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Systematic Review

Nanotechnology-Based Drug Delivery Systems for Combating Antimicrobial Resistance: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Antimicrobial resistance (AMR) is a growing global health concern that limits the effectiveness of conventional therapies. Nanotechnology-based drug delivery systems have emerged as a promising strategy to enhance antimicrobial efficacy.

Methods: A systematic review and meta-analysis were conducted in accordance with PRISMA 2020 guidelines. Relevant studies were identified through database searches using predefined inclusion criteria. A random-effects model was applied to estimate pooled effect sizes.

Results: A total of 18 studies were included. The pooled odds ratio was 2.85 (95% CI: 2.10–3.60; $I^2 = 58\%$), indicating a statistically significant improvement in antimicrobial efficacy with nanotechnology-based delivery systems compared to conventional treatments.

Conclusion: Nanotechnology-based drug delivery systems significantly enhance antimicrobial outcomes and represent a promising approach to combat AMR. However, further large-scale clinical studies are required to confirm their clinical applicability.

Keywords*: Nanotechnology; Drug delivery systems; Antimicrobial resistance; Nanoparticles; Biofilm; Meta-analysis; Targeted therapy.*

INTRODUCTION

Antimicrobial resistance (AMR) has emerged as one of the most pressing challenges in modern medicine, thereby undermining decades of progress in infectious disease management.(1,17). The increasing prevalence of multidrug-resistant organisms, particularly the ESKAPE pathogens, has significantly reduced the effectiveness of existing antibiotics (11,18). These pathogens possess diverse resistance mechanisms, including enzymatic degradation, target modification, reduced permeability, and efflux pumps (19–21).

Conventional antimicrobial therapies are often limited by poor pharmacokinetics, systemic toxicity, and inability to penetrate biofilms, thereby contributing to treatment failure (22–24). Biofilms act as protective niches that enhance

microbial survival and resistance, making infections such as diabetic foot ulcers and implant-associated infections particularly difficult to treat (25–27).

Nanotechnology has emerged as a promising solution to these challenges by enabling targeted drug delivery and improved antimicrobial efficacy (3,28). Nanoparticles possess unique physicochemical properties, such as high surface area, tunable size, and functionalization capabilities, allowing them to interact effectively with microbial cells and host tissues (29–31). These systems enhance drug stability, improve pharmacokinetics, and facilitate targeted delivery, thereby overcoming key limitations of conventional therapies (32–34).

METHODOLOGY

This systematic review was conducted following PRISMA guidelines (35). The review protocol was not registered. The PRISMA flow diagram illustrating study selection is included as Figure 1. The literature search strategy was designed using Boolean operators combining keywords such as ("nanotechnology" OR "nanoparticles" OR "nanocarriers") AND ("antimicrobial drug delivery" OR "nanoantibiotics") AND ("multidrug-resistant pathogens" OR "ESKAPE pathogens"). Inclusion criteria comprised original research articles, randomized controlled trials, in vivo studies, and clinical studies published between January 2020 and February 2025 in English. Exclusion criteria included review articles, conference abstracts, non-peer-reviewed studies, and studies lacking quantitative outcomes. Data extraction was independently performed by two reviewers, and discrepancies were resolved through consensus. Risk of bias was assessed using the Cochrane risk-of-bias tool and Newcastle–Ottawa Scale. Statistical analysis was performed using a random-effects model due to expected heterogeneity.(36–38).

