

Review

Magnetic nanoparticles as a promising antimicrobial agent for combating multidrug resistant bacteria: a review

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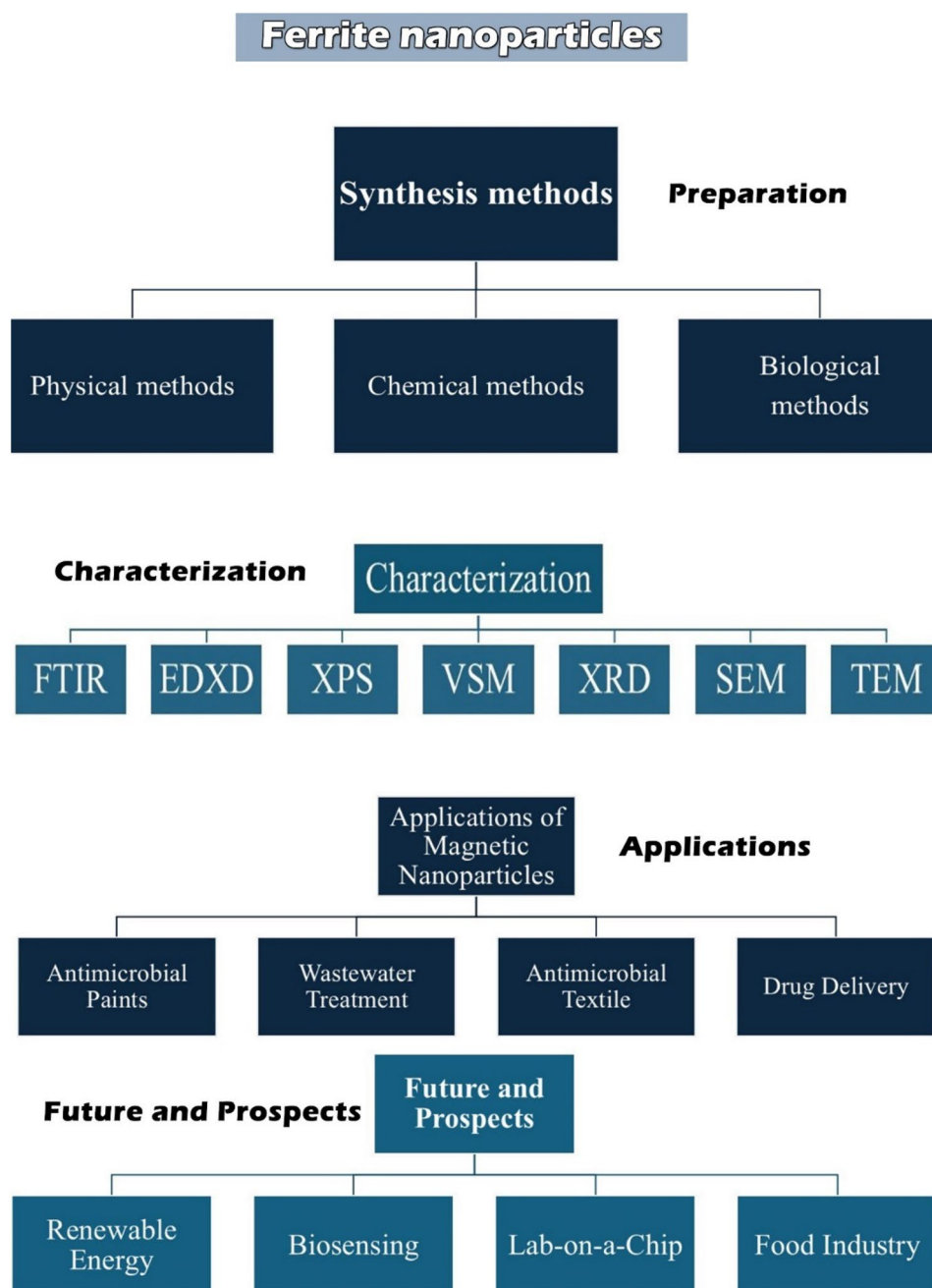
Abstract

Modern medicine has relied heavily on antibiotics to efficiently treat bacterial infections that were previously fatal. However, since the global rise in antibiotic resistance currently poses a danger to the effectiveness of many of these medications, there is an urgent need for alternative antimicrobial strategies. The mechanisms and historical relevance of antibiotic action are discussed, along with the multifactorial causes of resistance and the possible applications of nanotechnology—specifically, magnetic nanoparticles (MNPs)—to these issues. High surface area, magnetic responsiveness, and functionalization potential are some of the unique characteristics that MNPs offer and can be used to boost antibacterial activity. In addition to increasing MNPs' stability and bioavailability, surface modification using stabilizing agents such as citric acid, chitosan, and olive oil expands their uses in targeted antibacterial therapy, drug delivery, and environmental remediation. In addition, the synthesis techniques, antibacterial characteristics, and particular advantages and disadvantages of MNPs are discussed in contrast to traditional antibiotics. This review aims to simplify complex concepts in the MNP field, making them accessible to scientists across disciplines while offering insights into the synthesis, antibacterial properties, and potential of MNPs as innovative solutions to combat antibiotic resistance. In summary, this review seeks to particular attention is given to future perspectives, including emerging trends like lab-on-a-chip technologies and biosensors, which require further investigation.

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Graphical abstract



Article Highlights

- The main purpose of this study is to demonstrate that magnetic nanoparticles can effectively improve the efficacy of antibiotics to overcome the multidrug resistance crisis.
- This review highlights the different types as well as the different methods used in the synthesis and characterization of different magnetic nanomaterials.
- This study provides a comprehensive comparison of different types of magnetic nanoparticles (MNPs), evaluating their potential across various applications, including antibacterial activity, drug delivery, and biosensing.

Keywords Antibiotic resistance · Magnetic · Surface modification · Antimicrobial activity

1 Introduction

Antibiotics have played a crucial role in revolutionizing medicine by providing potent remedies for infections caused by bacteria that were previously incurable and frequently lethal. Since the beginning of the twentieth century, when penicillin was discovered, antibiotics have prevented millions of deaths and enabled major medical advancements, including organ transplants and routine surgeries [1]. However, despite their obvious importance, antibiotic overuse and abuse in both human and animal medicine have resulted in an alarming increase in resistance to antibiotics, which is now one of the most pressing health issues worldwide. In addition to making patient care more difficult, the emergence of antibiotic-resistant illnesses poses a threat to undo decades of advancements in medicine [2].

Antibiotics function by interfering with bacterial processes that are necessary for their survival and reproduction. These include preventing the production of cell walls, interfering with the function of cell membranes, preventing the synthesis of proteins, and interfering with the replication of nucleic acids and other vital metabolic activities [3]. However, bacteria have developed remarkable genetic variety and adaptability, enabling them to endure the selective pressures produced to antibiotic exposure. The growing resistance crisis is caused by several causes, such as uncontrolled antibiotic use in agriculture, population density and urbanization, selective pressure from the widespread consumption of antibiotics, and public misconceptions about antibiotics. All of these factors accelerate the emergence and transmission of bacteria resistant to antibiotics, highlighting the urgent need for innovative techniques to counter this threat [4].

Enhancing or substituting conventional antibiotics with cutting-edge antimicrobial agents—among which nanotechnology-based strategies hold great promise—is a crucial field of research in the fight against antibiotic resistance. With its ability to precisely manipulate molecules and atoms, nanotechnology presents a new avenue for the development of antimicrobials [5]. Nanoparticles (NPs), particularly magnetic nanoparticles (MNPs), like ferrites, have special physicochemical characteristics that allow them to target bacterial cells in novel ways. These characteristics include a high surface area-to-volume ratio, ease of functionalization, and controlled release capabilities [6]. In contrast to traditional antibiotics, which could encounter resistance mechanisms including efflux pumping and enzyme degradation, MNPs are able to avoid these challenges and demonstrate their own antimicrobial properties [7].

Magnetic nanoparticles can be widely classified according to their structure and content. Maghemite ($\gamma\text{-Fe}_2\text{O}_3$) and magnetite (Fe_3O_4) are the most often used materials; magnetite is preferred because of its superior magnetic and biocompatible qualities [8]. MNPs can be synthesized in a number of ways, such as core-shell structures, doped nanoparticles, and composite materials. Each of these forms has unique benefits for applications in imaging, targeted medication delivery, and the environment [9]. For example, core-shell MNPs frequently combine other materials' functionalization capabilities with iron oxide's magnetic properties to improve stability and bioactivity [10]. Additional antibacterial properties may be provided by doped MNPs, such as those containing copper or zinc [11, 12], while composite MNPs can be designed for a variety of applications, such as sensing and catalysis [13].

MNPs have a wide range of uses outside of medicine, such as water purification, biosensors, and environmental cleanup [14]. Because of their special qualities, medications may be delivered to bacterial cells precisely, minimizing adverse effects and improving therapeutic results [15]. Furthermore, MNPs may be easily isolated and extracted from the system due to magnetic separation, which makes them a perfect fit for use in environmental and medicinal settings [16]. The performance comparison of these many MNP types reveals that their efficiency levels differ depending on their size, surface modification, and intended application. For instance, doped MNPs may exhibit improved antibacterial activity [17], and core-shell MNPs may provide better drug encapsulation [18].

Physical, chemical, and biological techniques can all be used to create MNPs, and each offers special benefits in terms of surface characteristics, particle size, and shape [19]. In order to maximize these MNPs' stability, biocompatibility, and antibacterial effectiveness, functionalization and surface modification are essential [20]. MNPs have been successfully stabilized and functionalized by substances including olive oil, chitosan, and citric acid. Citric acid's carboxyl groups allow it to bind to MNP surfaces strongly and make conjugation with other functional molecules easier [21]. Chitosan, an antibacterial biocompatible polymer, offers extra advantages by increasing cellular absorption and bioavailability [22]. Olive oil, which is abundant in phenolic compounds, provides a naturally occurring hydrophobic coating that gives MNPs antioxidant qualities and prevents oxidation and aggregation [23].

