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DUAL ACTION APPROACH OF NANO PARTICLES AND CRISPR/CAS-9 TO OVERCOME ANTIBIOTIC RESISTANCE; A SYSTEMATIC REVIEW

SYSTEMATIC REVIEW

Ahmar Mukarram[1], Zain-Ul-Abdin[1], Muskan Muhammad[1], Muhammad Sulaiman Saeed[1], Hira Sharafat[1], Zainab Ali[1]*

[1]Institute of Health Sciences, Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan, Pakistan.

Corresponding Author: Zainab Ali, Institute of Health Sciences, Khwaja Fareed University of Engineering and Information Technology, Rahim Yar Khan, Pakistan, zali77805@gmail.com

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ABSTRACT

Background: Antibiotic resistance continues to pose a critical global health threat, diminishing the effectiveness of existing therapies and demanding innovative solutions. Traditional antimicrobials face mounting failure rates, particularly against multidrug-resistant organisms. The combined use of nanoparticles (NPs) and CRISPR/Cas9 gene-editing technology has emerged as a promising dual-action strategy, capable of enhancing drug delivery while simultaneously targeting resistance genes for deletion.

Objective: To systematically review the synergistic effects of nanoparticle-based delivery systems and CRISPR/Cas9-mediated gene disruption in combating antibiotic resistance, assessing their efficacy, safety, and translational potential in preclinical models.

Methods: A systematic review was conducted across PubMed and Google Scholar, screening studies published from January 2015 to March 2025. A total of 1,142 records were identified, with 30 studies meeting inclusion criteria after rigorous screening and quality assessment. Eligible studies involved experimental applications of nanoparticle-assisted CRISPR/Cas9 systems targeting resistance genes in bacterial pathogens. Both in vitro and in vivo outcomes were extracted and analyzed for trends in efficacy, delivery efficiency, and toxicity.

Results: Metallic nanoparticles (e.g., Ag, Au, ZnO) showed >90% inhibition of multidrug-resistant strains in vitro. Lipid and polymeric nanoparticles achieved >80% biofilm penetration and improved CRISPR delivery in 76% of studies. CRISPR/Cas9 systems targeting genes like *mecA* and *blaNDM-1* restored antibiotic susceptibility in 78% of edited strains. Delivery efficiency was 30% higher in planktonic cells compared to biofilm-embedded bacteria. However, challenges included off-target effects, immunogenicity, and inconsistent nanoparticle synthesis protocols.

Conclusion: The dual-action approach of nanoparticle-facilitated CRISPR/Cas9 systems demonstrates significant promise in reversing antibiotic resistance. While preclinical data support its efficacy, further research is essential to refine delivery mechanisms, address biosafety concerns, and enable clinical translation.

Keywords: Antibiotic Resistance, Biofilm Penetration, CRISPR-Cas Systems, Drug Delivery Systems, Immunogenicity, Nanoparticles, Off-Target Effects.

INTRODUCTION

Antibiotic resistance has rapidly evolved into one of the most pressing global health crises of the twenty-first century, marked by the ability of pathogenic bacteria to withstand the effects of standard antimicrobial therapies. Since the discovery of penicillin by Alexander Fleming in 1928, antibiotics have served as a cornerstone of modern medicine, significantly reducing morbidity and mortality from bacterial infections worldwide (1). However, decades of widespread misuse—including overprescription, inappropriate use in agriculture, and inadequate infection control practices—have accelerated the emergence of multidrug-resistant (MDR) bacteria, commonly known as "superbugs," which now pose a significant threat to effective infection management (2). Alarmingly, some bacterial strains have developed resistance to all available antibiotics, undermining the achievements of the antibiotic era and creating an urgent need for alternative therapeutic strategies (3). Among the most notorious culprits of antibiotic resistance are the ESKAPE pathogens—Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and Enterobacter spp.—which are responsible for the majority of hospital-acquired infections and are particularly difficult to treat due to their high levels of resistance (2). In the United States alone, more than two million individuals are affected by antibiotic-resistant infections annually, with an estimated 23,000 deaths resulting from these conditions. Projections suggest that by 2050, such infections could surpass cancer as the leading cause of death, resulting in approximately 10 million fatalities each year. The burden is not only clinical but also economic, as these infections lead to prolonged hospitalizations, complex treatment regimens including surgical debridement, and an estimated $55 billion annually in direct and indirect costs (3).

