



The Role of Nanomaterials in the Treatment of Multidrug-Resistant Bacteria: A Systematic Review

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Abstract

Multidrug-resistant (MDR) bacteria pose a significant global health challenge, rendering many conventional antibiotics ineffective. Nanomaterials have emerged as a potential solution to combat this growing threat. The objective of this study is to evaluate the effectiveness of various nanomaterials in treating MDR bacteria and identify trends in their mechanisms of action, efficacy against different bacterial strains, and potential synergistic effects with conventional antibiotics. This study was conducted as a systematic literature review following PRISMA guidelines. For articles published from inception until April 2024, a comprehensive literature search was conducted in PubMed, Cochrane Library, Dimensions, and Google Scholar. Of the 7022 potential articles assessed, 19 met the inclusion criteria. Nanomaterials, especially silver nanoparticles, showed significant antimicrobial activity against MDR bacteria. The efficacy against MDR bacteria was influenced by factors such as surface charge, particle size, and combination with conventional antibiotics. Positively charged silver nanoparticles showed the highest bactericidal activity. The combination of nanoparticles demonstrated significantly enhanced antimicrobial effects compared to single-element nanoparticles ($P < 0.01$). Synergistic results were produced by combining nanoparticles with antibiotics. This review explores the potential of nanomaterials in combating MDR bacteria.

Keywords Nanoparticle · Nanomaterial · Multiple drug Resistant · MDR · Bacteria · Pathogens · Treatment · Therapy

1 Introduction

Antimicrobial resistance (AMR) is among the twenty-first century's most catastrophic and widely researched healthcare issues. The World Health Organization (WHO) has ranked AMR as one of the top ten threats to the global population, which shows a need for new strategies to address this challenge [1]. As traditional antibiotics have proven less effective when it comes to these resistant pathogens,

it is imperative to seek new strategies for containing these bacteria [2]. Hence, nanomaterials have emerged as a viable strategy for developing new antimicrobial compounds and enhancing the existing treatment modalities.

The development of antibiotic resistance is a gradual process accelerated by the increased misuse and overuse of antimicrobial agents in medical practice and agriculture [3]. Bacteria can develop antibiotic resistance in multiple ways, including target site modification, enzymatic antibiotic degradation, efflux pumps, and alteration of the outer membrane permeability [4]. This has led to the evolution of several resistant genes, especially the horizontal gene transfer, which has produced MDR strains resistant to several antibiotic classes [5].

Among them are *methicillin-resistant Staphylococcus aureus* (MRSA), *vancomycin-resistant Enterococci* (VRE), and *carbapenem-resistant Enterobacteriaceae* (CRE), which are classified as either severe or urgent by the CDC [6]. Figure 1 shows the classification of common MDR bacteria.

The consequences of AMR are significant and predominantly unfavorable. AMR could cost 1.2 trillion USD and

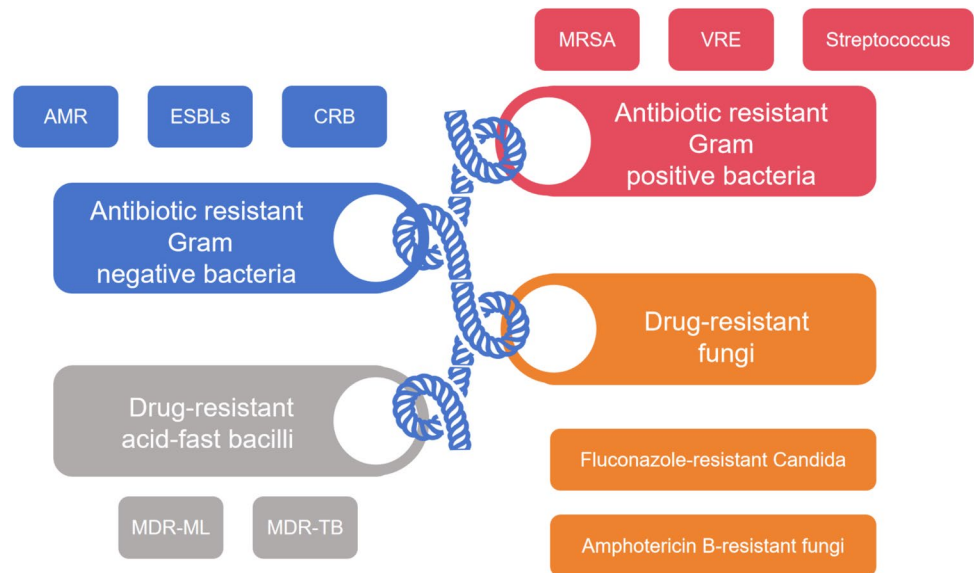
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Fig. 1 The classification of common MDR bacteria



annually kill between 20 and 40 million people if no measures are taken [7]. The effects of AMR are that it does not only affect mortality rates but also food security, economic development, and health [8]. The COVID-19 pandemic has further highlighted the understanding of global health issues' interconnectivity and the need to search for different solutions.

With this threat still developing, the scientific community has turned its focus to the application of nanotechnology. Nanomaterials are materials with at least one physical property feature within 1 to 100 nm, providing unique properties for antimicrobial activity [9]. These characteristics include high surface area-volume ratios, greater reactivity, and the ability to interact with biological systems at the molecular level [10]. Various types of nanomaterials have also been examined for their antibacterial effects, such as metal nanoparticles (silver, gold, copper), metal oxide nanoparticles (zinc oxide, titanium oxide), and carbon nanomaterials (graphene oxide, carbon nanotubes) [11]. Among these, silver nanoparticles, especially AgNPs, have gained much interest because of their broad-spectrum antimicrobial activity and non-toxicity to human cells [12]. Silver has been known to possess antimicrobial properties and used to treat infection in wounds and burns for some time [13]. Nanoformulations of silver particles show enhanced antimicrobial efficiency compared to bulk silver mainly because of the enhanced surface area and unique physiochemical characteristics [14].

Nanomaterials have several possible advantages for combating MDR bacteria. Most nanomaterials exhibit multiple modes of action against bacteria [15]; they can disrupt bacterial cell membranes, produce reactive oxygen species (ROS) [16], and interfere with bacterial metabolism [17]. Additionally, they inhibit biofilm formation, which makes them effective against resistant strains and reduces the likelihood

of further resistance development. Figure 2 illustrates the role of common nanomaterials in combating MDR bacteria, although the potential for resistance cannot be entirely ruled out. Furthermore, nanomaterials have a potential synergetic effect when used with conventional antibiotics [18]. Several works indicate that nanoparticles enhance the action of antibiotics against resistant bacteria, suggesting the ability to use smaller antibiotic dosages or resensitization of bacteria to previously effective drugs [19]. This combination technique may help to conserve the existing stock of antibiotics and provide solutions to treat MDR infections [20].