Conjugation with conventional antibiotics is one of the most promising uses of MNPs. This method not only improves antibiotic targeting but also permits controlled drug release, which may lower dosage requirements and minimize

adverse effects [11]. Additionally, the intrinsic magnetic characteristics of MNPs facilitate magnetically guided targeting, which would further enhance treatment precision [24]. MNPs' antibacterial properties make them useful applications for environmental decontamination, including soil treatment and water purification, in addition to their medical uses [25].

In this review, we provide a thorough investigation of the history of antibiotics, their vital function in medicine, the ways by which they fight bacteria, and the causes of the present resistance crisis. As possible antibacterial agents, we additionally examine the synthesis, surface modification, and structure of MNPs. This article provides insights into how recent developments in MNP technology could help tackle the rising threat of antibiotic resistance by emphasizing the advantages and disadvantages of nanotechnology-based antimicrobials. This review highlights the novel approach of conjugating magnetic nanoparticles (MNPs) with antibiotics to combat multidrug-resistant (MDR) bacteria, providing a comprehensive comparison of MNP types and their applications in antibacterial therapy, drug delivery, and biosensing. In order to provide a thorough overview of the existing and developing approaches in antibiotic research and resistance mitigation, we conclude by examining the prospects for MNPs in the future as well as their possible uses in environmental and medical contexts.

2 History of antibiotics

Important turning points in medical history were reached with the discovery and development of antibiotics, which have been essential in fighting against bacterial illnesses as demonstrated in Fig. 1. In 1947 Waksman defined an “antibiotic” as a chemical made by microorganisms that could inhibit or even kill bacteria and other germs. According to Waksman's definition, the term “antibiotic” can now be used to describe (I) any organic compound, synthetic or natural, that inhibits or kills pathogenic bacteria; (II) any antimicrobial agent; or (III) antimicrobial chemicals derived from microbes [26].

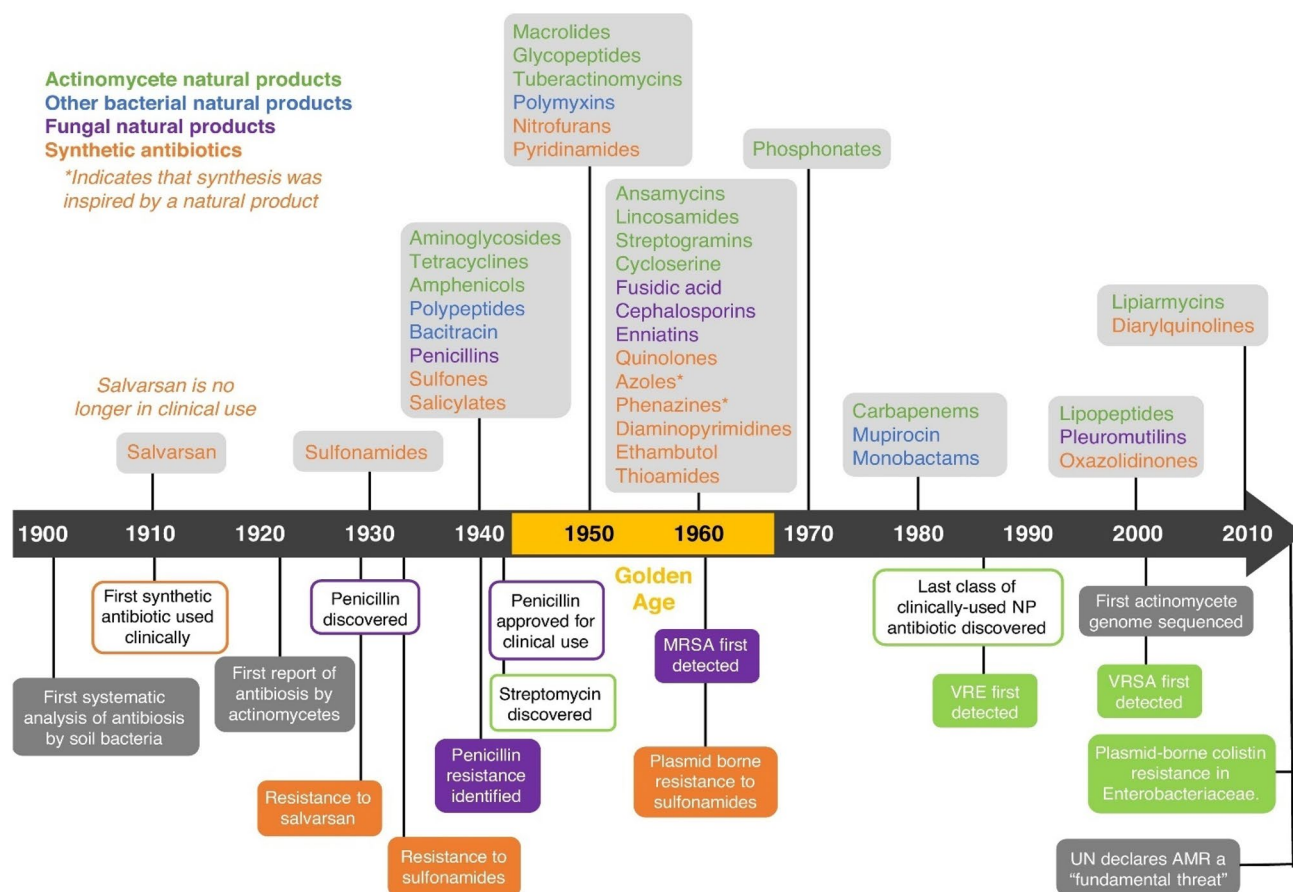


Fig. 1 Timeline shows the decades that marked the introduction of novel antibiotic classes into clinical use [35]

It is well known that ancient Egypt, Greece, China, and other countries used microorganisms to cure microbiological infections [27]. The modern era of antibiotics started in 1928 when Sir Alexander Fleming discovered penicillin [28]. Since then, antibiotics have saved millions of lives and transformed modern medicine [29].

To treat severe illnesses, physicians started administering antibiotics in the 1940s [30]. During World War II, penicillin was successful in treating bacterial infections among soldiers [27]. By the 1950s, penicillin resistance had become a serious clinical problem that threatened many of the medical advances of the decade before. New beta-lactam antibiotics were found, created, and released to solve this issue, which contributed to the restore of confidence [27]. Methicillin-resistant *Staphylococcus aureus* (MRSA) was first discovered in that decade; in 1968 cases showed up in the United States and in 1962 in the United Kingdom [31]. Vancomycin was initially employed clinically in 1972 to address methicillin resistance in coagulase-negative staphylococci and *Staphylococcus aureus* [32]. Vancomycin resistance was considered unlikely to occur in the clinical setting since it was so difficult to induce [27]. However, in 1979 and 1983, reports of vancomycin resistance in coagulase-negative staphylococci were made [32]. To address the issue of antibiotic resistance, the pharmaceutical industry introduced a large number of new antibiotics between the late 1960s and the early 1980s. But after then, the supply of antibiotics started to decline, and fewer new drugs were released [33]. As a result, bacterial infections were once again a serious concern by 2015, some decades after antibiotics were first employed to treat patients [34].

Actinomycetes are represented by green, other bacteria by blue, fungi by purple, and synthetic chemicals by orange. At the bottom of the timeline are significant dates pertaining to the discovery of antibiotics and the rise of antimicrobial resistance. These dates emphasize the initial reports of drug-resistant strains, including plasmid-borne colistin resistance in *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and vancomycin-resistant *Staphylococcus aureus* (VRSA).

2.1 Importance of antibiotics

Infections that may occur in patients taking chemotherapy, those with long-term conditions like diabetes, end-stage renal disease, or rheumatoid arthritis, or those who have had complicated surgical procedures like heart surgery, joint replacements, or organ transplants can be prevented or treated with antibiotics [36]. By altering the course of bacterial infections, antibiotics have also contributed to the extension of anticipated life spans. In contrast to the 1920 expectation of approximately 56.4 years, the average longevity in the United States is today around 80 years [37].

2.2 Mode of antibiotic action

Since each antibiotic has a different structure and a different affinity for specific target locations within bacterial cells, its modes of action are different as demonstrated in Fig. 2.

2.2.1 Inhibitors of cell wall synthesis

Cell walls are essential for bacterial survival even though they are absent from human and animal cells. Bacterial species can be specifically killed or inhibited by medications that target their cell walls [38]. Examples: Penicillins, amoxicillin, bacitracin, cephalosporins, and vancomycin.

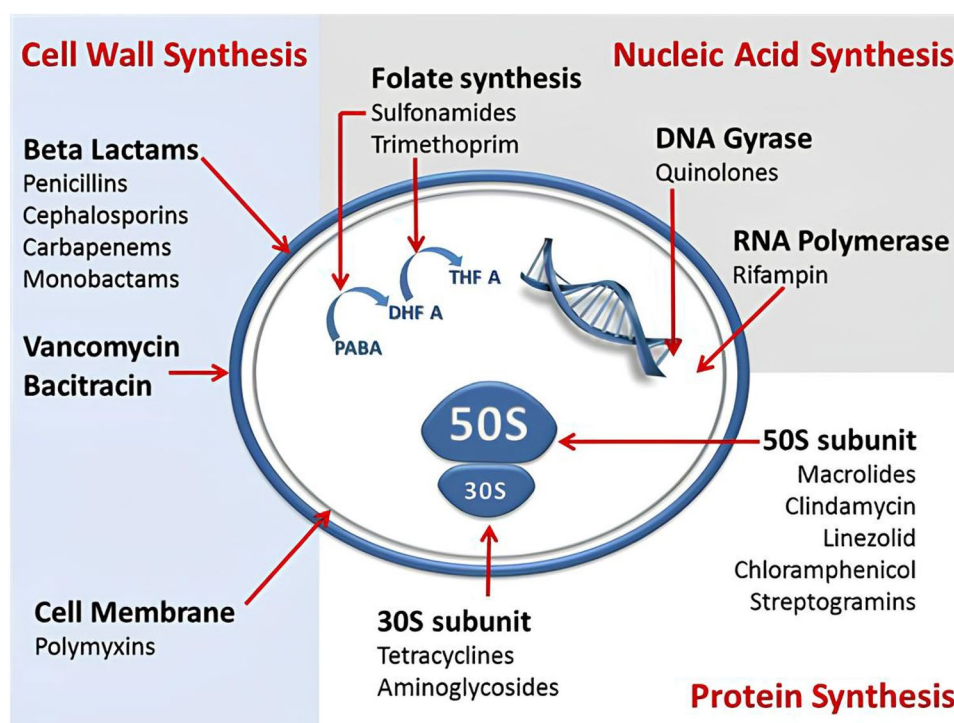
2.2.2 Inhibitors of cell membrane function

Cell membranes are important barriers that regulate the movement of materials into and out of cells. Essential solutes required for cell survival may be lost because of membrane damage or disruption. Since both prokaryotic and eukaryotic cells have cell membranes, antibiotics that target them are typically not very selective and can be harmful when administered systemically to mammals. Therefore, these antibiotics are generally applied topically in clinical settings [39]. Examples: colistin and polymyxin B.