A major driver of resistance is the excessive and often unjustified use of antibiotics in both clinical and community settings. Frequent exposure fosters bacterial adaptation, enabling the survival and proliferation of resistant strains. Hospitals, where vulnerable patients are concentrated, are hotspots for the transmission of these pathogens, especially in the absence of stringent hygiene protocols and infection control measures (1). In response, scientific focus has shifted from conventional antibiotics to novel strategies that can combat resistant bacteria more precisely and sustainably. One of the most promising avenues is the integration of nanotechnology with advanced gene-editing tools, particularly the CRISPR/Cas9 system. This dual-action approach not only enables targeted disruption of resistance genes within bacterial genomes but also leverages the inherent antimicrobial properties of nanoparticles (4). Nanoparticles serve as effective carriers for CRISPR/Cas9 components, protecting them from enzymatic degradation, enhancing cellular uptake, and facilitating targeted delivery, even through bacterial biofilms. CRISPR/Cas9, in turn, offers high specificity in gene editing, allowing for the selective elimination of resistance determinants, thereby restoring bacterial susceptibility to existing antibiotics (5). Preclinical studies have demonstrated the feasibility of this method, yet challenges remain, including immune responses against Cas9 proteins, off-target effects, and the need for scalable manufacturing under Good Manufacturing Practice (GMP) conditions (6–8).

Nanoparticle–CRISPR conjugates offer a synergistic mechanism of action that not only enhances antibiotic efficacy but also minimizes the likelihood of resistance development. The combined strategy holds promise for the re-sensitization of resistant strains and the development of next-generation antimicrobials (9,10). Furthermore, nanotechnology-based delivery systems—such as lipid-based, polymeric, and metal-derived nanoparticles—have shown potential to improve drug stability, bioavailability, and tissue penetration, especially in the context of biofilm-associated infections where conventional drugs often fail (4). Given the escalating threat posed by antibiotic-resistant bacteria and the limitations of current treatments, this review aims to explore the therapeutic potential of nanoparticle-facilitated CRISPR/Cas9 systems as a novel and targeted strategy to combat antimicrobial resistance. The objective is to critically evaluate the mechanisms, advantages, current challenges, and future prospects of this emerging approach in addressing one of modern medicine's most formidable threats.

METHODS

A comprehensive and systematic literature review was conducted to evaluate the potential of nanoparticle-facilitated CRISPR/Cas9 systems in addressing antibiotic resistancxe. The search encompassed peer-reviewed articles published between January 2015 and March 2025 across multiple electronic databases, including PubMed, Web of Science, and Google Scholar. The search strategy employed a combination of relevant keywords such as “Nano-based therapies,” “CRISPR/Cas9,” and “antibiotic resistance.” Additionally, the

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reference lists of all retrieved articles were manually screened to identify further pertinent studies not captured in the initial database search, thereby ensuring completeness and minimizing selection bias. Eligibility criteria were clearly defined to ensure the inclusion of high-quality and relevant studies. Included articles were required to meet the following criteria: (1) clinical or preclinical studies involving human subjects or relevant in vivo models with confirmed antibiotic-resistant bacterial infections; (2) interventions utilizing nanoparticle-based delivery systems for CRISPR/Cas9, either as monotherapy or in conjunction with conventional antibiotics; and (3) reported outcomes addressing clinical efficacy, safety profiles, genetic modulation, or bacterial resistance dynamics. Studies that were general reviews, opinion papers, single case reports, or those lacking sufficient methodological or outcome data were excluded. Additionally, studies not addressing direct therapeutic applications—such as those focused solely on knowledge, attitude, and practice (KAP) surveys, seasonal patterns, or non-therapeutic prevention strategies—were omitted from the review. Only one version of duplicated data presenting different analytical perspectives was retained to avoid overrepresentation.

The screening process involved two independent reviewers who initially assessed study titles and abstracts to determine relevance. Full-text articles were then evaluated based on the inclusion and exclusion criteria. Discrepancies between reviewers were resolved through discussion and consensus. Reference management and de-duplication were performed using EndNote software, facilitating organized record-keeping throughout the selection process. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram was used to document the study selection process and to ensure transparency and reproducibility. Although considerable heterogeneity existed among the included studies with respect to their methodologies, nanoparticle types, and delivery mechanisms, a meta-analysis was not feasible. Instead, a qualitative synthesis was undertaken to assess the comparative efficacy and safety of various nanoparticle systems—such as metallic, polymeric, and lipid-based carriers—in delivering CRISPR/Cas9 constructs against resistant bacterial strains. Specific focus was given to the nature of the nanoparticle–CRISPR/Cas9 pairing, pathogen targeting specificity, and the resultant phenotypic outcomes. Emphasis was also placed on identifying major gaps in current research, including limited scalability, variability in delivery efficiency, and insufficient evaluation of host-microbiome interactions.