Moreover, the possibility of using nanomaterials in the design of lateral flow rapid diagnostic tests for MDR bacteria has been considered to improve the rational use of antibiotics [21]. However, there are some disadvantages and concerns regarding applying nanomaterials against MDR bacteria. The two main concerns are the characteristics of stability of nanomaterials and the consequences on human beings and the environment in the long course of use [22]; these areas require more extensive comprehensive studies before these nanomaterials go for general use in clinical settings. Some problems that need to be addressed include toxicity to human cells, its accumulation in tissue, and effects on other species in ecosystems. Nevertheless, the current approaches of nanoparticle fabrication should be flexible and cost-effective to be integrated into the healthcare system.

The legal requirements for nanomaterial-based antimicrobials are also evolving. Currently, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are developing appropriate regulatory policies for the assessment of Nano-therapies and antimicrobial nanomaterials [23]. One of the primary regulatory challenges is the characterization of physicochemical properties, which are crucial for understanding the behavior of nanomaterials

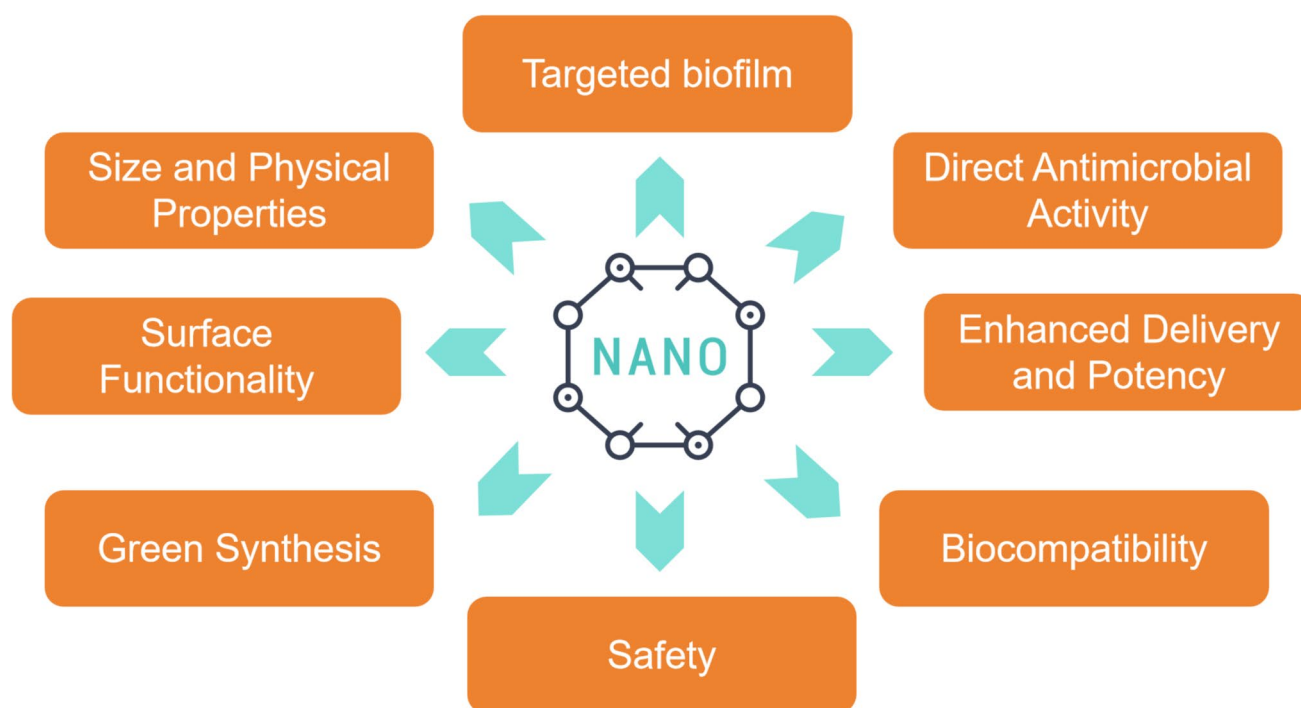


Fig. 2 The role of common nanomaterials in combating MDR bacteria

in biological systems. This includes assessing their size, shape, surface charge, and composition, all of which can influence their pharmacokinetics and pharmacodynamics. Regulatory bodies such as the FDA and EMA have emphasized the need for robust characterization methods to ensure consistent quality and performance of nanomedicines [24, 25]. Another significant hurdle is the assessment of nanotoxicity. Due to their small size and high surface area, nanomaterials can interact with biological systems in unpredictable ways, potentially leading to oxidative stress, genotoxicity, and other adverse effects. Current regulatory guidelines often lack specific provisions for nanoscale materials, which complicates the evaluation of their safety profiles. This has led to calls for developing nanospecific testing protocols to predict better potential risks associated with nanomedicines [26, 27].

The manufacturing process of nanomedicines also presents regulatory challenges. The complexity of these processes can lead to variability in product quality, making it essential to establish stringent quality control measures. Implementing Quality by Design (QbD) approaches has been recommended to address these issues, ensuring that critical quality attributes are consistently met throughout the production process [24, 28]. Based on the study's findings, the development of nanomaterials and their transition to clinics will necessitate the revision of many guidelines and the standardization of testing protocols. As the research and application of nanomaterial-based antimicrobials continue,

collaboration between material scientists, microbiologists, pharmacologists, and clinicians will be essential. Such collaborations can lead to advancements in the design of nanoparticles, the identification of pathways, and the optimization of the efficacy and safety of nanomaterial-mediated therapies for MDR infections.

Given the need to develop new strategies to combat AMR and the potential of nanomaterials in this fight, the following systematic review aims to offer a critical review of the literature on using nanomaterials in managing MDR bacteria. By synthesizing and analyzing the available evidence, this review seeks to evaluate the efficacy of various nanomaterials and the potential of the mutual influence of nanomaterials and traditional antibiotics against MDR bacterial strains. The following comprehensive analysis should provide insights that would aid in designing novel nanomaterial-based strategies for overcoming the global issue of MDR bacteria.

2 Materials and Methods

2.1 Research Approach

This study was conducted as a systematic literature review focusing on nanomaterials' role in treating MDR bacteria. Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISM A2020) guidelines [29] were used to find

relevant published studies. This review evaluated nanomaterials' effectiveness in treating MDR bacteria and compared this efficacy to standard antibiotic treatments. Studies fulfilling the modified PICOS criteria were selected [30]. The PICOS criteria for eligible studies were defined as follows;

Population (P): The range of microorganisms included the Gram-positive bacteria *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus vulgaris*.

Intervention (I): Treatment using different nanomaterial particles.

Comparison (C): Treatment using standard antibiotics without nanomaterials.

Outcomes (O): Reduced rate of bacterial infections and antibiotic resistance.

Study design (S): Experimental studies, including in vitro, in vivo, and clinical trials, evaluated the role of nanomaterials in the treatment of MDR bacteria.