2.2.3 Inhibitors of protein synthesis

Protein synthesis is essential for the survival and reproduction of bacterial cells, as proteins are the primary building blocks of enzymes and cellular structures. Certain antibacterial substances function by attaching to the 30S or 50S subunits of bacterial ribosomes and preventing protein production. Bacterial mortality or the prevention of growth and

Fig. 2 Different mechanisms of antibiotics action [42]



replication result from this activity, which interferes with normal cellular metabolism [40]. Examples: Aminoglycosides, macrolides, streptogramins, lincosamides, tetracyclines, and chloramphenicol.

2.2.4 Inhibitors of nucleic acid synthesis

All living organisms, including bacteria, depend on DNA and RNA for their ability to replicate. Some antibiotics work by binding to elements that are necessary for the synthesis of DNA or RNA, interfering with regular biological functions, and eventually preventing the growth and survival of bacteria [40]. Examples: quinolones, rifampin, and metronidazole.

2.2.5 Inhibitors of other metabolic processes

Certain cellular functions that are essential to bacterial survival are targeted by specific antibiotics. For example, trimethoprim and sulfonamides disrupt the folic acid pathway, which is essential for the synthesis of bacterial DNA precursors. Trimethoprim inhibits dihydrofolate reductase, whereas sulfonamides bind to dihydropteroate synthase. The synthesis of folic acid, a vitamin that bacteria but not humans produce, depends on both enzymes [41].

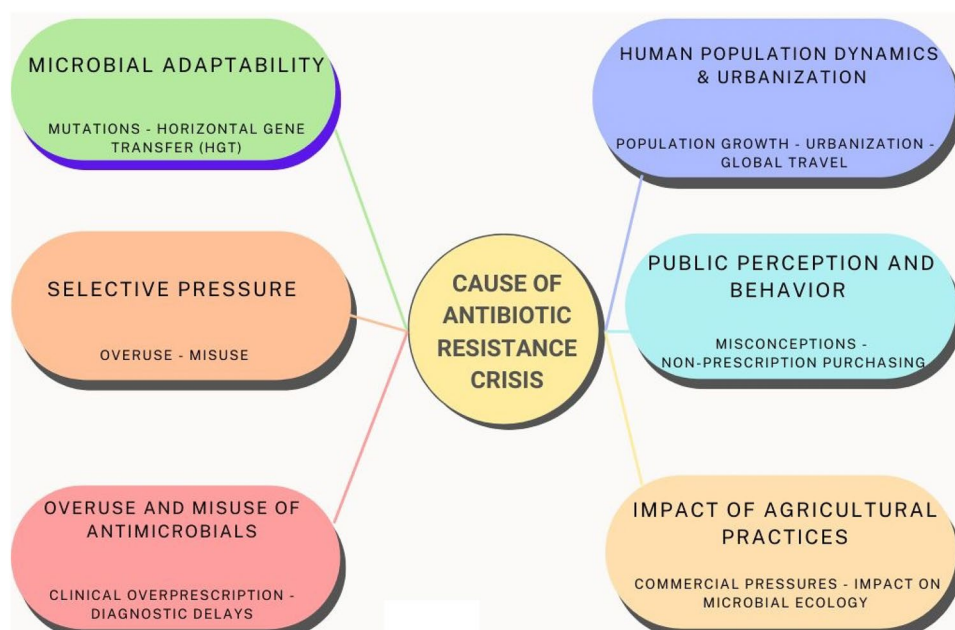
2.3 Causes of the antibiotic resistance crisis

The ecosystem of the Earth has long included infectious diseases in which microbes feed on larger organisms. Throughout history, epidemics such as influenza and the bubonic plague have happened [43]. But more than any other infectious disease, the current crisis presents an extraordinary risk to human health. A combination of natural variables and the role of humans in this environment have brought this issue to a critical stage as illustrated in Fig. 3.

2.3.1 Microbial adaptability and genetic variability

Having existed for over 3.5 billion years, microbes are remarkably numerous and varied [44]. Their ability for rapid adaptation to changes in their surroundings is what makes them successful. Large populations and quick generation rates, which permit frequent genetic alterations, are the main drivers of microbial adaptation. Mutations and horizontal gene transfer (HGT) are the two main causes of genetic variety. HGT allows adaptive genes, such as those that confer antibiotic resistance, to be exchanged [45].

Fig. 3 Factors contributing to the crisis of antibiotic resistance



2.3.2 Selective pressure from antimicrobials

By destroying susceptible microorganisms and promoting the growth of resistant ones, the application of antimicrobials produces selective pressure. This pressure is increased by the extensive and ongoing use of antibiotics, which accelerates the emergence of resistance. Human behaviors like the overuse and abuse of antibiotics exacerbate this selection pressure [46].

2.3.3 Human population dynamics and urbanization

More urbanization and the world's population, which is currently over seven billion, have made it easier for infectious diseases to spread. Pathogens and antimicrobial-resistant microorganisms spread quickly due to large populations living close to one another and widespread international travel [47].

2.3.4 Overuse and misuse of antimicrobials

The extensive use of antibiotics in agriculture and excessive prescribing in clinical settings are major causes of resistance. Strong selective pressure is applied to microbial communities by unnecessary or excessive usage, which is motivated by factors such as patient demand and diagnostic delays. This promotes the development of resistance [48].

2.3.5 Public perception and behavior

Resistance is exacerbated by misconceptions regarding the effectiveness of antibiotics as well as practices like hoarding and buying without a prescription. Antimicrobials are abused because the general population believes they are a quick fix, which makes the situation worse [49].

2.3.6 Impact of agricultural practices

Resistance develops because of the selective pressure that antimicrobial communities are subjected to when they are used in agriculture to enhance the health of crops and livestock. Commercial pressures have led to this extensive use, which has a significant effect on microbial ecology [50].

2.3.7 Vaccination reluctance

Reduced vaccination rates increase the reservoirs of infections, some of which may become resistant to antibiotics, and cause diseases to arise again. Herd immunity is weakened by vaccination hesitancy, which also exposes communities to diseases that were previously under control [50]. To boost immunity, other therapies have also been investigated, such as convalescent plasma (CP) therapy, which is used to treat respiratory diseases like SARS, MERS, and COVID-19. But depending only on passive immunotherapies, such as CP, without encouraging immunization makes people more susceptible to newly emerging and re-emerging diseases [51].

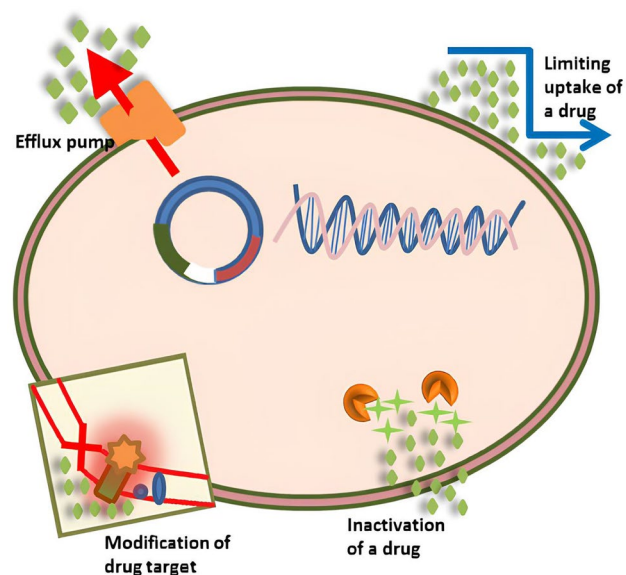
2.4 Mechanism of antibiotic resistance

There are four primary categories of antimicrobial resistance mechanisms: (1) limiting uptake of a drug; (2) modifying a drug target; (3) inactivating a drug; and (4) active drug efflux. Intrinsic resistance can involve reducing drug uptake, drug inactivation, and drug efflux, while acquired resistance may include modifying drug targets, inactivating drugs, and drug efflux. Due to structural differences, Gram-positive and Gram-negative bacteria employ different resistance mechanisms. Gram-positive bacteria lack some drug efflux mechanisms and less frequently restrict drug uptake (because they lack the lipopolysaccharide layer, LPS), while Gram-negative bacteria use all four mechanisms [52] as demonstrated in Fig. 4.