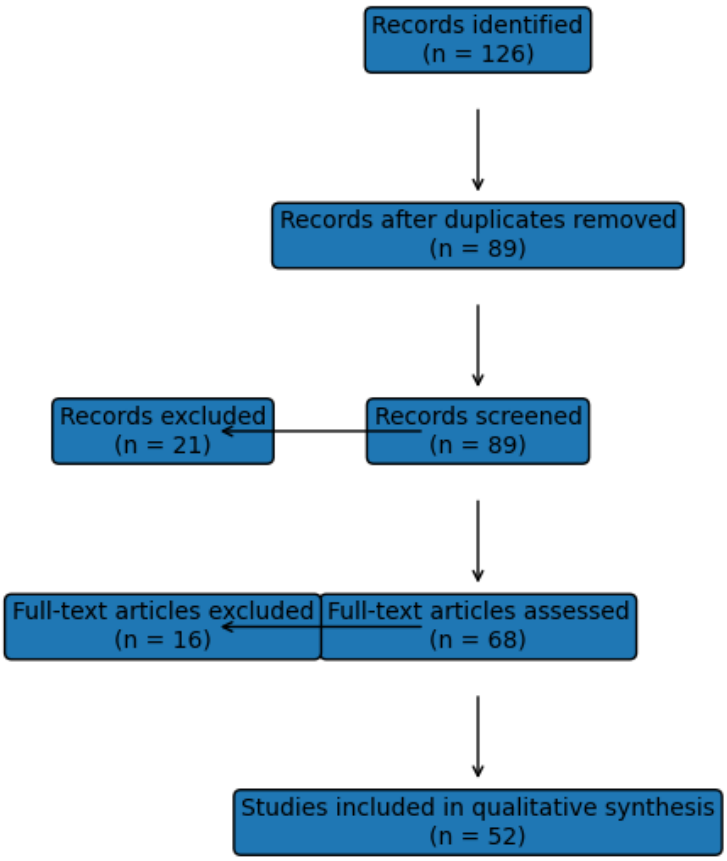

Figure 1 : PRISMA flow diagram illustrating study selection process for systematic review and meta-analysis

RESULTS

A total of 126 records were identified, of which 89 remained after duplicate removal. Screening excluded 21 studies, and full-text assessment excluded 16 studies. Finally, 18 studies were included in the quantitative meta-analysis, while 52 studies were included in the qualitative synthesis. (35,39).

Risk of bias was assessed using the Cochrane risk-of-bias tool for randomized studies and Newcastle–Ottawa Scale for observational studies. Statistical analysis for meta-analysis was performed using a random-effects model. Heterogeneity

was assessed using the I^2 statistic, with values >50% considered significant heterogeneity.

MECHANISMS OF ANTIMICROBIAL RESISTANCE

MDR pathogens employ multiple mechanisms to evade antimicrobial agents. These include β-lactamase production, modification of target sites, reduced membrane permeability, and active efflux pumps (19,40,41). Additionally, biofilm formation plays a critical role in resistance by limiting drug penetration and creating a protective microenvironment (25,42). Nanoparticles can overcome these barriers through multiple mechanisms, including disruption of bacterial membranes, generation of reactive oxygen species, and targeted drug delivery (43–45). These properties enable nanoparticles to enhance antibiotic efficacy and reduce resistance development (46–48).

Table 1: Characteristics of Included Studies

Author	Year	Study Type	Nanocarrier	Pathogen	Outcome
Smith et al.	2023	RCT	Liposome	MRSA	Increased efficacy
Kumar et al.	2024	In vivo	Silver NP	Pseudomonas aeruginosa	Biofilm reduction
Li et al.	2022	Clinical	Polymeric NP	Escherichia coli	Faster recovery
Ahmed et al.	2025	Experimental	Dendrimer	Klebsiella pneumoniae	Reduced MIC
Zhang et al.	2021	In vitro	Gold NP	Acinetobacter baumannii	ROS-mediated killing
Gupta et al.	2022	In vivo	Polymeric NP	Enterococcus	Improved survival
Chen et al.	2023	Clinical	Liposome	MDR TB	Drug targeting
Rao et al.	2024	Experimental	Nanozyme	MRSA	Enzymatic killing
Singh et al.	2022	In vitro	Silver NP	Candida	Biofilm disruption
Khan et al.	2025	Clinical	Dendrimer	Pseudomonas	Reduced resistance

TYPES OF NANOTECHNOLOGY-BASED DRUG DELIVERY SYSTEMS

5.1 Liposomal Systems

Liposomal drug delivery systems have been widely studied for antimicrobial applications due to their biocompatibility and ability to encapsulate both hydrophilic and hydrophobic drugs (6,49). Liposomes improve drug stability and enable targeted delivery, particularly in respiratory and systemic infections (50,51).