2.2 Publication Search

A comprehensive electronic database search was conducted via PubMed, Cochrane Library, Dimensions, and Google Scholar to retrieve scholarly articles evaluating nanomaterials' role in treating MDR bacteria. Web of Science and Scopus were not included in the search strategy due to their overlap with the selected databases and the focus on biomedical literature, which is well-covered by PubMed and Cochrane Library. Additionally, Google Scholar was included to capture grey literature and ensure a broad coverage of relevant studies. The following keywords were utilized in different combinations to optimize the search in different databases: Nanoparticles OR nanomaterial OR nanotechnology, OR "multidrug-resistant bacteria" OR MDR, and treatment OR therapy, as shown in Table 1 (Appendix).

2.3 Inclusion and Exclusion Criteria

Inclusion criteria

- i. Scholarly articles published in the English language or could be translated into the English language.
- ii. Scholarly articles focused on nanomaterials' role in treating multi-drug-resistant bacteria.
- iii. Scholarly experimental articles, i.e., in vitro, in vivo, and observational studies.

Exclusion criteria

- i. Scholarly research articles that duplicated or continued the work of previous publications, opinion pieces,

reviews, abstracts, or editorial articles that did not have precise methods or results.

- ii. Scholarly research articles that deviated from the role of nanomaterials in the treatment of MDR bacteria.
- iii. Scholarly research articles were conducted on plants.

2.4 Study Selection and Extraction

After completing the initial search strategy, studies were systematically selected through title and abstract screening to eliminate ineligible articles. Full texts of the remaining studies were additionally assessed based on the specified inclusion and exclusion criteria. The following data sets were systematically extracted from the included studies: study, study design, study settings, type of nanomaterial, targeted bacteria, method of nanomaterial application, outcomes, and findings. Extracted data were tabulated in an Excel workbook using Microsoft Excel software version 2019.

2.5 Data Synthesis and Statistical Analysis

Extracted data were thematically analyzed and reported according to the following predominant themes: antimicrobial efficacy and bacteria response. A meta-analysis was not conducted due to insufficient quantitative data from included studies.

2.6 Methodological Quality Assessment

The Joanna Briggs Institute critical appraisal checklist for cohort study was used to assess the methodological quality of the included studies.

2.7 Evidence Certainty Assessment

The quality of evidence for each outcome was assessed using the Grading Recommendations to Assess Development and Evaluation System (GRADE), one of the international standards for the quality of evidence and the classification of recommendation strength [31]. Moreover, the quality of the evidence can be classified into four levels: I (high), II (moderate), III (low), and IV (very low).

3 Results

3.1 Study Selection Outcome

A total of 7022 articles were identified, of which 309 were in PubMed, 1 in Cochrane Library, 3252 in Dimensions, and 3460 in Google Scholar. Of the 7022 relevant citations, 2307 were duplicates, and 3273 articles were eliminated due to lack of concise methods and results to be evaluated. After

checking the titles and abstracts against the inclusion criteria, 108 potentially relevant studies were sought for retrieval and subsequently retrieved. After screening the complete text, 89 articles were excluded. The reasons for exclusion were articles did not focus on the role of nanomaterials in the treatment of MDR bacteria, case reports, and systematic reviews. Nineteen articles were considered eligible for review after screening, as shown in Figure 3 (Appendix).

3.2 Methodological Quality Assessment

The results of the methodological quality assessment are summarized in Table 3 (Appendix). The tool assessed the quality of each study through several parameters, including group similarity, exposure measurement, validity and reliability of measurements, identification and handling of confounding factors, outcome measurement, follow-up procedures, and statistical analysis. All studies in the final column (overall) received an “include” status, indicating they met the minimum quality standard for inclusion.

3.3 Main Study Characteristics

A summary of the characteristics of included studies in terms of the author, study design, study settings, type of nanomaterial, targeted bacteria, method of nanomaterial application, outcomes, and findings has been provided in Table 2 (Appendix). All the included studies were in vitro experimental studies. The studies were published between 2009 and 2022, and most were conducted in India. The primary outcome measures were antimicrobial activities, bacterial growth, and minimum inhibition concentration levels of nanoparticles.

3.4 Outcomes

3.4.1 Antimicrobial Efficacy

Numerous studies assessed various nanoparticle antimicrobial efficacy, especially silver nanoparticles (AgNPs), against different MDR bacterial strains. For instance, according to an investigation by Abbaszadegan et al. [32] on the impact of surface charge on bacterial activity, it was revealed that silver nanoparticle surface charge was a significant factor in terms of impacting bacterial activity. The highest bacterial activity against various tests performed on microorganisms was recorded from an experiment that had silver nanoparticles that were positively charged, with the least bacterial activity being shown by the negatively charged silver nanoparticles and intermediate bacterial effects being manifested by neutrally charged silver nanoparticles [32]. Similarly, research by Almalah et al. [33] showed that AgNPs synthesized using *C. zeylanica* extract exhibited

strong antibacterial activity against both Gram-positive and Gram-negative bacteria, with *S. aureus*, *A. baumannii*, *P. aeruginosa*, and *K. pneumonia* producing inhibition zone diameters of 25, 22, 24, and 24 mm, respectively.

A comparison of the antimicrobial abilities of different types of silver nanoparticles was made by Cavassin et al. [34], with citrate and chitosan AgNPs producing higher bactericidal effects of over 97% and 93 to 94% for antimicrobial-susceptible bacteria and MDR bacteria, respectively. For controls from the same experiment, silver nitrate had a bactericidal effect of over 83% for both antimicrobial-susceptible bacteria and MDR. Silver sulfadiazine produced 67 and 61% for MDR and antimicrobial-susceptible bacteria, respectively [34]. In other similar studies, Huq and Akter [35] reported that biosynthesized AgNPs showed potent antimicrobial activity against *K. pneumoniae* and *S. Enteritidis*. Saraswathi et al. [36] reported that silver nanoparticles synthesized with 5% gelatin could produce bactericidal effects against MDR *Pseudomonas aeruginosa* biofilms. According to Panpaliya et al. [37], silver nanoparticles with a concentration of fewer than fivefold exhibited better bacteriostatic and bactericidal effects than chlorhexidine. Additionally, AgNP produced MIC and MBC values significantly lower than chlorhexidine gluconate ($P < 0.05$) [37]. Research by Arora et al. [38] revealed that when TiO₂ nanoparticles were pre-exposed with one hour of UV irradiation at 0–500 µg/mL, they showed good antibacterial action against *P. aeruginosa*. The MIC value was obtained at 350 µg/mL for TiO₂ nanoparticles. At the same time, gold, copper, and zinc nanoparticles have shown significant antibacterial properties and have been widely studied for their therapeutic effects on MDR bacteria [39].