2.4.1 Limiting drug uptake

As mentioned before, bacteria naturally vary in their capacity to restrict the absorption of antimicrobial drugs. Certain chemicals are blocked by the LPS layer of Gram-negative bacteria, which confers on them an innate resistance to particular potent antimicrobial drugs [53]. Because *mycobacteria* have a lipid-rich outer barrier, hydrophobic medications like fluoroquinolones and rifampicin can enter the cell more readily. On the other hand, because of this lipid-rich membrane, hydrophilic medications have restricted access [54]. All antibiotics that target the cell wall, including β -lactams and glycopeptides, are inherently ineffective against bacteria without a cell wall, such as *Mycoplasma* and similar species [55]. Because they don't have an outer membrane, gram-positive bacteria are less likely to impede medicine access. For instance, *enterococci* are intrinsically resistant to aminoglycosides due to the difficulties polar molecules have entering

Fig. 4 General antimicrobial resistance mechanisms [53]



their cell wall. Furthermore, vancomycin resistance has recently emerged in *Staphylococcus aureus*. One of the two ways by which *Staphylococcus aureus* fights vancomycin is through an unknown process in which the bacteria produce a denser cell wall that prevents the drugs from entering the cell and causes intermediate resistance. These strains are known as VISA (Vancomycin Intermediate *Staphylococcus aureus*) strains [53].

2.4.2 Modification of drug targets

Antimicrobial drugs can target different parts of bacterial cells, and bacteria can alter these targets to become resistant. Changes in penicillin-binding proteins (PBPs) are one β -lactam drug-specific resistance mechanism in Gram-positive bacteria. PBPs are transpeptidases that are essential for the cell wall's synthesis of peptidoglycans. Drug binding is impacted by variations in the quantity or composition of PBPs. The amount that a drug binds to its target, for example, can be affected by an increase in PBPs with decreased drug affinities or a decrease in PBPs with normal drug binding. The introduction of the *mecA* gene, which results in PBP2a in *Staphylococcus aureus*, is one example of a structural alteration that can drastically decrease or stop drug binding [56]. Lipopeptides, like daptomycin, function by altering the polarity of the cell membrane, whereas glycopeptides, like vancomycin, prevent the production of cell walls. Gram-negative bacteria are inherently resistant to these medications due to their thick LPS coating [57]. Vancomycin resistance has emerged as a major issue in *Staphylococcus aureus* (MRSA—Methicillin-Resistant *Staphylococcus aureus*) and *enterococci* (VRE—vancomycin-resistant *enterococci*). The acquisition of *van* genes mediates this resistance by changing the composition of peptidoglycan precursors, which decreases vancomycin's capacity to bind [58].

2.4.3 Drug inactivation

There are two main ways that bacteria can render medications inactive: either by directly breaking down the drug or by incorporating a chemical group into it. A broad class of enzymes known as β -lactamases is in charge of hydrolyzing and deactivating β -lactam antibiotics [59]. Acetyl, phosphoryl, or adenylyl groups are frequently added to drugs in order to inactivate them by transferring a chemical group. These changes have been attributed to a variety of transferases. The most common mechanism, acetylation, is used to combat aminoglycosides, fluoroquinolones, streptogramins, and chloramphenicol. Adenylation and phosphorylation, on the other hand, are mostly employed to combat aminoglycosides [60].

2.4.4 Drug efflux

The efflux pump genes found in bacteria are chromosomally encoded and can be constitutively expressed or induced/overexpressed according to environmental stimuli or the presence of particular substrates. Mutations that change the transport channel are frequently the cause of high-level resistance. These efflux pumps, also known as multi-drug resistant (MDR) efflux pumps, are mostly used by bacteria to expel harmful chemicals, but they can also carry a variety of other molecules. These pumps' ability to provide resistance can be affected by the carbon sources that are accessible [61].

2.5 Impact of antimicrobial resistance on individual bacteria

Knowing the variety of mechanisms of resistance that different bacteria have is essential. MRSA is a prominent example [62]. Longer hospital stays, more testing needed, and the requirement for more comprehensive medical and rehabilitative treatments are the main causes of the greater expenses linked to MRSA infections. Furthermore, MRSA has a major effect on morbidity and mortality, which results in more serious disease consequences. Numerous virulence factors, including surface chemicals that promote colonization and secreted compounds that facilitate invasion and host cell injury, are shared by strains of Methicillin-Susceptible *Staphylococcus aureus* (MSSA) and MRSA. The bacteria can cause a variety of infections because of these features. MRSA is extremely contagious, especially in healthcare facilities and is well-known for causing infections of the skin and associated tissues. According to estimates, MRSA infections have a death rate that is two to three times higher versus that of MSSA strains. Additionally, MRSA bacteria frequently show multidrug resistance, which lessens the efficacy of current antimicrobial therapies [63]. Numerous additional bacteria, like *Klebsiella pneumoniae* and *Escherichia coli*, have different pathways and are becoming more resistant to the majority of antimicrobial drugs on the market.

2.5.1 Antibiotic resistant bacteria

Once-effective antibiotics have become less potent against some microorganisms. For example, benzylpenicillin, a medication that is used to effectively treat *Staphylococcus aureus* (also known as “golden staph” or MRSA) and *Neisseria gonorrhoeae* (the bacteria that causes gonorrhea), are now almost invariably ineffective against these diseases. A major public health concern is that certain bacteria have become resistant to almost all commonly available antibiotics, making them capable of causing serious illnesses [64]. Notable examples include:

- Methicillin-resistant *Staphylococcus aureus*
- Vancomycin-resistant *Enterococcus*
- Carbapenem-resistant *Enterobacteriaceae* gut bacteria
- Multi drug resistant *Pseudomonas aeruginosa*
- Multi-drug-resistant *Mycobacterium tuberculosis*

A list of priority pathogens has been established by the World Health Organization (WHO) to direct research and development activities in the fight against antibiotic resistance. Because of their high rates of resistance and few available treatments, the bacteria on this list represent the most significant risk to human health. The WHO hopes to address the increasing threat of antimicrobial resistance by concentrating on these priority infections in order to promote the development of novel antibiotics and alternative therapeutic approaches as illustrated in Fig. 5.

- A *Methicillin-resistant Staphylococcus aureus* (MRSA) refers to a group of Gram-positive bacteria that are genetically distinct from other *Staphylococcus aureus* strains. MRSA is known to cause several difficult infections in people. It includes any *Staphylococcus aureus* strain that has developed multiple drug resistance mechanisms for beta-lactam antibiotics because of natural selection and horizontal gene transfer. Penams (like methicillin and oxacillin) and cepheims (like cephalosporins) are both members of the large class of beta-lactam antibiotics [66]. Methicillin-susceptible *S. aureus* (MSSA) strains are those that are unable to resist these antibiotics. People who have open wounds, intrusive equipment like catheters, and compromised immune systems are more susceptible to hospital-acquired infections, and MRSA is common in jails, nursing homes, and hospitals [67].
- B *Vancomycin-resistant Enterococcus* (VRE): Gram-positive, cocci-shaped bacteria known as *enterococci* are commonly found in the gut but can infect other parts of the body. Vancomycin used to be a dependable treatment for enterococcal infections, despite their resistance to several antibiotics. However, several *enterococci* have become resistant to vancomycin in recent years. Vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* are the two main species of concern; *Enterococcus faecium* is the most common species of VRE. These bacteria are not the same as *Escherichia coli* or other typical fecal bacteria. A susceptible enterococcus develops vancomycin resistance when it picks up a particular DNA fragment called a plasmid, which makes the bacteria resistant to the antibiotic. VRE are the strains that develop from this process. Vancomycin-Resistant *Staphylococcus aureus* (VRSA) strains are a serious problem since VRE strains can spread vancomycin resistance to unrelated bacteria, such as MRSA. Furthermore, VRE pathogens frequently exhibit multi-antibiotic resistance, similar to MRSA [68].
- C *Multi-drug-resistant Tuberculosis* (MDR-TB): *Mycobacterium tuberculosis*, the causative agent of MDR-TB, is resistant to at least isoniazid and rifampin, the two primary first-line anti-TB medications. Even more resistant to second-line medications is extensively drug-resistant TB (XDR-TB). Primary MDR-TB can result via direct transmission of MDR-TB from an infected individual. When a non-resistant strain is not adequately treated, resistance develops, resulting in acquired MDR-TB [69].
- D *Carbapenem-resistant Enterobacteriaceae* (CRE): Because they produce carbapenemase enzymes, CRE are Gram-negative bacteria that are resistant to carbapenem antibiotics. These enzymes include VIM (Verona Integron-Mediated Metallo-beta-lactamase), that also leads to carbapenem resistance; NDM (New Delhi Metallo-beta-lactamase), that hydrolyzes a wide range of beta-lactam antibiotics, such as carbapenems; and KPC (*Klebsiella pneumoniae* carbapenemase), which degrades carbapenems and other beta-lactam antibiotics, making them ineffective. CRE infections are linked to high mortality rates and can be quite serious. These carbapenemases are produced by certain strains of CRE, and other Gram-negative bacteria, such as *Pseudomonas*, have also been identified to contain similar enzymes like VIM [70].
- E *Multi-drug-resistant Pseudomonas aeruginosa* (MDR-Psae): The opportunistic Gram-negative pathogen *Pseudomonas aeruginosa* is frequently found in moist conditions. Infections of the urinary tract, pneumonia, and infections of



Fig. 5 WHO list of priority bacterial pathogens [65]

wounds are among the infections it can cause, especially in patients in hospitals with compromised immune systems or long-term respiratory disorders. Antibiotic resistance mechanisms and biofilm development are among its virulence factors [71].

3 Improvement of antimicrobials

The WHO action strategy plan placed a strong emphasis on reducing infections, improving the use of antibiotics, boosting health systems, and promoting the development of new drugs in order to reduce AMR [72]. Disinfectants, antiseptics, and preservatives are among the new groups of antimicrobials that have appeared since the 1930s. The emphasis on nanoparticle-based antimicrobial treatments has grown as a result of the emergence of drug-resistant strains and infections linked to biofilms [73].

