oxidative damage that depletes bacterial antioxidant defenses; (ii) physical disruption of the cell wall and cytoplasmic membrane, which increases intracellular antibiotic accumulation; (iii) destabilization and penetration of the extracellular polymeric substance (EPS) matrix of biofilms, restoring antibiotic efficacy against sessile communities; and (iv) interference with efflux pump activity and plasmid-mediated resistance determinants. Across reported studies, co-administration of MONPs substantially lowers the minimum inhibitory concentration (MIC) of partner antibiotics, with ZnO and CuO nanoparticles showing the most consistent synergy against Gram-negative MDR isolates. MONP–antibiotic nanohybrids represent a credible strategy to resensitize resistant pathogens to existing drugs, provided that rigorous standardization of nanoparticle characterization, FICI-based interpretation, and toxicological evaluation is achieved before clinical translation.

Keywords: metal oxide nanoparticles; antibiotic synergy; antimicrobial resistance; reactive oxygen species; biofilm; FICI; nanohybrid.

INTRODUCTION

The therapeutic arsenal against bacterial infection is contracting. The inappropriate and excessive prescription of antibiotics, their widespread use in agriculture, and the environmental dissemination of resistance genes have jointly accelerated the emergence of multidrug-resistant (MDR) pathogens, including extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae, methicillin-resistant Staphylococcus aureus (MRSA), Acinetobacter baumannii, and vancomycin-resistant Enterococcus faecalis [1]. Systematic evidence indicates that resistance factors now extend beyond

clinical prescribing: plasmid-mediated horizontal gene transfer, broad-spectrum antimicrobial consumption, and pharmaceutical contamination of ecosystems all contribute to the accelerating diffusion of resistant clones and their mobile genetic elements [1].

Two structural features of modern antimicrobial failure motivate the present review. The first is the **biofilm barrier**. A biofilm is a cooperative assembly of sessile cells adhering to each other and to a substrate, encapsulated within a matrix of extracellular polymeric substance (EPS) [1]. Conventional antibiotics exhibit limited efficacy against such communities because the EPS restricts drug penetration, sessile cells adopt slow-growing phenotypes that reduce target vulnerability, and locally high cell densities facilitate the exchange of resistance genes [1]. Chronic infections of cystic fibrosis airways, catheter-associated urinary tract infections, and implant-associated osteomyelitis are sustained by this mechanism and routinely resist standard therapy.

The second is the **mechanistic homogeneity of existing drugs**. Most antibiotic classes exploit a small set of cellular targets — ribosomes, DNA gyrase, folate biosynthesis, or peptidoglycan cross-linking — and resistance to any one of them can be acquired through a single mutational or plasmid-borne event, most visibly through extended-spectrum β-lactamases [1]. Nanomaterials attack bacteria along fundamentally different axes: metal and metal oxide nanoparticles (M/MO-NPs) such as ZnO, CuO, Fe_2O_3, TiO_2, MgO, and Al_2O_3 particles generate reactive oxygen species (ROS), impose mechanical and electrostatic damage on cell walls, and provoke metal cation leakage from the cell envelope [1]. Because these physicochemical insults do not correspond to the canonical antibiotic targets, they are not neutralized by the dominant resistance determinants — β-lactamases, ribosomal methylation, or target-site mutation — and can therefore act as force multipliers for drugs whose targets have been compromised.

Importantly, the nanoscale itself confers activity. When ZnO is reduced to the nanometer range (1–100 nm), its high surface area-to-volume ratio and high surface reactivity enable intimate interaction with the bacterial surface and penetration into the cellular interior, where nano-ZnO exhibits bactericidal activity that the bulk material lacks [4]. The same size dependence has been documented across oxide systems, with antibacterial performance governed by particle size, morphology, surface charge, surface defects, and concentration [4].

Against this background, the present systematic review pursues three objectives. First, it consolidates the mechanistic evidence for synergy between MONPs and conventional antibiotics, distinguishing genuinely synergistic from merely additive interactions. Second, it evaluates the methodological framework — FICI interpretation, checkerboard design, and imaging validation — used to declare synergy, and identifies the standardization deficits that currently impede cross-study comparison. Third, it analyzes resistance patterns that emerge, or fail to emerge, when bacteria are challenged with combined MONP–antibiotic treatment, and distills the implications for clinical translation.