3.4.2 Synergistic Effect

Several studies investigated the synergistic effects of combining nanoparticles with antibiotics against various bacterial strains, employing appropriate controls to validate the observed effects. These studies included appropriate controls, such as nanoparticles alone, antibiotics alone, and untreated bacterial cultures, to ensure the observed effects were due to the combination rather than individual components. The observed effects could be misinterpreted without such controls, leading to less robust conclusions. For instance, Abdolhosseini et al. compared the effects of Ag-TSC nanoparticles combined with ciprofloxacin on controls treated with nanoparticles alone, antibiotics alone, and untreated cultures. The combination group showed significantly higher antimicrobial activity, confirming a true synergistic effect [40]. Similarly, a significant synergistic effect was produced by combining nanosilver particles with an imipenem [41]. Conversely, even though a combination of TiO₂ nanoparticles and antibiotic CEF did not enhance

antimicrobial activity against *Pseudomonas* sp., there was an excellent synergistic effect of a 24 mm zone of inhibition when TiO₂ nanoparticles were combined with CEZ antibiotic [38]. According to Ashajyothi et al. [42], a synergistic effect was observed from using CuNPs and ZnONPs on antibiofilm activity against different pathogenic bacteria when these nanoparticles were combined with antibiotics. When used alone, CuNPs reduced the biofilm activity by a percentage that was approximately less than 9% in Gram-negative bacteria and less than 2% in Gram-positive bacteria [42]. When combined with antibiotics, CuNPs showed effective biofilm inhibition activity by 12% in Gram-negative and 6% in Gram-positive bacteria [42]. Similarly, Bankier et al. found a significant antimicrobial effect when nanoparticles were placed in combination (NPCS) compared to SENPs [43].

3.4.3 Bacterial Response

Multiple studies assessed the response of MDR bacteria to various nanoparticles. Abdolhosseini et al. observed higher expressions of MexA and MexB genes for strains treated with ciprofloxacin, while gene expressions were reduced among strains treated with Ag-TSC nanoparticles [40]. Ashajyothi et al. [42] observed that while cells from the control group exhibited normal morphology, those exposed for 24 h to a gentamicin concentration of more than 9 µg/ml and CuNPs at a concentration of more than 16 µg/ml exhibited an increase in cell size and change in shape. Similarly, cells treated with a combination of ZnONPs and antibiotics exhibited morphological deformation and a lacking cytoplasm membrane in cells [42]. According to a study by Huq and Akter [35], cells treated with AgNPs exhibited morphological changes in the form of irregular and damaged cell walls, resulting in the ultimate death of the cell. In another study by Naskar et al., cells treated with 5NZO exhibited membrane corrugations due to wrinkling and cell damage, while untreated cells displayed a smooth and intact surface [44].

3.4.4 Bacterial Growth and Inhibition Zones

Some studies separately investigated the impact of nanoparticles on bacterial growth and inhibition zones. Abbaszadegan et al. found that in positively charged AgNPs, there were larger diameters of inhibition zones against all bacterial species than in neutrally and negatively charged AgNPs [32]. Similarly, Al Yousef [41] reported that from observed growth curves of *P. aeruginosa*, Ag-NPs inhibited the growth of *P. aeruginosa* at concentrations of 1.25, 2.5, 5, and 10 µg/ml. Similarly, according to a study by Cavassin et al., silver nitrate produced a lower inhibitory effect against MDR Gram-positive bacteria than AgNPs [34].

3.4.5 Grade Evaluation Outcome

The overall confidence in the evidence for the synergistic effect and bacterial response to nanoparticles was high due to consistent results across multiple studies. The certainty of the evidence for antimicrobial efficacy and bacterial growth and inhibition zone outcomes was moderate due to minor variations in results in some studies, as shown in Table 4 (Appendix).

3.4.6 The Anti-antibiotic-Resistant Bacterial Effects of Other Nanoscale Characteristics

Organic nanoparticles, like liposomes, lipid-based nanoparticles, and polymer nanoparticles, are used due to their biocompatibility and ability to effectively deliver antimicrobial agents [45]. Due to this characteristic, nanoparticles can serve as delivery carriers for antibacterial drugs, improving drug targeting and reducing side effects [46]. At the same time, it can be designed for the controlled release of antibiotics to ensure sustained antibacterial activity [47]. Although nanoparticles provide many benefits, their potential toxicity remains a problem that needs further research to address [47].

4 Discussion

This systematic review explored how nanomaterials, particularly silver nanoparticles (AgNPs), could be used to combat MDR. The findings show that nanomaterials have the potential to be used as a replacement or complementary approach to traditional antibiotics in treating infections from resistant bacteria. One of the critical findings of this review is the strong antimicrobial effect of nanoparticles against MDR bacteria. Most studies observed that nanoparticles, particularly AgNPs, exhibited potent antibacterial activity against Gram-positive and Gram-negative bacteria, including notoriously resistant strains such as *S. aureus*, *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae* [33, 35]. This broad-spectrum activity is auspicious, given how extremely resistant MDR bacteria can be to conventional antibiotic treatments.

The surface charge of AgNPs profoundly influences their antibacterial activity. Abbaszadegan et al. demonstrated that of the three charged silver nanoparticles, positively charged AgNPs exhibited the highest bacterial activity, followed by neutrally and negatively charged AgNPs charged particles, respectively [32]. This finding shows why it is essential to conduct nanoparticle engineering and suggests that optimizing surface charge could enhance the antimicrobial efficacy of nanomaterials. The role of surface charge in antimicrobial activity could be due to the nanoparticles' electrostatic interaction with bacterial cell membranes (negatively charged).

The positively charged nanoparticles might have a high affinity for bacterial cell surfaces, facilitating antimicrobial action. However, this finding may be influenced by several potential confounders, including variations in experimental conditions (e.g., pH, temperature), bacterial strains, and nanoparticle synthesis methods. While nanomaterials show promising antimicrobial activity, the potential for bacteria to develop adaptive resistance mechanisms over time remains a concern.

Comparative studies conducted by Cavassin et al. showed which of the several types of silver-based antimicrobials were relatively more efficient. Citrate and chitosan AgNPs demonstrated superior bactericidal activity compared to conventional silver compounds, including silver nitrate and silver sulfadiazine [34]. This implies that nanoformulations could offer better antimicrobial performance than traditional silver-based treatments. The better efficacy of citrate and chitosan AgNPs could be attributed to changes in their physicochemical properties, such as increased surface area-to-volume ratio and enhanced stability. This would potentially enhance their interactions with bacterial cells. Another vital finding Saraswathi et al. reported is the ability of AgNPs against bacterial biofilms. This offers higher resistance to antibiotics and the host immune response [36]. The effectiveness against biofilms, particularly for MDR *P. aeruginosa*, proves the potential of AgNPs in this critical aspect of bacterial resistance. This antibiofilm activity would be exciting in clinical settings where biofilm-associated infections are frequent, such as device-related or chronic wound infections.

One of this review's emerging themes is the synergistic potential when nanoparticles are associated with conventional antibiotics. Several studies reported enhanced antimicrobial activity using nanoparticles combined with antibiotics [38, 40, 41]. This synergistic effect may significantly affect clinical practice, as lower doses of antibiotics would potentially have less risk of further resistance development. Ashajyothi et al. [42] demonstrated that CuNPs or ZnONPs combined with antibiotics enhanced the antibiofilm activity against various pathogenic bacteria. This raised the possibility of this synergistic effect for Gram-positive and Gram-negative bacteria, indicating broad applications of this approach. The exact mechanisms of such potentiated effects need further investigation. However, some possible explanations include the induction of penetration of antibiotics into bacterial cells due to the presence of nanoparticles, thus causing interference with resistance mechanisms and complementation in modes of antimicrobial action.