3.1 Antimicrobial approaches based on nanotechnology

3.1.1 Nanomaterials

The term “nano,” derived from the Greek word for dwarf, represents one-billionth of any unit (10^{-9} m). Nanomaterials are defined as materials with external dimensions or internal or surface structures in the nanoscale, that typically spans from 1 to 100 nm [74]. One billionth of a meter is identified as a nanometer. In the multidisciplinary field of nanotechnology, materials with dimensions of one billionth are studied for their physical, chemical, and biological structures as well as their potential applications [75]. The fundamental components of nanotechnology are nanomaterials, which have special optical, magnetic, and electrical characteristics. Through careful management of the size, shape, synthesis conditions, and suitable functionalization, the properties of the nanomaterial can be modified as required. A fantastic example of an emerging technology is nanotechnology, which offers designed nanomaterials with the potential to create goods with significantly better performance [76].

3.1.2 Advantages of using MNPs/nanotechnologies as antibacterial agents compared with traditional antibiotics

The following is a summary of the various characteristics that MNPs typically display that set them apart from traditional materials:

- (1) Overcoming the existing antibiotic resistance mechanisms, such as disrupting bacterial membranes and preventing biofilm formation.
- (2) Targeting microbes through multiple mechanisms at once.
- (3) Serving as effective carriers for antibiotics [77].

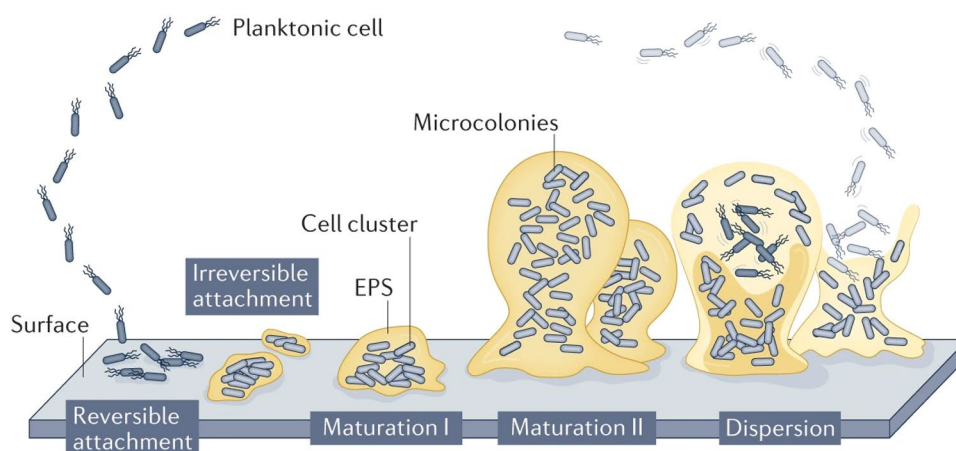
- (1) Overcoming the existing antibiotic resistance mechanisms.

At least one of the major resistance processes can be counteracted by a variety of MNP types. Their bactericidal qualities, which stem from their distinct physicochemical features, are what give them this efficacy [78]. MNPs, compared to conventional antibiotics, are smaller than 100 nm in size. Due to their incredibly small size, they have special qualities like improved cell interaction because of a higher surface area-to-mass ratio with the capacity to be used in a variety of controlled ways [79].

Since biofilms play a major role in the emergence of bacterial resistance, it is essential to inhibit biofilm formation in addition to disrupting bacterial membranes.

The formation of biofilms is a cyclic process that occurs in a five-stage-specific and progressive manner as illustrated in Fig. 6. The process is initiated following surface contact by single planktonic cells [80]. Several developmental steps are discernible, including reversible attachment, irreversible attachment, biofilm maturation (maturation I and maturation II) and, finally, dispersion. During reversible attachment, bacteria attach to the substratum via the cell pole or via the flagellum, followed by longitudinal attachment. Transition to irreversible attachment coincides with a reduction in flagella reversal rates, a reduction in flagella gene expression and the production of biofilm matrix components. This stage is also characterized by attached cells demonstrating drug tolerance [81]. Biofilm maturation stages are characterized by the appearance of cell clusters that are several cells thick and are embedded in the biofilm

Fig. 6 Steps of biofilm formation [83]



matrix (maturation I stage), which subsequently fully mature into microcolonies (maturation II stage). Dispersion has been reported to coincide with the decrease in and degradation of matrix components, with dispersed cells being motile and demonstrating increased drug susceptibility relative to biofilm cells [82].

The microorganisms within bacterial biofilms are protected by their unique structure and composition, which enables them to avoid most antibiotics. Additionally, biofilms enable the exchange and adaptation of these changes among different bacterial cells and act as a “breeding ground” for common resistance mutations [84]. Numerous MNPs, including ZnO, Fe₃O₄ MNPs [85] and Mg-based NPs, have been shown to inhibit or prevent the formation of biofilms [85]. MNPs with a larger surface area-to-mass ratio and a smaller size prevent biofilm formation more effectively. Furthermore, the form of the MNPs is important in disrupting biofilms, because rod-shaped MNPs work better than spherical ones [86].

(2) Targeting microbes through multiple mechanisms at once.

The emergence of bacterial resistance can be partially explained by the generally simple processes by which traditional antibiotics work. On the other hand, MNPs use several active mechanisms simultaneously to target microorganisms [87]. This multi-faceted approach reduces the likelihood of resistance, as it is less probable that a microbe will have multiple mutated genes to counteract all the different mechanisms simultaneously [88].

(3) Serving as effective carriers for antibiotics.

As was previously mentioned, MNPs are not only efficiently fighting bacterial and microbial resistance when used alone, but they can also act like “vehicles and carriers” carrying antibiotics. MNP-based medication delivery works in other ways than those described above. Nowadays, a variety of NPs, including liposomal NPs, are employed in medication delivery [86], solid lipid (SL) NPs [89], polymer-based NPs, polymer micelles, and inorganic nanodrug carriers, which encompass magnetic NPs, mesoporous silica NPs, carbon nanomaterials, and quantum dots. Terpenoid-based NPs are also utilized in drug delivery systems [90], and dendrimer NPs [91]. NPs provide several benefits over traditional delivery methods when employed as carriers for the delivery of antibiotics.

3.1.2.1 Advantages of magnetic nanoparticles as carriers for antibiotics

1. Size and penetration

The small size and controllable dimensions of MNPs make them perfect for carrying out antibacterial activities and focusing on intracellular microorganisms [92].

2. Protection of antibiotics

By raising the serum concentrations of antibiotics and protecting the medications against bacterial resistance, MNP carriers provide protection. Drugs are protected from damaging chemical interactions within these carriers, maintaining their potency. Another significant benefit is shielding medications from bacterial resistance mechanisms [93].

3. Enhanced targeting and precision

By delivering antibiotics directly to infected sites, MNP carriers improve safety and accuracy while lowering systemic side effects. Efficient absorption of drugs at the targeted site without producing adverse effects like toxicity is frequently a challenge for conventional antibiotics. This is addressed by MNP-based drug delivery systems, which minimize side effects by accurately delivering the medication to the site of action [94].

4. Controlled and sustained release

Antibiotics can be released in a flexible, controlled, and prolonged manner thanks to MNP carriers. Blood medication levels fluctuate often as a result of traditional delivery techniques, sometimes surpassing the maximum tolerable dose or falling below the minimum therapeutic dose [95].

5. Combination therapies

By encapsulating several medications or antimicrobials at once, MNPs might strengthen their antibacterial qualities. Two degrees of combination are included in this strategy, as explained in the article. This combinatorial approach can prolong the medications' duration of action and dramatically reduce the risk of bacterial resistance [96].

3.2 MNPs biodistribution and metabolism

MNPs' biodistribution patterns and duration of circulation throughout the body are influenced by both their surface chemistry and mode of delivery [97]. The ideal range for delivery for some purposes is 10–100 nm because MNPs smaller than 10 nm can be eliminated via renal clearance, whereas MNPs larger than 200 nm are known to be collected by the spleen through mechanical filtration [98]. These particles' biodistribution patterns have been determined to be 80–90% in the liver, 5–8% in the spleen, and 1–2% in the bone marrow [99]. Any changes to the MNPs' surface affect their interaction and biodistribution, as well as their internalization process within cells and organs, metabolism, and potential toxicity [100].

3.3 MNPs cytotoxicity

Although magnetic nanoparticles (MNPs) show promise in combating antibiotic resistance, there are significant concerns regarding their toxicity, which has been less studied in the context of healthcare applications. Toxicology remains a primary concern, as these particles may cause harmful effects on both test animals and the environment [101]. Toxicity studies typically evaluate the impact of MNPs through physical, chemical, and biological effects on organisms [102]. Hemolysis, LDH leakage test, and MTT test can all be used to quantify in vitro cellular toxicity. Numerous animal models, including zebrafish, rodents (mice and rats), and nonhuman primates, are used in in vivo investigations. Ex vivo research, such as precision-cut liver slice (PCLS) models and ex vivo potency assays, are frequently utilized to determine the toxicity and usefulness of functional compounds [103]. Additionally, because these particles are poisonous, they may cause reduced therapeutic efficacy as well as MNP migration and accumulation in organs, which may trigger immunological or inflammatory reactions [104]. These MNPs have the capacity to penetrate cells, where their toxicity may impact nuclear processes or result in membrane leakage or blockage, which may have detrimental effects on cell survival, proliferation, and metabolic activity [105]. As a result, toxicity studies in all aspects of manufactured MNPs are necessary. Even though numerous studies demonstrate MNPs' potential as strong antibacterial agents, certain circumstances may unintentionally encourage antibiotic resistance. For example, this effect may be influenced by experimental parameters including temperature, pH, and the amount of water [88]. Key concerns related to MNP toxicity include:

- Cellular toxicity: MNPs have the potential to induce reactive oxygen species leading to cellular damage, which can result in inflammation and interference with cellular processes [106].
- Organ toxicity: Certain organs, including the liver, kidneys, and lungs, can be impacted by MNPs, which may result in hepatotoxicity, respiratory issues, and renal impairment [107].
- Genotoxicity: Certain MNPs have the potential to harm DNA, raising the risk of cancer and mutations [108].

- Environmental toxicity: Due to their durability and capacity for bioaccumulation, MNPs can harm aquatic life, soil, and water in ecosystems [109].