Mechanisms of Synergistic Action

The synergy reported between MONPs and antibiotics is not a single phenomenon but the convergence of four mechanistic axes, each of which independently compromises bacterial viability and which, in combination, produce effects larger than the sum of their parts.

ROS-Mediated Oxidative Damage

The most extensively documented mechanism of MONP toxicity is the generation of reactive oxygen species. For ZnO nanoparticles, the leading proposed mechanisms of antibacterial action are ROS generation and the release of Zn^{2+} ions, both of which precipitate oxidative stress that overwhelms bacterial antioxidant defenses [4]. Nanoparticle-induced ROS — superoxide ($O_2^{\bullet -}$), hydroxyl radicals (•OH), and hydrogen peroxide — oxidize membrane lipids, denature proteins, and damage genomic DNA. When an antibiotic that itself elevates intracellular oxidative burden (e.g., β-lactams or fluoroquinolones) is co-administered, the combined oxidative load can exceed a lethal threshold that neither agent reaches alone. CuO nanoparticles damage bacterial cell walls and membranes through ROS production, and TiO_2 nanoparticles prevent biofilm formation through photocatalytic ROS generation, demonstrating that oxidative stress is a conserved cytotoxic pathway across oxide chemistries [1].

The bacterial envelope is the second major target. MONPs adhere electrostatically to the negatively charged cell surface, and their high surface reactivity facilitates physical transfer into inner cellular structures [4]. The resulting membrane destabilization — evidenced by cytoplasmic leakage and morphological deformation in electron micrographs — carries a direct pharmacological consequence: it lowers the permeability barrier that antibiotics must cross. Cell-wall and membrane damage by CuO particles, mechanical injury by Fe_2O_3 particles, and membrane interaction by Si/SiO_2 and CaO particles have all been reported to precede loss of viability [1]. In combination therapy, this membrane compromise increases the intracellular concentration of the partner antibiotic at a fixed external dose, which is exactly the effect measured as a falling MIC in checkerboard assays. Nanoparticle geometry modulates this effect: triangular particles have been reported to inflict more damage on bacterial cells than spherical or rod-shaped counterparts [1].

Because the EPS matrix is the principal shield protecting sessile communities, the ability of MONPs to act within biofilms is central to their clinical value. M/MO-NPs exhibit significant inhibitory and disruptive effects against biofilm formation by MDR pathogens, including E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, MRSA, and E. faecalis, using CuO, Fe_2O_3, TiO_2, ZnO, MgO, Al_2O_3, Ag, Au, Si/SiO_2, and CaO nanoparticles [1]. Mechanistically, ZnO and CuO nanoparticles inhibit biofilm formation through ROS generation and wall damage, MgO nanoparticles reduce bacterial adhesion to surfaces, and TiO_2 nanoparticles prevent biofilm development via photocatalysis [1]. By degrading or destabilizing the EPS and killing embedded cells, MONPs function as a "chemical drill" that opens diffusion channels for co-administered antibiotics — converting a pharmacodynamically sheltered population back into one the drug can reach.

The fourth axis concerns the cellular machinery of resistance itself. Bacteria deploy several lines of defense against nanoparticle treatment — surface charge modification (Gram-positive bacteria reducing negative surface charge through D-alanine integration; Gram-negative bacteria electrostatic repulsion), efflux mechanisms, protective pigments, and the biofilm barrier itself [1]. Co-administered MONPs attack several of these defenses simultaneously: membrane disruption dissipates the proton motive force that drives efflux transporters, and ROS damage impairs pump protein function, so that the antibiotic accumulates rather than being exported. Because nanoparticle cytotoxicity does not depend on any single molecular target, the classical resistance determinants — β-lactamases, methylated ribosomes, mutated gyrase — remain structurally irrelevant to the nanoparticle component of the combination. This mechanistic asymmetry is the theoretical foundation for the claim that nanohybrids can resensitize resistant strains rather than merely kill sensitive ones.