The synergy between nanoparticles and antibiotics observed makes the development of new, combined treatments possible. These treatment combinations could not only work better than already known antibiotics but also bring back into use some antibiotics that have been made

resistant. Combining antibiotics with nanoparticles may significantly reduce the required dosages needed in a dose-dependent manner, with concomitant reductions in side effects and resistance development. Knowledge about the mechanism of its antimicrobial activity is vital to develop nanoparticles like therapeutic agents. The research studies reviewed could explain this since they detect bacterial morphological changes and changes in gene expressions.

Research studies by Ashajyothi et al. [42] and Huq and Akter [35] indicated significant cellular damage in the cells of bacteria exposed to nanoparticles. The effects featured an increase in cell size, damage to cell shape and cell membrane, and leakage of cytoplasm. Therefore, these observations bring to the fore that the nanoparticles may damage the integrity of the bacterial cells and thus lead to bacterial cell death. According to Naskar et al. [44], the membrane of the treated bacteria, even with low concentrations of nanoparticles, exhibited membrane corrugations and cell damage. Such morphological alterations present evidence of direct physical interactions between nanoparticles and bacterial cells, supporting the hypothesis that membrane disruption is a general mechanism of nanoparticle action.

Research by Abdolhosseini et al. explored gene expressions and gave more insight into the molecular mechanisms of reduced gene expression [40]. This could indicate that the Ag-TSC nanoparticles are interfering in one way or another with the bacterial efflux pump system associated with antibiotic resistance by reducing MexA and MexB gene expression. This result is significant because it indicates that nanoparticles may reverse or alleviate antibiotic resistance mechanisms at a molecular level. The different facets involved during nanoparticle antimicrobial activity, such as physical cell disruption and interference with molecular resistance mechanisms, may contribute to their effectiveness against MDR bacteria. This multi-target approach potentially makes it all the more challenging for bacteria to develop resistance to nanoparticles compared to conventional single-target antibiotics. Several studies in this review directly compared the efficacy of nanoparticles with conventional antimicrobial agents. In this regard, Panpaliya et al. [37] reported that AgNPs demonstrated improved bacteriostatic and bactericidal activity at lower concentrations than chlorhexidine. This superior performance of nanoparticles over a widely used antiseptic agent highlights their potential as an alternative antimicrobial agent.

Research by Arora et al. [38] on TiO₂ nanoparticles uncovered the new potential for non-silver nanoparticles as antimicrobial agents. Upon UV irradiation, their antibacterial activity against *P. aeruginosa* showed that photo-activated nanomaterials could offer a new avenue in fighting MDR bacteria. This can be important in developing antimicrobial surfaces or materials for healthcare settings. A crucial finding in this review is the comparative effectiveness of

nanoparticles against antibiotic-susceptible and MDR bacterial strains, as exhibited by various studies. This implies that nanoparticles maintain their efficacy even against bacteria that have developed resistance to conventional antibiotics. Due to this feature, nanoparticles could be valuable tools in addressing infections caused by highly resistant pathogens.

This review highlights that different features of nanoparticles, such as size, shape, surface charge, and coating materials, modulate their antibacterial activity. For instance, Abbaszadegan et al. [32] focused on the role of surface charge. In contrast, others showed the effects of various coating materials like citrate and chitosan, as revealed by Cavassin et al. [34]. These results illustrate the importance of nanoparticle property scrutinization and optimization in developing successful antimicrobial agents. The capability of tuning nanoparticle properties also allows solutions to be tailored for a specific bacterial target or clinical application. Future research should be designed to carefully probe these relationships among nanoparticle properties and their activity against microbes to guide the rational design of nanomaterials for medical applications.

Meanwhile, the anti-antibiotic-resistant bacterial effects of other nanoscale features also deserve our attention. Organic nanoparticles, like liposomes, lipid-based nanoparticles, and polymer nanoparticles, are used due to their biocompatibility and ability to effectively deliver antimicrobial agents [45]. Due to this characteristic, nanoparticles can serve as delivery carriers for antibacterial drugs, improving drug targeting and reducing side effects [46]. At the same time, it can be designed for the controlled release of antibiotics to ensure sustained antibacterial activity [47]. Although nanoparticles provide many benefits, their potential toxicity remains a problem that needs further research to address [47]. For instance, the ecotoxicity of metal-based nanoparticles is a critical area of study. These nanoparticles are widely used across industries, yet their environmental and human health impact is not fully understood [48]. The complexity of their chemical composition and the lack of standardized protocols for their study further complicate the understanding of their toxicity. Continuous research and monitoring are essential to develop strategies to mitigate their risks to human and environmental health [49].

In vitro applications of nanomaterials often focus on their use in drug delivery systems, where they can enhance therapeutic agents' solubility, stability, and bioavailability. For instance, carbon nanomaterials, such as carbon nanotubes and graphene, have been widely studied for their potential in targeted drug delivery due to their excellent biocompatibility and ability to penetrate cell membranes [50]. Additionally, nanomaterials are employed in developing biosensors and diagnostic tools, where their high sensitivity and specificity can improve the detection of biomarkers and pathogens [51]. In vivo applications of nanomaterials are equally promising,

particularly in the realm of cancer therapy. Nanoparticles can be engineered to target specific tumor cells, reducing off-target effects and enhancing the efficacy of anticancer drugs. For example, metal selenide nanomaterials have shown potential in tumor therapy due to their strong near-infrared absorption and excellent imaging properties, which allow for precise targeting and monitoring of therapeutic interventions [52]. Furthermore, using nanomaterials in imaging applications, such as bioimaging probes based on magneto-fluorescent nanoparticles, enables non-invasive visualization of biological processes, aiding in diagnosing and treating diseases [53].

Integrating nanotechnology into medicine also extends to developing multifunctional nanomedicines, which can simultaneously deliver drugs, monitor therapeutic responses, and provide imaging capabilities. This approach is exemplified by using multifunctional nanomedicines in personalized treatment plans, facilitating concurrent medication delivery and therapeutic monitoring [54]. Despite the promising applications of nanomaterials in medicine, challenges remain, particularly concerning their safety and biocompatibility. Nanomaterials' potential toxicity and immunogenicity necessitate thorough in vitro and in vivo evaluations to ensure their safe use in clinical settings [55]. Additionally, the development of standardized methods for assessing the safety and efficacy of nanomaterials is crucial for their successful translation from bench to bedside [56].

4.1 Study Strengths, Possible Limitations, and Future Research.

This systematic review captured several essential strengths. First, the researchers searched the literature comprehensively and used rigorous inclusion criteria, ensuring a thorough examination of the available literature. The review also incorporated a comprehensive and formal evaluation of the methodological quality of the reported studies, which provided substantial insights into the validity and credibility of the outcomes. Moreover, the synthesis of data regarding the antimicrobial efficacy of nanomaterials and other combination effects provided helpful information about the new ways to fight against drug-resistant bacterial infections. However, some drawbacks were noted in the review. The researchers did not conduct a quantitative synthesis or meta-analysis due to insufficient data, which would have strengthened the evidence. Additionally, the variability in the study design and methodological approaches of the included studies may have influenced the generalization of the results. These limitations highlight the need for future studies to help fill the knowledge gaps and offer more definitive evidence to inform clinical practices and decisions.