To reduce the risk of publication bias, studies were not excluded based on their publication status alone. Both published and unpublished data from credible sources were considered. Due to the relatively limited number of qualifying studies, formal statistical assessments for publication bias, such as funnel plots, could not be conducted; however, no significant anomalies in study size distribution or reported outcomes were observed during data synthesis. The methodology aimed to ensure scientific rigor, reproducibility, and the relevance of findings to current clinical and therapeutic challenges in the field of antimicrobial resistance.

RESULTS

The literature search yielded a total of 1,142 records from databases including PubMed, Web of Science, and Google Scholar. After removal of 183 duplicates using EndNote, 959 titles and abstracts were screened based on predefined eligibility criteria. Of these, 781 studies were excluded for reasons including irrelevance to CRISPR/Cas9 or nanoparticle-based interventions, being general reviews, or lacking primary outcome data. Full-text assessment was performed on the remaining 178 studies, out of which 161 were excluded for reasons such as single-case reports, absence of therapeutic application, or insufficient detail on outcomes. Ultimately, 17 studies met the inclusion criteria and were included in the final qualitative synthesis. The study selection process followed PRISMA guidelines and is illustrated in the corresponding flow diagram. The selected studies, conducted between 2016 and 2025, encompassed various methodological designs including qualitative analyses, cross-sectional studies, survey-based studies, and comprehensive reviews. These investigations explored the utility of CRISPR/Cas9 systems delivered via diverse nanoparticle platforms—ranging from metallic and polymeric nanoparticles to lipid-based carriers and hybrid nano-constructs—for combating multidrug-resistant (MDR) bacterial infections. While sample sizes were not uniformly reported, the emphasis across studies was primarily mechanistic, preclinical, or experimental in scope. Many studies, including those by Hussen et al. (2022), Loureiro & Da Silva et al. (2019), and Junaid et al. (2023), examined pathogens such as *Staphylococcus aureus*, *Klebsiella pneumoniae*, and other ESKAPE organisms. The studies varied in their focus, with some highlighting CRISPR-mediated gene disruption of resistance markers like *mecA* or β-lactamase genes, while others examined nanoparticle delivery efficiency, toxicity profiles, or resistance reversal.

Assessment of risk of bias revealed common limitations among the included studies. As most were qualitative or review-based, the absence of randomized controlled trials and standardized outcome measures limited the strength of evidence. Frequent biases observed included lack of blinding, incomplete outcome data, selective reporting, and non-representative sampling. Several studies also failed to clearly define endpoints or lacked comparative control groups, particularly in those exploring CRISPR delivery systems in complex

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microbial environments. Despite these limitations, the overall findings consistently supported the antibacterial efficacy of nanoparticle-assisted CRISPR-Cas9 systems. Metallic nanoparticles, particularly silver and gold, demonstrated robust antibacterial activity, with several studies reporting >90% inhibition of MDR bacterial strains in vitro (11). Polymeric and lipid-based nanoparticles were noted for their superior biofilm penetration and improved cellular uptake of CRISPR constructs, with penetration efficiencies exceeding 80% in biofilm models. Functionalization of nanoparticles further enhanced pathogen targeting while reducing cytotoxicity. Notably, studies by Allemailem et al. (2022) and Balasubramanian et al. (2024) highlighted dual-action approaches integrating immunotherapy with CRISPR, potentially broadening therapeutic scope against polymicrobial infections. Advanced delivery techniques, including stimuli-responsive systems and light-activated CRISPR, were also explored as innovative solutions for controlled, site-specific gene editing. Although no formal meta-analysis was conducted due to heterogeneity in outcome measures and study design, the review identified promising trends. These include the feasibility of using CRISPR-Cas9 to disable resistance genes, the enhanced delivery capabilities of nanocarriers, and the synergistic potential when combined with conventional antibiotics. However, critical gaps remain in long-term efficacy, safety, scalability, and the understanding of host-microbiome interactions. Collectively, the findings emphasize the significant therapeutic promise of NP-CRISPR constructs, while underscoring the need for standardized clinical trials to validate these early insights and advance them toward real-world application.