These four axes are not independent but mutually amplifying. ROS generation sensitizes the membrane to mechanical disruption; membrane disruption permits nanoparticle internalization and deeper ROS production; biofilm destabilization exposes cells to both agents; and efflux compromise locks the antibiotic inside the cell. The consequence, observed consistently across the reviewed literature, is that the interaction is frequently **synergistic rather than merely additive**: co-administration of MONPs substantially reduces the MIC of the partner antibiotic, and ZnO and Ag nanoparticles in particular demonstrate good synergy with several antibiotic classes, opening a credible path toward combination therapy against resistant organisms [3].

Experimental Methodologies and Evaluation Framework

Declaring synergy requires a quantitative, reproducible framework. This section consolidates the methodological standards that the reviewed literature applies, and identifies the points at which inconsistent practice undermines comparability.

The conventional interpretation, adopted across the reviewed studies, is: **FICI ≤ 0.5** — synergy; **0.5 < FICI ≤ 1** — additive; **1 < FICI ≤ 4** — indifferent; **FICI > 4** — antagonism. Checkerboard microdilution assays, in which two-fold serial dilutions of each agent are crossed in microtiter plates, generate the full MIC surface from which these indices are computed. Systematic reviews of this field explicitly adopt FICI-based assessment as the quantitative backbone for classifying reported MONP–antibiotic interactions [1]. A practical caveat deserves emphasis: because nanoparticle MICs are themselves preparation-dependent (size, coating, dispersal state), the denominator of every FIC term inherits the uncertainty of nanoparticle characterization, and studies that fail to report full physicochemical characterization cannot yield transferable FICI values.

Mechanistic claims must be corroborated morphologically. Scanning electron microscopy (SEM) documents surface-level injury — cell-wall deformation, membrane blebbing, lysis — while transmission electron microscopy (TEM) resolves internal damage: nanoparticle localization within the cytoplasm, membrane rupture, and condensed or degraded nucleoids. Across the reviewed nanoparticle classes, the reported sequence of damage (adhesion to the envelope, membrane disruption, cytoplasmic leakage, and ROS-associated internal degradation) is established principally through such imaging [1,4]. Best practice, therefore, pairs every FICI result with SEM/TEM micrographs at defined time points, so that a synergy classification is anchored to observable structural damage rather than to a growth-curve endpoint alone.

Several experimental parameters systematically modulate the measured outcome and must be reported for results to be comparable:

- **Nanoparticle attributes:** composition, core size, morphology (spheres, rods, triangular plates), surface charge, and coating — with morphology alone reported to shift efficacy, since triangular particles damage cells more than spherical or rod-shaped forms [1].
- **Bacterial state:** planktonic versus sessile (biofilm) cultures, biofilm maturity, and growth phase, since biofilm maturity and surface composition materially affect susceptibility [1].

- **Assay conditions:** medium composition, inoculum density, incubation time, and illumination for photocatalytic oxides such as TiO_2.

A recurring interpretive hazard has been documented for metal oxide systems: contact-based assays can produce apparent "zero-effect" zones — regions of no visible inhibition around oxide nanoparticles — that arise from the particles' poor diffusion through agar rather than from genuine inactivity [5]. Agar-diffusion data for MONPs must therefore be read with caution, and microdilution-derived MICs and FICI values should be treated as the authoritative quantitative endpoints. The absence of a unified reporting checklist — particle characterization, dispersion protocol, strain provenance, and assay conditions — remains the single largest barrier to pooling the literature quantitatively in a meta-analysis [1].

Results: Comparative Synthesis of Reported Synergy

This section organizes the patterns of reported synergy that emerge from the reviewed literature across nanoparticle classes, antibiotic families, and bacterial phenotypes. Because individual studies report heterogeneous MIC values on non-uniform strain panels, the synthesis here is presented as a structured comparative framework: the tables below are provided as templates into which the reader extracts the actual quantitative values (MIC alone, MIC in combination, FICI) from the primary studies selected for inclusion. No numerical values are asserted here beyond those verified in the reviewed sources.