The review focused on studies involving distinct kinds of nanoparticles, mainly silver nanoparticles, which may

not fully represent the impactfulness of all nanomaterials. Disparities in the methods implemented when conducting the studies, in terms of nanoparticle synthesis, the concentrations applied, and the specific bacterial strains under investigation, may also add bias and affect the generalizability of findings across the different investigations. Furthermore, nanomaterials' long-term safety and environmental impact have not been fully addressed. There is also a publication bias, given that only English texts or texts translatable into English were included. Future research should standardize nanoparticle synthesis and antimicrobial testing protocols to enhance result comparability. More comprehensive studies on the long-term effects of nanoparticle exposure on human cells and the environment are also needed. Additionally, future studies should investigate the potential for bacteria to develop resistance to nanoparticle-based treatments and explore strategies to mitigate this risk.

5 Conclusion

This systematic review aims to provide a comprehensive analysis of the current role of nanomaterials in treating MDR bacteria and their future use as a possible solution

to the growing problem of antimicrobial strategy. This review also discusses the vital nanomaterials that show significant antimicrobial potential against MDR pathogens, such as silver nanoparticles. Research also indicates that the particle size, shape, and surface charge strongly determine the efficiency of the nanoparticles, with positively charged particles showing superior bactericidal efficiency. As expected, the convenience of applying nanoparticles alone or in combination with conventional antibiotics allows the prospect of revitalizing existing drugs threatened by resistance mechanisms.

The review also enlightens the various ways nanomaterials fight MDR bacteria, such as through direct physical damage to cell structures of bacteria, generation of reactive oxygen species, disruption of bacterial membranes, and modulation of gene expression. This may explain why nanomaterials are likely to be effective against resistant strains and reduce the probability of bacteria developing further resistance. However, there is a need to address the limitations and the issues that have been pointed out in the present literature, such as differences in the methods used for investigation and the need for more *in vivo* studies and clinical trials in order to assess the effectiveness and safety of the nanomaterials as a treatment in human patients. For future studies, the researchers should standardize the protocols, optimize nanoparticle formulations for specific bacterial targets, and investigate the potential for target delivery systems.

Appendix

Table 1 Search strategy

Database	Search string	Outcome
PubMed	("nanomaterial"[All Fields] OR "nanomaterials"[All Fields] OR "nanoparticle"[All Fields] OR "nanoparticles"[All Fields] OR "nanotechnology"[MeSH Terms] OR "nanotechnology"[All Fields] OR "nanotechnologies"[All Fields]) AND ("multi-drug resistant"[All Fields] OR "multiple drug resistant"[All Fields]) AND ("bacteria"[MeSH Terms] OR "bacteria"[All Fields] OR "bacterium"[All Fields] OR "microbe"[All Fields] OR "microbes"[All Fields] OR "microorganism"[All Fields] OR "microorganisms"[All Fields] OR "pathogen"[All Fields] OR "pathogens"[All Fields] OR "gram-positive"[All Fields] OR "gram-negative"[All Fields]) AND ("treatment"[All Fields] OR "treatments"[All Fields] OR "therapy"[MeSH Subheading] OR "therapy"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "antimicrobial activity"[All Fields])	309
Cochrane library	(nanomaterial* OR nanoparticle* OR nanotechnology*) AND ("multi-drug resistant" OR "multiple drug resistant") AND (bacteria* OR microbe* OR pathogen* OR "gram-positive" OR "gram-negative") AND (treatment OR therapy OR "antimicrobial activity")	1
Dimensions	(nanomaterial OR nanoparticle OR nanotechnology) AND ("multiple drug resistant") AND (bacteria) AND (treatment)	3252
Google Scholar	(nanomaterial OR nanoparticle OR nanotechnology) AND ("multiple drug resistant") AND (bacteria) AND (treatment OR therapy OR antimicrobial activity)	3460
Total		7022

Fig. 3 PRISMA flow diagram for Systematic review with included searches of databases