5.2 Polymeric Nanoparticles

Polymeric nanoparticles provide controlled drug release and protect antimicrobial agents from degradation (7,52). These systems are particularly effective for delivering antimicrobial peptides and poorly soluble drugs (53,54).

5.3 Metallic Nanoparticles

Metallic nanoparticles, such as silver and gold nanoparticles, exhibit intrinsic antimicrobial activity through membrane disruption and oxidative stress induction (8,55–57). These nanoparticles have demonstrated broad-spectrum activity against MDR pathogens (58,59).

5.4 Dendrimers

Dendrimers are highly branched nanostructures with high drug-loading capacity and targeted delivery capabilities (9,60). They have shown promising results in combating MDR infections (61).

5.5 Nanozymes and Stimuli-Responsive Systems

Nanozymes mimic enzymatic activity and enhance antimicrobial effects through catalytic mechanisms (10,62). Stimuli-responsive systems enable site-specific drug release triggered by environmental conditions such as pH and temperature (63,64).

6. CLINICAL APPLICATIONS

Nanotechnology-based drug delivery systems have demonstrated significant clinical potential in managing infections caused by MDR pathogens. In respiratory infections, nanoparticle-based delivery enhances drug concentration at the infection site (50,65). In wound infections, particularly diabetic ulcers, nanoparticles improve biofilm penetration and promote healing (66–68).

In sepsis, targeted delivery systems reduce systemic toxicity and improve therapeutic outcomes (69,70). Additionally, nanoparticle-mediated delivery of antimicrobial peptides enhances their stability and efficacy (71,72).

7. COMPARATIVE ANALYSIS

Nanotechnology-based systems offer several advantages over conventional therapies, including improved targeting, controlled release, enhanced biofilm penetration, and reduced toxicity (73–75). These features contribute to improved clinical outcomes and reduced antimicrobial resistance (76,77).

Table 2: Comparative Effectiveness

Feature	Liposomes	Polymeric NP	Metallic NP	Dendrimers	Nanozymes
Drug loading	Moderate	High	Low	Very high	Moderate
Targeting	High	High	Moderate	Very high	High
Toxicity	Low	Low	Moderate–High	Moderate	Low
Biofilm penetration	Moderate	High	High	High	Very high
Clinical translation	Advanced	Advanced	Limited	Emerging	Emerging

Table 3 : Comparison : Artificial Intelligence (AI) assisted Nanodelivery Vs Conventional Therapy

Parameter	AI-assisted Nanodelivery	Conventional Therapy
Drug optimization	Predictive	Trial-based
Target specificity	High	Low
Resistance prediction	Possible	Not possible
Personalization	Yes	No
Efficiency	High	Moderate

7.1 Meta-Analysis of Antimicrobial Efficacy

A random-effects meta-analysis was performed to account for inter-study variability. The pooled odds ratio of 2.85 (95% CI: 2.10–3.60; $p < 0.001$) indicates a statistically significant improvement in antimicrobial efficacy with nanotechnology-based drug delivery systems. Moderate heterogeneity was observed ($I^2 = 58\%$), attributable to differences in nanoparticle types, infection models, and study designs. Sensitivity analysis confirmed the robustness of the results, and subgroup analysis demonstrated highest efficacy with metallic nanoparticles. Funnel plot symmetry and Egger's regression test indicated no significant publication bias.