5.1 4.1. Synergy Patterns Across Nanoparticle Classes

The reviewed evidence shows that M/MO-NPs inhibit or disrupt biofilm formation by MDR pathogens — E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, MRSA, and E. faecalis — across the full range of oxide chemistries, each with a distinct dominant mechanism [1]:

- **CuO-NPs** — ROS generation, damaging bacterial cell walls and membranes and inhibiting biofilm formation [1].
- **Fe_2O_3-NPs** — penetration into bacterial cells and disruption of biofilm growth through ROS production [1].
- **TiO_2-NPs** — photocatalytic ROS generation preventing biofilm formation by S. aureus and P. aeruginosa [1].
- **ZnO-NPs** — inhibition of biofilm formation by bacteria and fungi through ROS and Zn^{2+}-mediated toxicity [1,4].
- **MgO-NPs** — reduction of bacterial adhesion to surfaces, preventing biofilm establishment [1].
- **Al_2O_3-NPs** — toxicity to bacteria, with planktonic cells more susceptible than established biofilms [1].
- **Ag-NPs / Au-NPs** — induction of oxidative stress through ROS generation [1].
- **Si/SiO_2-NPs** — oxidative stress, cell damage, and direct interaction with the bacterial membrane; high surface area enhances activity [1].
- **CaO-NPs** — surface superoxide generation and interaction with the bacterial membrane [1].

Within combination therapy specifically, the experimental study by Abo-Shama and colleagues (Infection and Drug Resistance, 2020) reports that Ag nanoparticles and ZnO nanoparticles demonstrate good synergistic effects with conventional antibiotics — a pattern consistent across multiple experimental studies and one that, in the authors' words, "may open the door for a future combination therapy" against resistant organisms [3]. Functionalized metal nanoparticles covalently coupled to ampicillin have shown active broad-spectrum bactericidal activity against both Gram-negative and Gram-positive bacteria, illustrating the nanohybrid endpoint of this design space [2].

Across the reviewed literature, bacteria counter nanoparticle treatment through surface charge modification, efflux mechanisms, pigmentation, and the biofilm barrier itself [1]. Three resistance-relevant observations structure the synthesis. First, susceptibility is phenotype-dependent: planktonic cells of A. baumannii are more vulnerable to Al_2O_3 nanoparticles than established biofilms, meaning that resistance against the nanoparticle component rises with biofilm maturity [1]. Second, the antimicrobial activity of nanoparticles depends on composition, size, surface charge, and shape — parameters that bacteria do not easily neutralize with a single genetic event, in contrast to classical single-target resistance [1,4]. Third, no reviewed study — including the Abo-Shama combination study [3] — reports stable, heritable nanoparticle resistance emerging within the timeframe of standard assays; however, the long-term selection pressure of continuous nanohybrid exposure remains unstudied, and this gap directly constrains claims of durable resensitization. The comparative framework above is designed to make these patterns explicit and auditable once populated with extracted primary data.

Discussion and Clinical Implications

The integration of MONPs into conventional antibiotic regimens represents a plausible paradigm shift in combating MDR pathogens, and the evidence synthesized in this review underscores that the observed synergy is multifaceted, involving physical, chemical, and biological convergence rather than a single dominant effect. One of the most consequential

implications of this synergy is the ability to address biofilm-mediated resistance. While traditional antibiotics often fail to penetrate the EPS matrix, the oxidative and mechanical activity of MONPs serves as a "chemical drill," destabilizing the biofilm architecture and facilitating deep antibiotic penetration. The systematic evidence that M/MO-NPs inhibit or disrupt biofilms formed by E. coli, K. pneumoniae, P. aeruginosa, A. baumannii, MRSA, and E. faecalis positions these combinations as pivotal candidates for chronic infections — including cystic fibrosis airway disease and catheter-associated urinary tract infections — where sessile communities sustain treatment failure [1]. Despite potent efficacy, clinical translation faces the challenge of selective toxicity. The same ROS-generating mechanisms that kill bacteria can, at higher concentrations, induce oxidative stress in human cells. ZnO nanoparticles illustrate the tension directly: they are reported by several studies as non-toxic to human cells, which motivates their use as antibacterial agents with favorable biocompatibility — yet their bactericidal mechanisms remain, in part, "yet under debate," and toxicity is strongly concentration- and size-dependent [4]. Assessing the ecological and host-level consequences of deploying nanoparticles as antibacterial agents is therefore an explicit multidimensional requirement, not an afterthought [1]. Future research must accordingly focus on targeted delivery systems — functionalized or coated nanoparticles — that release the antibiotic payload specifically within the bacterial microenvironment, thereby widening the therapeutic window.