Additionally, aluminum nanoparticles (Al NPs) have raised concerns regarding their potential to promote plasmid transfer (such as RP4, PK2, and pCF10) raises serious concerns since it can aid in the emergence of multidrug resistance (MDR) in both bacterial species and genera [110]. Factors influencing this process include:

- Al NPs induce oxidative stress, which harms the bacterium membranes.
- The concentration of Al NPs and bacterial mating cells.
- Environmental factors such as pH and temperature have an impact on the transfer of plasmids within water which can carry genes, especially antibiotic resistance genes.
- Selective promotion of specific genes (e.g., *trfAp*, *trfA*, and *trbB*) is crucial for plasmid transfer and replication [111].

These issues highlight the need for a careful evaluation of MNP applications to prevent the unintended promotion of MDR, which could present significant environmental and public health risks.

4 MNPs (Ferrites)

Metal and iron oxides make up the family of magnetic materials known as ferrites. “M” stands for a divalent metal ion, which can comprise elements like Mn, Fe, Mg, Ni, Zn, Cd, Co, Cu, Al, or different combinations of these metals. They usually have the chemical formula $MO \cdot (Fe_2O_3)$. Since MNPs are inexpensive, have little toxicity, and have unique magnetic properties, they are presently the subject of intensive research for biomedical applications [112]. Metals such as Fe, Ag, Ni, and Co, or metal oxides, are the building blocks of magnetic MNPs. Among metal oxides, iron oxide NPs (IONPs) are a popular choice since they are easily manufactured and found in nature [113]. While there are several pure iron oxide phases found in nature, nanoscale zero-valent iron (nZVI), FeO_4 , and α - FeO_3 are the most commonly employed magnetic nanoparticles. Because of differences in their iron oxidation states, these NPs have unique physicochemical characteristics. The most studied of them is magnetite (Fe_3O_4), that includes both ferromagnetic Fe (II) and Fe (III). The presence of Fe^{2+} ions, which can act as electron donors, makes magnetite frequently preferred [114].

Three distinct crystal forms can be observed when ferrites crystallize. The general formula for the spinel type's cubic crystal structure is $M^{2+}Fe_2O_4$, where M can be any of the following elements: Fe, Mn, Mg, Ni, Zn, Cd, Co, Cu, Al, or a mixture of these. With the formula $Ln^{3+}_3Fe_5O_{12}$, the garnet form also has a cubic crystal structure, where Ln stands for elements like Y, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, or Lu. The formula $M^{2+}Fe_{12}O_{19}$, where M can be either Ba or Sr, describes the hexagonal crystal structure of the third kind, magnetoplumbite [115].

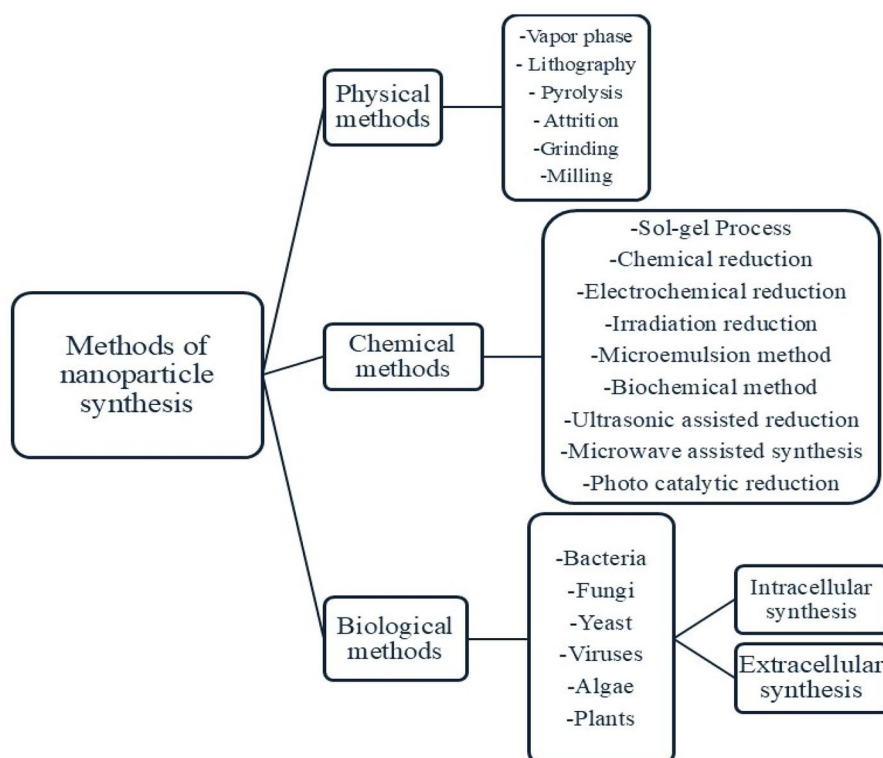
4.1 Synthesis of MNPs

In the literature, a variety of techniques for creating MNPs have been reported [116]. Co-precipitation, carbon arc, laser pyrolysis, microemulsion, thermal breakdown, sonochemical, microwave-assisted, solvothermal, chemical vapor deposition, and combustion are examples of common methods [117]. Additionally, other approaches such as electrochemical synthesis [118], laser pyrolysis [117], and biological methods using microorganisms like magnetotactic and iron-reducing bacteria have been utilized [119]. Additionally, novel techniques have been developed to create FeO_4 nanoparticles in a variety of morphologies, such as hierarchical superstructures, nanorods, and nanotubes [116] as illustrated in Fig. 7.

4.1.1 Physical methods

Commonly utilized physical methods for creating MNPs include laser pyrolysis, evaporation–condensation, high-energy ball milling, laser ablation, and electrospraying. Arc discharge, metal sputtering, and annealing are additional techniques. Since they can create thin films free of solution impurities and distribute MNPs uniformly, these physical techniques are frequently preferred over chemical ones. Physical techniques are also useful for producing MNPs for long-term inhalation toxicity investigations and calibrating MNP measurement equipment [120].

Fig. 7 Different methods of NPs synthesis [123]



4.1.2 Chemical methods

Commonly used techniques including hydrothermal, sol–gel, microemulsion, and chemical vapor deposition are examples of chemical methods for creating MNPs. Using reducing agents such as NaBH₄, hydroquinone, gallic acid, sodium citrate, and elemental hydrogen—all of which can be either organic or inorganic—chemical reduction is a popular method. Usually occurring in liquids, these reactions result in materials with colloidal characteristics. The general process including several events, such as nucleation, coarsening, reduction, growth, and agglomeration, is referred to as coprecipitation. Chemical reduction techniques have a lot of disadvantages, including the usage of hazardous chemicals and the production of hazardous byproducts, even though they can create enormous amounts of MNPs [121].

4.1.3 Biological methods

The physical and chemical synthesis of nanoplateforms requires intense radiation, stabilizing agents, and extremely toxic reducing agents. Both human life and the environment may be harmed by these. As a result, researchers are currently exploring green synthesis to produce magnetic nanoparticles, seeking more sustainable and environmentally friendly alternatives. In line with the growing trend of green synthesis in nanotechnology, biological approaches for synthesizing magnetic nanoparticles (MNPs) utilize bacteria, algae, yeast, fungi, or plants. Both bacteria and fungi are capable of both external and intracellular production methods [122]. These biological techniques aim to overcome the limitations of conventional methods, such as complex reactions, high costs, and safety concerns. By incorporating green chemistry principles—such as atomic economy, environmentally benign chemistry, and the creation of non-toxic chemicals—these approaches not only minimize environmental impact but also enhance human health and safety in the manufacturing process [123].

4.2 Antimicrobial activity of MNPs

MNPs are potential prospects as treatment options against diseases that are infectious because of their innate antibacterial qualities. The direct antibacterial, antibiofilm, and antioxidant properties of MNPs have been demonstrated in numerous investigations [124–127]. Iron oxide nanoparticles, for example, have demonstrated strong antibacterial action against a variety of pathogens, such as *Candida albicans*, *Shigella*, *A. niger*, *B. subtilis*, *S. aureus*, and *E. coli*. Higher

quantities of nanoparticles were found to enhance antibacterial effectiveness. These nanoparticles demonstrated effective antioxidant activity in addition to their antibacterial qualities, as demonstrated by their capacity to scavenge free radicals such as hydroxyl radicals, hydrogen peroxide, and DPPH [126]. Furthermore, magnetic nanoparticles such as manganese-cobalt ferrite (MnCoFeO), copper-cobalt ferrite (CuCoFeO), zinc-cobalt ferrite (ZnCoFeO), and cobalt ferrite oxide (CFO) have also been evaluated for their antibacterial activity. These nanoparticles exhibited notable antibacterial effects against *S. lentus*, *S. sciuri*, *S. vitulinus*, *S. aureus*, *A. viridans*, and *E. columbae*. Additionally, ZnCoFeO demonstrated significant antibiofilm activity against *S. aureus*, *A. viridans*, and *E. columbae* [127].

The three main ways that magnetic nanomaterials have antimicrobial effects are by rupturing cell membranes, releasing toxic metals which interfere with protein function and prevent or eliminate microorganisms, and producing reactive oxygen species (ROS), that can damage proteins, DNA, and RNA and cause microbial damage [128]. In Fig. 8, magnetic nanoparticles (MNPs) are represented as circles containing a pie-chart-like shape, with Fe_3O_4 (magnetite) in blue serving as an example of MNPs. Fe_3O_4 -based iron oxide nanoparticles (IONPs) are one of the most extensively studied MNPs due to their biocompatibility and ability to generate reactive oxygen species (ROS), which play a critical role in their antimicrobial activity.