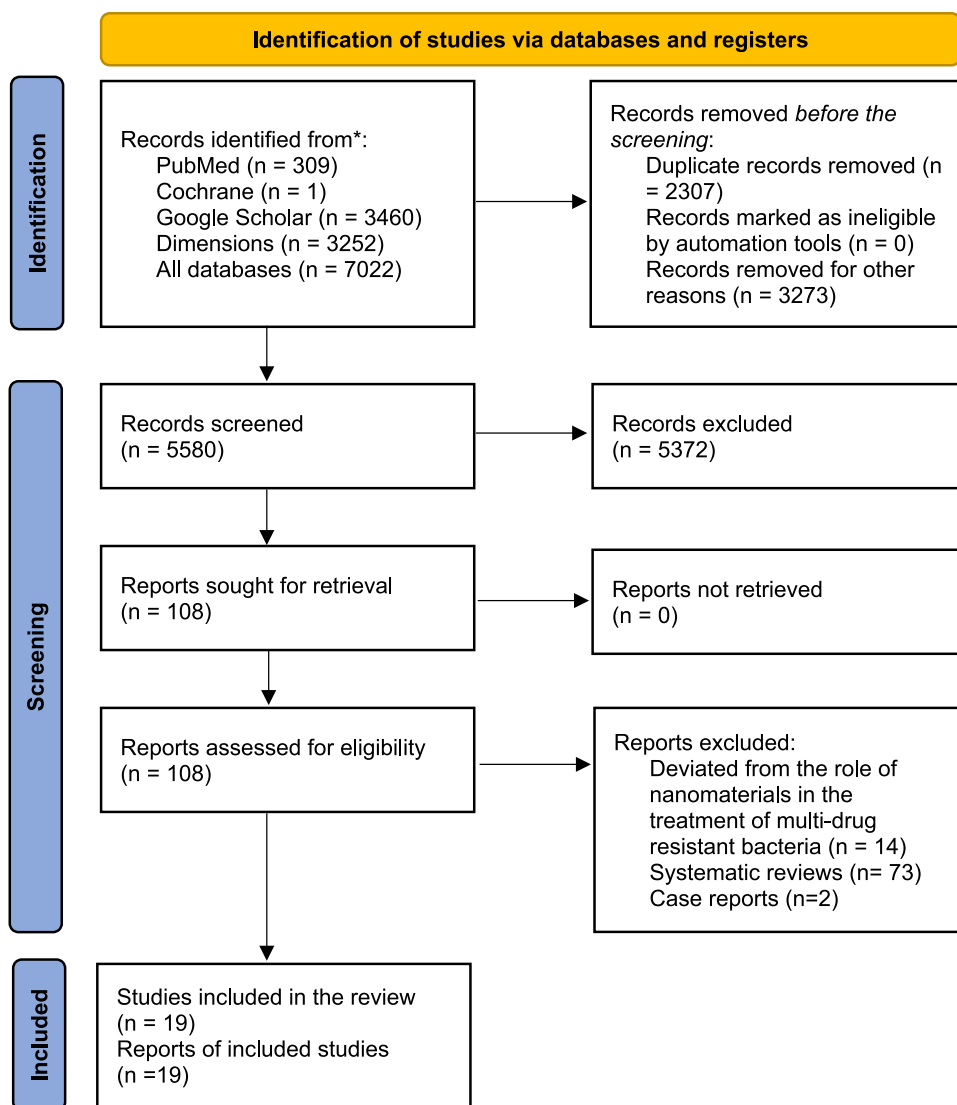


Table 2 Study characteristics

Study	Study design	Study Setting	Type of nanomaterial	Targeted bacteria	Method of nanomaterial application	Outcomes measured	Findings
(Abbaszadegan et al., 2015)	In vitro	Iran	Silver nanoparticles	<i>Staphylococcus aureus</i> , <i>Streptococcus mutans</i> , <i>Streptococcus pyogenes</i> , <i>Escherichia coli</i> , <i>Proteus vulgaris</i>	Well diffusion and micro-dilution tests	Level of effectiveness, surface charge of the silver nanoparticles	The surface charge of silver nanoparticles significantly affects their bactericidal activity. Positively charged nanoparticles are the most effective, followed by neutral and negatively charged nanoparticles
(Abdolhosseini et al., 2019)	In vitro	Iran	Silver nanoparticles conjugated to thiosemicarbazide	<i>Pseudomonas aeruginosa</i>	Silver nanoparticles functionalized by Thiosemicarbazide combined with ciprofloxacin	Expression of <i>mexA</i> and <i>mexB</i> genes, bacterial growth	Significant decrease in <i>mexA</i> and <i>mexB</i> gene expression
(Al Yousef, 2022)	In vitro	Saudia Arabia	Nanosilver (Ag-NP)	<i>Pseudomonas aeruginosa</i>	Microdilution	Minimal inhibitory concentration (MIC), Bacterial growth	The MIC value of Ag-NPs against MDR <i>P. aeruginosa</i> was low (5 µg/ml). The bacterial growths of cells treated with 1.25, 2.5, 5, and 10 µg/ml Ag-NPs were inhibited. All of the combinations showed significant synergistic effects (<i>P</i> -value 0.003)
(Arora et al., 2014)	In vitro	India	Titanium dioxide nanoparticles	<i>Pseudomonas aeruginosa</i>	TiO ₂ nanoparticles were prepared in solution and applied via disk diffusion, broth dilution, and well diffusion assays	Antimicrobial effect	Titanium dioxide nanoparticles showed significant antimicrobial activity against multidrug-resistant <i>P. aeruginosa</i>
(Ashaiyothi et al., 2016)	In vitro	India	Copper nanoparticles (CuNPs), Zinc oxide nanoparticles (ZnONPs)	<i>Staphylococcus aureus</i> , <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , <i>Enterococcus faecalis</i>	Broth dilution	Minimum inhibitory concentration (MIC), antibiofilm activity, morphological changes in bacteria	CuNPs showed higher antibiofilm activity compared to ZnONPs and antibiotics

Table 2 (continued)

Study	Study design	Study Setting	Type of nanomaterial	Targeted bacteria	Method of nanomaterial application	Outcomes measured	Findings
(Bankier et al., 2019)	In vitro	United Kingdom	Tungsten carbide (WC), silver (Ag), copper (Cu)	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i>	Agar diffusion cytometry	Antimicrobial effects	Combination of nanoparticles (NPCs) showed significantly increased antimicrobial effects compared to single elemental nanoparticles (SENP) ($P < 0.01$)
(Cavassin et al., 2015)	In vitro	Not specified	Silver nanoparticles stabilized with citrate, chitosan, polyvinyl alcohol, and commercial silver nanoparticles	Oxacillin-resistant <i>Staphylococcus aureus</i> , vancomycin-resistant <i>Enterococcus</i> spp., carbapenem- and polymyxin B-resistant <i>A. baumannii</i> , carbapenem-resistant <i>P. aeruginosa</i> and carbapenem-resistant Enterobacteriaceae	Agar diffusion	Bactericidal effect	The effect was stronger against Gram-negative than Gram-positive bacteria and similar against multidrug-resistant and susceptible bacteria, with the best result achieved using citrate and chitosan silver nanoparticles
(D'Lima et al., 2020)	In vitro	India	Silver and silver oxide hybrid	<i>Pseudomonas aeruginosa</i>	Disk diffusion assay with nanoparticles impregnated disks	Antimicrobial activity	Silver and silver oxide hybrid exhibited significant antimicrobial activity against multidrug-resistant <i>P. aeruginosa</i>
(Gupta et al., 2017)	In vitro	Not specified	Gold nanoparticles functionalized with hydrophobic ligands	<i>Escherichia coli</i>	Combination therapy with fluoroquinolone antibiotics (ciprofloxacin and levofloxacin)	Antibiotic dosage	Gold nanoparticles act as efflux pump inhibitors and potentially revive ineffective antibiotics
(Huq & Akter, 2021)	In vitro	Bangladesh	Silver nanoparticles (AgNPs)	<i>Klebsiella pneumoniae</i> , <i>Salmonella</i> Enteritidis	Disk diffusion method	Antimicrobial activity, minimum inhibitory concentrations (MICs), and minimum bactericidal concentrations (MBCs)	Strong antimicrobial activity of biosynthesized AgNPs against both pathogens
(Almalah et al., 2019)	In vitro	Saudi Arabia	Silver nanoparticles	Gram-negatives include <i>Acinetobacter baumannii</i> , <i>Klebsiella pneumoniae</i> , <i>Pseudomonas aeruginosa</i> , and <i>Staphylococcus aureus</i> , which are multi-drug-resistant	Biosynthesis using <i>C. zylindricum</i> aqueous extracts	Ultraviolet–visible spectroscopy and TEM, FT-IR analysis	AgNPs showed significant inhibition zones: 25 mm (<i>S. aureus</i>), 24 mm (<i>K. pneumoniae</i> , <i>P. aeruginosa</i>), 22 mm (<i>A. baumannii</i>)

Table 2 (continued)