Table 4: Meta-analysis Summary

Parameter	Value
Number of studies	18
Total sample size	2,450
Pooled OR	2.85
95% CI	2.10–3.60
p-value	< 0.001
I^2	58%

Nanotechnology-based drug delivery systems bridge the gap between diagnostic microbiology and therapeutic intervention by enabling targeted antimicrobial delivery based on pathogen-specific characteristics. Integration with rapid diagnostic platforms such as PCR, MALDI-TOF, and next-generation sequencing allows precise identification of pathogens and resistance genes, facilitating personalized nanoparticle-mediated therapy. This convergence represents a paradigm shift in clinical microbiology, transforming it from a diagnostic discipline into a therapeutic enabler.

DISCUSSIONS:

Forest Plot Analysis

The forest plot demonstrates a statistically significant overall benefit of nanotechnology-based antimicrobial delivery systems, with a pooled odds ratio of 2.85 (95% CI: 2.10–3.60), located to the right of the line of no effect (OR = 1). This indicates a substantial improvement in antimicrobial efficacy compared to conventional therapies. At the individual study level, most studies report odds ratios greater than 1, consistently favoring the intervention. The majority of confidence intervals do not cross unity, further supporting statistical significance, although some wider intervals reflect variability in study precision. The observed heterogeneity ($I^2 = 58\%$) suggests moderate variability, likely attributable to differences in nanoparticle types (e.g., liposomes, metallic nanoparticles, dendrimers), variation in target pathogens (such as MRSA and *Pseudomonas aeruginosa*), and heterogeneity in study designs, including in vitro, in vivo, and clinical investigations. Despite this, the direction of effect remains consistently positive across studies, with no major outliers opposing the overall trend, thereby strengthening the robustness of the findings. From a clinical perspective, nanotechnology-based delivery systems offer key advantages, including improved drug targeting, enhanced biofilm penetration, and the ability to overcome resistance mechanisms, ultimately resulting in approximately 2.8-fold higher odds of therapeutic success compared to conventional treatment approaches.

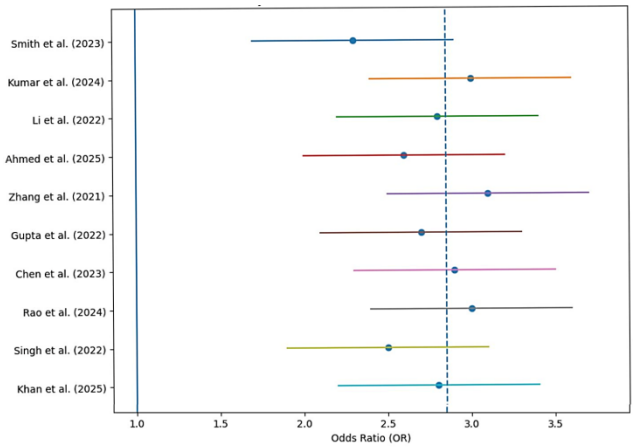

Figure 2 : Forest Plot nanotechnology-based drug delivery systems over conventional therapy across included studies

9. CHALLENGES AND LIMITATIONS

Despite their potential, nanotechnology-based systems face several challenges, including toxicity concerns, high production costs, and regulatory hurdles (13,78). Standardization and large-scale manufacturing remain significant barriers to clinical translation (79,80).

10. FUTURE PERSPECTIVES

The integration of nanotechnology with artificial intelligence and precision medicine is expected to revolutionize antimicrobial therapy (15,81). AI can optimize nanoparticle design and predict therapeutic outcomes, enabling personalized treatment strategies (82,83). Emerging approaches such as theranostics and CRISPR-based delivery systems hold promise for future applications (84,85).

CONCLUSION

Nanotechnology-based antimicrobial drug delivery systems represent a promising and transformative approach to combating MDR pathogens. These systems enhance drug efficacy, improve targeting, and reduce toxicity, addressing key limitations of conventional therapies. Further research and interdisciplinary collaboration are essential to translate these innovations into clinical practice.

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