4.3 Surface modification of MNPs

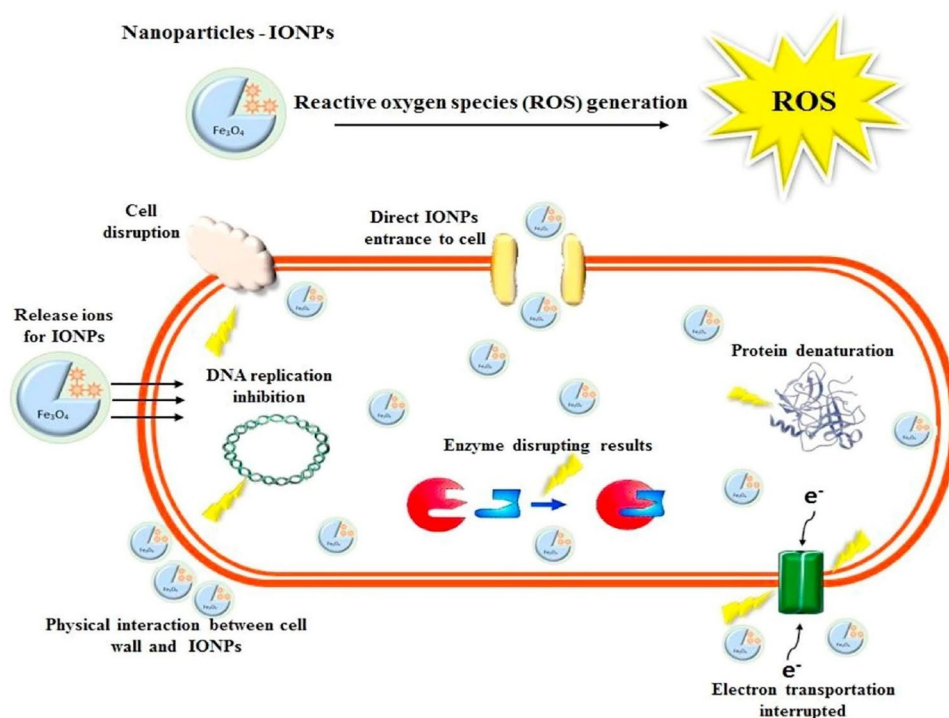
Surface modification of MNPs serves four key purposes [129]:

- 1- Enhancing or altering their dispersion.
- 2- Increasing their surface activity.
- 3- Strengthening their physicochemical and mechanical properties.
- 4- Improving their biocompatibility.

There are two types of materials utilized for surface modification: inorganic and organic. Small molecules and polymers make up organic materials, whereas silica, carbon, metals, and metal oxides or sulfides make up inorganic materials [129].

Stabilizing MNPs involves managing steric and electrostatic repulsive forces [130]. The density and molecular weight of polymers affect the steric effect, whereas the pH and ionic strength of the solution affect electrostatic

Fig. 8 Mechanisms of anti-microbial activity of the MNPs [124]



repulsion. These stabilizing factors can be altered by a variety of stabilizers, including monomeric stabilizers such as carboxylates like citric acid [130], inorganic substances like gold and silica [131], and phosphates [132]. Furthermore, MNPs can be effectively stabilized by polymeric stabilizers such as folic acid-functionalized composite copolymers [133], dextran [134], polyethylene glycol [135], polyvinyl alcohol [136], alginate [137], and chitosan [138].

4.3.1 Citric acid as a stabilizing and functionalizing agent for MNPs

Several carboxyl groups in citric acid make it an effective option for stabilizing and functionalizing MNPs. The stability of MNPs is increased by these groups' efficient binding to the metal ions on their surface. Furthermore, amid groups on compounds like amoxicillin can create covalent connections with carboxyl groups on citric acid. By facilitating the antibiotic's attachment to the NPs, this interaction makes it possible to create functionalized MNPs, which can improve therapeutic effects and drug delivery [139]. Furthermore, citric acid is known for being stable and non-toxic. Through the production of citrate ions, citric acid has been shown to function as an efficient capping agent, stabilizing MNPs [140].

4.3.2 Chitosan as a stabilizing and functionalizing agent for MNPs

A natural polymer made from chitin, chitosan has drawn a lot of interest as a stabilizing and functionalizing agent for MNPs because of its special chemical and physical characteristics. Chitosan, which is made up of repeating units of β -(1 $\rightarrow$ 4)-linked glucosamine and N-acetylglucosamine, provides an abundance of amino and hydroxyl groups that can create constant connections with the surfaces of MNPs, improving their dispersion and inhibiting aggregation [141]. Chitosan-coated MNPs are extremely adaptable for biomedical applications, including magnetic resonance imaging (MRI), targeted drug delivery, and the treatment of hyperthermia, because these functional groups also offer active sites for additional functionalization with different biomolecules, medications, or targeting ligands. Furthermore, chitosan is low in toxicity, biocompatible, and biodegradable, which makes it appropriate for use in environmental and medicinal domains [142]. Due to its cationic nature, it can interact with biological membranes that are negatively charged, promoting cellular absorption and increasing the bioavailability of medicinal drugs. By serving as a stabilizing matrix, chitosan expands the potential of MNPs in a variety of technological and medicinal fields by improving the colloidal stability of MNPs and imparting certain functions that can be customized for application-specific requirements [143].

4.3.3 Olive oil as a stabilizing and functionalizing agent for MNPs

In medicinal and environmental applications, olive oil, a naturally occurring lipid-rich material, has shown promise as a stabilizing and functionalizing agent for MNPs. In organic or lipid-rich applications olive oil, which is mostly made up of triglycerides, fatty acids, and antioxidant chemicals such as phenols, offers a hydrophobic coating that can dramatically improve the stability and dispersibility of MNPs. This coating improves MNPs' colloidal stability and maintains their magnetic characteristics by lowering their tendency to aggregate [144]. Additionally, oleuropein and hydroxytyrosol, two antioxidants found in olive oil, have intrinsic free-radical scavenging activity, adding functional value that may be advantageous for biomedical applications where oxidative stress is an issue [23]. Additionally, the hydrophobic layer makes it easier to interact with lipid membranes, which may increase MNP absorption in biological systems. Olive oil is a sustainable substitute for synthetic stabilizers since it is biocompatible, non-toxic, and naturally derived. This expands the range of MNP uses in environmental remediation, magnetic hyperthermia, and targeted drug delivery [145].

4.4 Antibiotics conjugation with MNPs

A number of antibiotics have been physically adsorbed onto IONPs coated with silver nanoparticles, including rifampicin, anthracycline, fluoroquinolone, tetracycline, and cephalosporin [146]. Silver nanoparticles' positive charge makes it easier for them to engage electrostatically with IONPs, which allows these antibiotics to adhere. Similarly, silver-decorated IONPs were bound to rifampicin, doxycycline, cefotaxime, and ceftriaxone using a variety of binding mechanisms, including hydrogen bonds and electrostatic interactions. The IONPs-Ag-rifampicin nanosystem was made using a green sonication-assisted technique, and the amount of adsorption varied according to the concentration of Ag [147].

Other therapeutic nanosystems, such as IONPs-ciprofloxacin, have also been investigated [148] and without the requirement for shell coating, IONPs directly coupled with a variety of antibiotics, such as amikacin, amoxicillin, bacitracin, cefotaxime, erythromycin, gentamicin, kanamycin, neomycin, penicillin, polymyxin, streptomycin, and vancomycin [147].

Fig. 9 Chemical structure of amoxicillin [149]

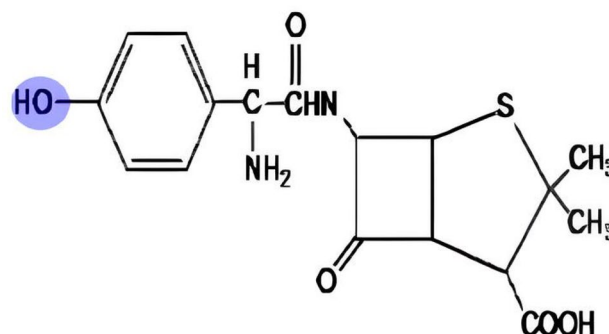
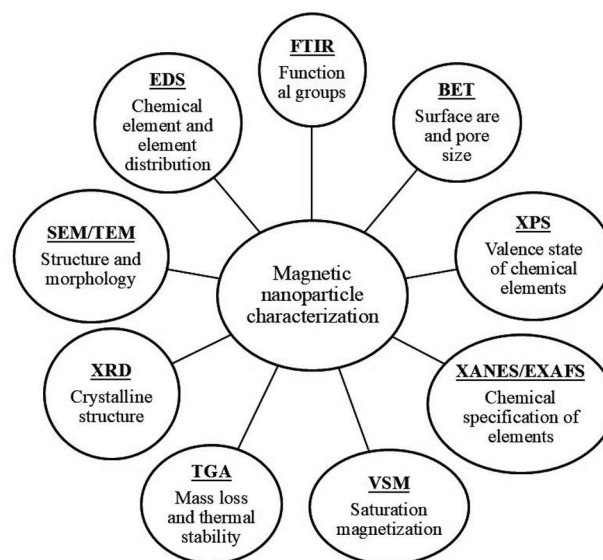


Fig. 10 Characterization techniques for magnetic nanoparticles



Amoxicillin is a common broad-spectrum antibiotic that is a member of the penicillin medication class. It stops bacteria from growing and replicating by blocking the manufacture of their cell walls. Amoxicillin is a versatile therapy option for infections like ear, throat, urinary tract, and skin infections since it works against a range of gram-positive and gram-negative bacteria. It works by attaching penicillin-binding proteins (PBPs) on the bacterial cell wall, which prevents the production of the peptidoglycan layer. Cell lysis and death are the ultimate results of this disturbance. Both adults and children can use amoxicillin because it is frequently taken orally and comes in a variety of forms, such as pills, capsules, and solutions. Despite its efficiency, the emergence of bacterial strains resistant to antibiotics has made its usage cautious and occasionally in conjunction with other antibiotics to increase efficacy and prevent resistance [149] (Fig. 9).