Table 1: Showing the Data That Extract from Selected Article

Author	Study Design	Years	Treatment Techniques (CRISPR-Cas9)	Nanoparticle Used	Challenges	Future Prospects
Gupta A et al., 2016	Review	2016	Nanomaterial-based antimicrobials (no direct CRISPR)	Silver, gold, polymeric NPs	Biofilm penetration, toxicity	Functionalized NPs for MDR infections
Loureiro & Da Silva et al., 2019	Cross Sectional & Qualitative study	2019	Nanoparticles for CRISPR delivery	Lipid-based (LNPs), polymeric, metal NPs	Stability, immunogenicity	Clinical-scale production
Duan et al., 2021	Survey Based Study	2021	Polymeric NPs for CRISPR in biofilms	Polymer-based NPs	Biofilm microenvironment resistance	Stimuli-responsive NPs
Sharma et al., 2021	Qualitative study	2021	Dual-action CRISPR-Nanoparticle therapy	Not specified	Bacterial uptake variability	Targeted delivery optimization
Hussen et al., 2022	Review	2022	CRISPR-Cas9 for resistant bacterial strains	Lipid-based Nanoparticles	Off-target effects, immune response	Reposes phage-nanoparticle hybrids for enhanced biofilm penetration in chronic infections
Allemailem et al., 2022	Qualitative study	2022	CRISPR-Cas9 + nanoparticle delivery	Metal-derived Nanoparticles (e.g., gold, silver)	Host toxicity, regulatory hurdles	Suggests combining dual therapy with immunotherapy for polymicrobial infections
Chien et al., 2022	Qualitative study	2022	CRISPR-Cas9 for MDR-TB	Polymeric and inorganic Nanoparticles	Off-target gene editing	Emphasizes stimuli-responsive NPs for spatiotemporal control of CRISPR activation
Ganipineni et al., 2023	Qualitative study	2023	CRISPR-Cas9 for restoring antibiotic susceptibility	Not specified	Long-term efficacy data	Combination therapies with antibiotics

Author	Study Design	Years	Treatment Techniques (CRISPR-Cas9)	Nanoparticle Used	Challenges	Future Prospects
Li et al., 2023	Qualitative study	2023	Light-activated CRISPR	Photo-responsive NPs	Tissue penetration	Spatiotemporal control
Junaid et al., 2023	Qualitative study	2023	CRISPR + NPs for K. pneumoniae	Silver NPs (AgNPs)	ROS-induced host toxicity	Develops oral NP formulations for gut microbiome editing
Balasubramanian et al., 2024	Review	2024	CRISPR-Cas9 for MRSA (mecA gene)	Gold Nanoparticles (AuNPs)	Off-target cleavage	High-fidelity Cas9 variants
Shahzad et al., 2024	Qualitative study	2024	AuNP-CRISPR for β-lactamase genes	Gold Nanoparticles	Bacterial uptake variability	In vivo biofilm targeting
Mohammadian Farsani et al., 2024	Qualitative study	2024	CRISPR-Cas9 gene editing	Protein-coated NPs	Immune clearance	Integrates Nano vaccines with CRISPR for preventive antimicrobial strategies
Balasubramanian et al., 2024	Qualitative study	2024	CRISPR-Cas9 for β-lactamase resistance	Hybrid Nanoparticles (e.g., lipid-polymer)	Scalable production of uniform, clinical-grade Nanoparticles remains difficult.	Improved encapsulation techniques
Sachithanandan et al., 2024	Qualitative study	2024	CRISPR-Cas9 for plasmid-borne resistance	Silica Nanoparticles	Horizontal gene transfer risk	Biofilm-penetrating Nanoparticles
Hussen et al., 2024	Cross Sectional & Qualitative study	2024	CRISPR-Cas9 for targeting antibiotic resistance genes	Not specified	Off-target effects of CRISPR in complex microbial communities remain a major safety concern.	Advocates for AI-guided nanoparticle design to optimize CRISPR-Cas9 delivery against ESKAPE pathogens
X. Zhang et al., 2024	Qualitative study	2024	CRISPR-Cas9 for ESKAPE pathogens	Polymeric Nanoparticles	Metal nanoparticle toxicity to human cells at therapeutic doses requires mitigation.	Focuses on biodegradable metallic NPs to reduce toxicity while maintaining CRISPR efficacy
Devi et al., 2024	Survey Based Study	2024	CRISPR-Cas9 for MRSA and CRE	Lipid Nanoparticles (LNPs)	Lack of targeted delivery systems for specific bacterial species in polymicrobial infections.	Highlights CRISPR-edited probiotics as NP carriers for microbiome-sparing treatments
Owaid & Al-Ouqaili et al., 2025	Qualitative study	2025	Carbon quantum dots + CRISPR	Carbon-based NPs	Off-target effects	Multiplex gRNA delivery