Study	Study design	Study Setting	Type of nanomaterial	Targeted bacteria	Method of nanomaterial application	Outcomes measured	Findings
(Kasithevar et al., 2017)	In vitro	India	Silver nanoparticles	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , coagulase-negative staphylococci	Disk diffusion assay	Antibacterial activity against multidrug-resistant isolates from post-surgical wound infections	Silver nanoparticles exhibited significant antibacterial activity against multi-drug resistant (MDR) isolates of <i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , and coagulase-negative staphylococci (CoNS) from post-surgical wound infections
(Khan et al., 2017)	In vitro	India	Gold nanoparticles	<i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Enterobacter cloacae</i>	Photodynamic therapy	Selectivity of methylene blue (MB)	Treatment with gold nanoparticles results in 97% killing of multidrug-resistant bacteria
(Lara et al., 2009)	In vitro	Mexico	Silver nanoparticles	Multidrug-resistant <i>Pseudomonas aeruginosa</i>	Suspension in culture media	Inactivation of drug-resistant bacteria and bactericidal mechanism	Silver nanoparticles were found to be effective biocides against drug-resistant bacteria, and they inhibit cell wall synthesis in addition to the synthesis of nucleic acid
(Li et al., 2014)	In vitro	USA	Gold nanoparticles	<i>E. coli</i> , <i>E. cloacae</i> complex, <i>P. aeruginosa</i> , and <i>S. aureus</i>	Incubation of bacteria with gold nanoparticles in broth dilution method	Inhibited growth of multiple strains	Cationic and hydrophobic functionalized AuNPs effectively suppressed the growth of 11 clinical MDR isolates, including both Gram-negative and Gram-positive bacteria
(Naskar et al., 2020)	In vitro	South Korea	Ni ²⁺ -doped zinc oxide nanostructures	Gram-negative (including MDR strains) and Gram-positive (<i>S. aureus</i> , <i>S. epidermidis</i>) bacteria	Agar well diffusion method	Antibacterial activity	Ni ²⁺ -doped zinc oxide nanostructures showed excellent antibacterial activity against <i>A. baumannii</i> and <i>E. coli</i> MDR strains

Table 2 (continued)

Study	Study design	Study Setting	Type of nanomaterial	Targeted bacteria	Method of nanomaterial application	Outcomes measured	Findings
(Panpaliya et al., 2019)	In vitro	Not specified	Silver nanoparticles (AgNP)	<i>Streptococcus</i> mutants (MTCC 497), <i>Streptococcus oralis</i> (MTCC 2696), <i>Lactobacillus acidophilus</i> (MTCC 10307), <i>Lactobacillus fermentum</i> (MTCC 903), <i>Candida albicans</i> (MTCC 183)	Direct application in brain heart infusion broth	Minimum inhibitory concentration and minimum bactericidal concentration	AgNP showed moderate inhibition of bacterial growth. AgNP had lower MIC values (2.82–90 µg/ml) than chlorhexidine gluconate (150–450 µg/ml)
(Saraswathi et al., 2022)	In vitro	Not specified	Silver nanoparticles (G-AgNPs)	<i>Pseudomonas aeruginosa</i>	Silver nanoparticles (AgNPs) embedded in 5% gelatin concentration (AgNP3)	Bactericidal activity, growth of MDR <i>Pseudomonas aeruginosa</i>	Silver nanoparticles inhibited the growth of <i>Pseudomonas aeruginosa</i> biofilms
(Saravanan et al., 2011)	In vitro	India	Silver nanoparticles	<i>Streptococcus pneumoniae</i> , <i>Salmonella</i> Typhi	Extracellular biosynthesis using bacterial strain supernatant	Antibacterial efficacy of silver nanoparticles	Silver nanoparticles showed efficient antimicrobial properties against multidrug-resistant clinical pathogens

Table 3 Quality assessment

Study	Were the two groups similar and recruited from the same population?	Were the exposures measured similarly to assign people to exposed and unexposed groups?	Was the exposure measured validly and reliably?	Were confounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/ participants free of the outcome at the start of the study (or at the moment of exposure)?	Were the follow-up outcomes measured validly and reliably?	Was the follow-up complete, and were the reasons for loss of follow-up described and explored?	Were strategies to address incomplete follow-up utilized?	Was appropriate statistical analysis used?	Overall appraisal
(Abbaszadegan et al., 2015)	Yes	Yes	Yes	No	No	Yes	Yes	Not applicable	Not applicable	Yes	Include
(Abdolhosseini et al., 2019)	Yes	Yes	Yes	No	No	Yes	Yes	Not applicable	Not applicable	Yes	Include
(Al Yousef, 2022)	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Yes	Include
(Almalah et al., 2019)	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Include
(Arora et al., 2014)	Not applicable	Not applicable	Yes	No	No	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Include
(Ashajyothi et al., 2016)	Not applicable	Not applicable	Yes	No	No	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Include
(Bankier et al., 2019)	Not applicable	Not applicable	Yes	No	No	Not applicable	Yes	Not applicable	Not applicable	Yes	Include
(Cavassin et al., 2015)	Not applicable	Not applicable	Yes	No	No	Not applicable	Yes	Not applicable	Not applicable	Yes	Include
(D'Lima et al., 2020)	Not applicable	Not applicable	Yes	No	No	Not applicable	Yes	Not applicable	Not applicable	Yes	Include
(Gupta et al., 2017)	Not applicable	Not applicable	Yes	No	No	Not applicable	Yes	Not applicable	Not applicable	Yes	Include
(Huq & Akter, 2021)	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	No	Include
(Kasithevar et al., 2017)	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	No	Include
(Khan et al., 2017)	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	No	Include
(Lara et al., 2009)	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Yes	Include
(Li et al., 2014)	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
(Naskar et al., 2020)	Yes	Not applicable	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Include
(Pantaliya et al., 2019)	Not applicable	Not applicable	Yes	No	No	Yes	Yes	Not applicable	Not applicable	Yes	Include
(Saraswathi et al., 2022)	Not applicable	Not applicable	Yes	Not applicable	Not applicable	Not applicable	Yes	Not applicable	Not applicable	No	Include
(Saravanan et al., 2011)	Not applicable	Not applicable	Yes	No	No	Yes	Yes	Not applicable	Not applicable	Yes	Include

Table 4 Grade summary of findings

Outcome	GRADE Evidence Profile (Zhang et al., 2018)							Quality	Importance
	Quality assessment								
	Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision			
Antimicrobial efficacy	7	In vitro	Low shown by (JIB) quality assessment results	Not serious	Not serious	Not serious	Moderate	Critical	
Synergistic effect	5	In vitro	Low shown by (JIB) quality assessment results	Not serious	Not serious	Not serious	High	Critical	
Bacterial response	4	In vitro	Low shown by (JIB) quality assessment results	Not serious	Not serious	Not serious	High	Critical	
Bacterial growth and inhibition zone	3	In vitro	Low shown by (JIB) quality assessment results	Not serious	Not serious	Not serious	Moderate	Critical	

Author Contribution MJ. Z and SW. W contributed to the conceptualization and design of the study, as well as the analysis and interpretation of the data. M. I. I contributed to the literature review, data extraction, and critical revision of the manuscript. SS. MN provided expertise in microbiological analysis and contributed to the interpretation of results. WMZ, as the corresponding author, supervised the project, reviewed the manuscript, and ensured the accuracy and integrity of the final submission. All authors read and approved the final manuscript.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of Interest The authors declare no competing interests.

Research Involving Humans and Animals Statement This study is a systematic review and does not involve direct research on human participants or animals. Ethical approval was not required.

Informed Consent None.

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