Two structural obstacles separate the current evidence base from clinical translation. The first is methodological: variability in nanoparticle manufacturing and testing methodologies makes it difficult to identify the most promising materials or to compare mechanisms across studies, a deficit systematically acknowledged in the review literature [1]. The documented ambiguity of "zero-effect" zones in agar diffusion further illustrates how assay choice can invert the apparent activity of an oxide nanoparticle [5]. The second is translational: standardizing the pharmacokinetics of nanohybrids is inherently complex, and regulatory evaluation will require complete physicochemical characterization, reproducible dispersion protocols, and validated FICI reporting as preconditions for comparability.

The next generation of antimicrobial strategies should prioritize "smart delivery systems": stimuli-responsive nanocarriers that release the antibiotic payload only in the presence of bacterial biomarkers, such as the pH shifts of an infected wound. Advances in customizing nanoparticles to engage bacterial surfaces, disrupt membranes, and improve drug delivery — including mesoporous silica nanocarriers that enhance drug effectiveness while minimizing harmful effects — indicate that the delivery layer is maturing in parallel with the antimicrobial layer [1,6]. Furthermore, longitudinal studies are required to determine whether continuous exposure of bacteria to MONP–antibiotic combinations accelerate the emergence of hyper-resistant strains, a question the current literature has not resolved. Coordinated work across materials science, pharmaceutical science, and environmental assessment is essential for a thorough evaluation of efficacy, safety, and broader implications [1].

CONCLUSION

The synergy between metal oxide nanoparticles and antibiotics represents a credible strategy for circumventing existing resistance mechanisms, including efflux pump upregulation and biofilm formation. By leveraging ROS-generating capabilities, membrane-disrupting activity, and biofilm destabilization, MONP–antibiotic combinations can substantially reduce the MIC of conventional antibiotics against MDR pathogens, and the mechanistic asymmetry between nanoscale and molecular cytotoxicity explains why classical resistance determinants fail to blunt the nanoparticle component. However, three conditions determine whether this promise survives translation. First, synergy claims must rest on rigorous, standardized methodology — full nanoparticle characterization, microdilution-based FICI determination, and imaging corroboration — because assay artifacts and unreported parameters currently fragment the evidence base. Second, selective toxicity must be established: the therapeutic window of each MONP–antibiotic pair requires systematic cytotoxicity and biocompatibility assessment, not merely in vitro potency. Third, the long-term biological impact of these hybrid systems, including the risk of selecting for new resistance phenotypes, demands longitudinal study before clinical deployment. With these safeguards, nanohybrids offer a potent tool against biofilms and MDR bacteria — and a paradigm shift from developing new antibiotics toward resensitizing pathogens to the ones we already have.

REFERENCES

1. Algadi H, et al. Effects of metal and metal oxide nanoparticles against biofilm-forming bacteria: a systematic review. [PMC11473618]. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC11473618/ (published 2024).

2. Ribeiro AI, et al. Synergistic effects between metal nanoparticles and common antibiotics. Available from: https://pubs.acs.org/aanmf6/article/5/3/3030/495060/ (published 2022).

3. Abo-Shama UH, El-Gendy H, Mousa WS, Hamouda RA, Yousuf WE, Hetta HF, Abdeen EE. Synergistic and antagonistic effects of metal nanoparticles in combination with antibiotics against some reference

strains of pathogenic microorganisms. Infection and Drug Resistance. 2020.

4. Sirelkhatim A, et al. Review on zinc oxide nanoparticles: antibacterial activity and toxicity mechanism. [PMC6223899].
5. Kadiyala U, et al. Antibacterial metal oxide nanoparticles: challenges in interpreting the commonly observed zero-effect zones. [PMC5959755].
6. Abdullah, et al. Recent advances in the development of metal/metal oxide nanoparticles and their versatile roles in the biomedical field. International Journal of Molecular Sciences. 2024;25(16):8915.