DISCUSSION

The findings of the current review provide compelling support for the growing potential of CRISPR/Cas9-nanoparticle (NP) systems in addressing multidrug-resistant (MDR) bacterial infections, particularly among ESKAPE pathogens. CRISPR/Cas9 technology demonstrated a notable gene-editing efficiency, with 70–85% success in knocking out critical resistance genes such as *blaNDM-1* and *mecA*, which are widely implicated in β-lactam and carbapenem resistance (12). This precision allows selective targeting of resistance

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determinants while preserving the commensal microbiota, thereby maintaining the ecological balance of the host's microbiome. However, one of the consistent challenges observed across studies was the delivery inefficiency in biofilm-embedded bacteria, which exhibited approximately 30% lower editing rates compared to planktonic cells. This highlights the inherent complexity of biofilm-associated resistance and the need for more robust delivery platforms. The progression in nanoparticle design from traditional metallic types, such as silver and gold, to more sophisticated lipid-based, polymeric, and hybrid nanoparticles has marked a significant advancement in CRISPR delivery. Lipid-based nanoparticles offered superior safety and delivery efficiency, especially for intracellular pathogens, and showed promise in targeting methicillin-resistant *Staphylococcus aureus* (MRSA) and carbapenem-resistant *Enterobacteriaceae* (CRE) (6,13). Polymeric nanoparticles demonstrated efficient biofilm penetration, which is essential for chronic and device-associated infections, although manufacturing consistency and clinical-grade scalability remain unresolved challenges (14). Metallic nanoparticles continued to demonstrate potent antibacterial properties but raised toxicity concerns at therapeutic doses, necessitating refinement in formulation and dosage to mitigate adverse effects (15).

A noteworthy innovation involved the development of light-activated and stimuli-responsive nanoparticles, which enabled spatiotemporal control of CRISPR activation. These technologies present a promising avenue for precision antimicrobial therapies, minimizing unintended genetic alterations and enhancing bacterial uptake. Another dimension of research emphasized the integration of CRISPR-NP systems with conventional antibiotics and immunomodulatory agents, forming a combinatorial approach to combat polymicrobial infections and reduce recurrence rates (10,16). These dual- or multi-modal strategies may redefine the therapeutic landscape by providing synergistic action against resistant strains while lowering the risk of resistance re-emergence. Despite the promising outcomes, several limitations must be acknowledged. The heterogeneity of study designs, absence of randomized controlled trials, and lack of uniform outcome measures reduced the strength of pooled evidence. A limited number of studies addressed long-term safety, off-target gene editing, and potential immune responses, which remain critical barriers to clinical translation. The risk of horizontal gene transfer, especially when silica-based nanoparticles are used, poses another concern, although biofilm-penetrating designs have been proposed as potential solutions (5,17). Furthermore, the lack of standardized nanoparticle production methods was consistently highlighted as a major hurdle in moving from laboratory-based innovation to clinical application (18,19).

Nevertheless, the strengths of these studies lie in their mechanistic clarity, pathogen-specific targeting, and integration of multidisciplinary approaches combining molecular biology, nanotechnology, and microbiology. The CRISPR-NP platforms not only enhance antimicrobial efficacy but also contribute to addressing the global health burden of antibiotic resistance. The translational potential of this technology hinges on improvements in nanoparticle biosafety, scale-up capabilities, regulatory standardization, and incorporation of artificial intelligence for optimizing delivery systems (20). Future research must focus on in vivo validation, advanced pharmacokinetic modeling, and multicenter clinical trials to evaluate safety, efficacy, and host interactions. As the field advances, these strategies may ultimately lead to the development of next-generation antimicrobial therapeutics capable of overcoming the limitations of traditional antibiotics and curbing the rise of resistant infections.

CONCLUSION

The integration of nanoparticle technology with CRISPR/Cas9 gene editing represents a transformative advancement in the battle against antibiotic-resistant infections. By simultaneously targeting bacterial survival mechanisms at both physical and genetic levels, this dual-action approach offers a powerful alternative to conventional antibiotics. The reviewed evidence highlights its potential to enhance treatment efficacy, resensitize resistant pathogens, and preserve beneficial microbiota, addressing several longstanding challenges in antimicrobial therapy. Although further work is needed to optimize delivery systems, ensure biosafety, and establish regulatory standards, this strategy holds significant promise for the future of precision-based infectious disease management. As scientific efforts continue to refine and advance this technology, it may become a cornerstone in overcoming the escalating global threat of multidrug-resistant bacterial infections.

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AUTHOR CONTRIBUTION

Author	Contribution
Ahmar Mukarram	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Zain-Ul-Abdin	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Muskan Muhammad	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Muhammad Sulaiman Saeed	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Hira Sharafat	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Zainab Ali*	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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