5 Characterization techniques for MNPs

The physical and chemical properties of magnetic nanoparticles (MNPs), such as size, shape, and surface characteristics and magnetic behavior, play a critical role in determining their functionality and applications. To ensure the efficient design and application of MNPs, a variety of characterization techniques are employed [150] as represented in Fig. 10. Understanding and improving MNP effectiveness requires specialized evaluations of particle size distribution, polydispersity index, zeta potential, and entrapment efficiency in addition to these general features. In stimuli-responsive nanoplateforms, which are intended for uses such as cancer treatment and medication delivery, these characteristics are very crucial [151].

5.1 Size and morphology

Transmission Electron Microscopy (TEM): A popular method for figuring out the size distribution, shape, and core size of nanoparticles is transmission electron microscopy (TEM). TEM can also show structural features like surface coatings and crystal defects. To achieve statistical reliability, however, a large number of measurements must be made during analysis, and sample preparation must be done with great care to prevent aggregation [152].

Scanning Electron Microscopy (SEM): SEM provides a comprehensive three-dimensional representation of particle size and shape at the micro and nanoscales. While TEM is more accurate in measuring core/shell structures or small particles, SEM is better at delivering information about surface topography [153].

5.2 Structure and elemental analysis

Energy Dispersive X-ray Diffraction (EDXD): The elemental composition of MNPs is investigated using EDXD, which offers information on elemental ratios and their spatial distribution. In order to customize the nanoparticles' characteristics for particular uses, it is essential to comprehend their phase composition and structural arrangement [154].

X-Ray Diffraction (XRD): XRD determines the average particle size and establishes phase purity and crystallographic characteristics. The XRD peaks are wider for smaller particles, reflecting their nanoscale dimensions. Furthermore, XRD is essential for determining which particular crystalline phases—such as magnetite or maghemite—are present in MNPs and have an impact on their thermal stability and magnetic behavior. This data is crucial for customizing the nanoparticles for specific uses where phase purity and size distribution are crucial, including targeted medication administration or magnetic resonance imaging (MRI) [155].

5.3 Magnetic properties

Vibrating Sample Magnetometer (VSM): VSM determines the saturation magnetization of MNPs, their magnetic behavior, including superparamagnetism, and how they react to magnetic fields [156].

X-Ray Photoelectron Spectroscopy (XPS): The elemental composition and chemical states on the surface of MNPs can be determined both quantitatively and qualitatively using XPS. It examines surface chemistry, verifying bonding and the presence of specific components [157].

5.4 Surface properties

Zetasizer: Zeta potential and surface charge, which are important markers of the stability and dispersion behavior of particles across a range of pH values, are measured by this device. It assists in forecasting aggregation tendencies and optimizing settings for uses like medication administration and colloidal stability by examining the electrostatic interactions between particles.

Fourier-Transform Infrared Spectroscopy (FT-IR): Functional groups on MNPs are identified by FT-IR, which enables the confirmation of chemical alterations and functionalization process steps. This method provides information about surface chemistry and interactions by identifying distinctive vibrational modes of bonds, which guarantees the successful attachment of stabilizing agents or active molecules [156].

These techniques are crucial for fully understanding and optimizing the properties and functions of MNPs in various applications.

6 Other applications of MNPs

MNPs are increasingly used in paints to enhance durability, functionality, and aesthetic properties. Advanced properties including self-cleaning, antimicrobial, and UV-protective properties are added to paints by adding MNPs such as zinc oxide, silver, and titanium dioxide (TiO₂). Titanium dioxide MNPs, for instance, degrade organic contaminants to maintain mold-resistant and clean surfaces [158]. Antimicrobial qualities added by silver MNPs inhibit the growth of microorganisms in places like hospitals where hygienic conditions are crucial [159]. By enhancing UV resistance and guarding against fading and sun damage, zinc oxide MNPs increase the paint's longevity [160].

Beyond painting, these MNPs are used in antimicrobial textiles, which are perfect for healthcare, sportswear, and other applications requiring hygienic conditions since silver and zinc oxide NPs inhibit bacterial development, lessen odor, and preserve fabric freshness. These developments show how materials and surfaces can benefit from the functional addition of MNPs [161]. Additionally, MNPs offer a wide range of uses because of their special magnetic characteristics, especially in drug delivery, wastewater treatment, tissue engineering, catalysis, and biofuels applications [162].

In drug delivery, MNPs are designed to deliver therapeutic chemicals directly to specific locations within the body, enabling localized, controlled treatment with little adverse effects. These particles can be precisely directed to particular tissues or tumors using an external magnetic field, improving the effectiveness of cancer and other illness treatments [163].

In wastewater treatment, MNPs are used to extract impurities from water, including organic dyes and heavy metals. The treatment method is both efficient and eco-friendly because of their large surface area, which allows for good adsorption of contaminants and their easy retrieval with a magnet [164].

In tissue engineering, the capacity of MNPs to interact with tissues and cells in a controlled way under the power of magnetic fields has made them extremely useful tools in tissue engineering. By attaching MNPs to particular cell types and functionalizing them with bioactive molecules, scientists can use external magnetic fields to direct and place them in scaffolds with three dimensions or particular areas of damaged tissue. This specific cell patterning promotes the regeneration of functioning tissues and makes it easier to create complex tissue structures [165]. Furthermore, MNPs can be added to hydrogels or other types of biomaterials to enhance tissue growth even more, and their magnetic responsiveness guarantees accurate spatial organization [166]. This method has shown unique potential in the engineering of tissues such as bone, cartilage, and brain networks, where optimal operation depends on the precise alignment of cells [167].

In catalysis, MNPs are essential because they can operate as active catalysts or as supports for catalytic species [168]. Their variable surface chemistry and high surface area-to-volume ratio allow for effective interactions with reactants, improving selectivity and reaction rates [112]. Functionalized MNPs offer a stable and reusable platform for a variety of chemical reactions, such as hydrogenation, oxidation, and coupling activities, by immobilizing catalytic molecules, enzymes, or metal complexes [169]. Their fast recovery and recyclability are among their greatest benefits. Indeed, MNPs may be extracted from the reaction solution utilizing an external magnetic field once the reaction is finished, which minimizes waste and lowers energy expenses. Consequently, MNPs are very useful in industrial applications, where efficiency and sustainability are crucial. Furthermore, their capacity to function in mild environments increases their potential for use in environmentally friendly processes and green chemistry [170].

MNPs have demonstrated significant promise in the production and optimization of biofuels. They can be utilized as catalysts or catalyst supports in the transesterification and biogas production processes that produce biofuel. Because of their magnetic characteristics, MNPs provide faster separation and reusing after the reaction and offer a wide surface area for reactions, which increases the effectiveness of these processes [171].

Additionally, MNPs can be integrated into microbial fuel cells, where their magnetic characteristics contribute to improved bioelectricity generation by stabilizing and boosting the performance of microbial communities involved in biofuel production. The combination of their ability to optimize biofuel processes and their recyclability makes MNPs a valuable tool for advancing sustainable energy technologies [172]. These applications demonstrate MNPs' adaptability in the environmental and medical domains, offering more focused and effective solutions. Table 1 listed the different applications utilized by various magnetic nanocomposites.

7 Future and prospects

The future applications of MNPs have enormous promise in a wide range of sectors in the future, due to their special nanoscale characteristics. MNPs are finding growing use in biosensing, targeted medication delivery, environmental monitoring, and renewable energy solutions because of their high surface area-to-volume ratio, adjustable optical characteristics, and functional diversity. By enabling the highly sensitive and selective detection of biomolecules including proteins, nucleic acids, and pathogens, MNPs are transforming the diagnosis of diseases and monitoring in the field of biosensors [192]. For instance, the plasmonic characteristics of gold and silver MNPs, which increase signal sensitivity when detecting molecular interactions, have demonstrated great promise in biosensing. Such sensitivity is essential for the detection of disease early since it enables medical professionals detect diseases such as cancer, heart disease, and infections early on, which improves patient outcomes and lowers healthcare expenses [193].

Table 1 Other applications of various magnetic nanoparticles

Magnetic nanoparticle	Coat	Preparation method	Size (nm)	Application	Refs.
Fe ₃ O ₄ NPs	Chitosan and gallic acid	Sonochemical	13	Drug delivery	[173]
Fe ₃ O ₄ NPs	Gelatin	Co-precipitation	5–13	Drug carrier system	[174]
Fe ₃ O ₄ NPs	Chitosan	Co-precipitation	21	Antimicrobial and photocatalysis	[175]
CoFe ₂ O ₄ NPs	Capsaicin	Co-precipitation	25–35	Antimicrobial and photocatalysis	[176]
NiFe ₂ O ₄ , CoFe ₂ O ₄ and Fe ₃ O ₄	Methoxy polyethylene glycol (PGE)	N/A	38–13–9	Drug delivery for cancer treatment	[177]
NiFe ₂ O ₄ NPs	Methionine	Reflux	27	Anticancer and antibacterial	[178]
Magnetite nanoparticles	Liposomes	Sonication	N/A	First clinical trials of magnetite for prostate cancer	[179]
ZnMn-IONPs	silicon naphthalocyanine	Co-precipitation	13.32 ± 4.11 nm	clinical trials for prostate cancer	[180]
Fe ₃ O ₄ NPs	<i>Cinnamomum tamala</i> (CT) leaves and <i>Jatropha curcas</i> (JC)	Co-precipitation	20–42 nm (JC Fe ₃ O ₄) and 26–35 nm (CT Fe ₃ O ₄)	Wastewater treatment, antioxidant and antibacterial	[181]
ZnFe ₂ O ₄ NPs	N/A	Co-precipitation	N/A	Wastewater treatment	[182]
ZnFe ₂ O ₄ NPs	Chitosan	Co-precipitation	30	Wastewater treatment	[183]
Ni-Cu-ZnFe ₂ O ₄ NPs	Graphene oxide (GO)	Microwave combustion	N/A	Wastewater treatment	[184]
ZnFe ₂ O ₄ NPs	Polyethylene Glycol	Hydrothermal	15	MRI contrast agent	[185]
ZnFe ₂ O ₄ NPs	Silica core shell	Solvothermal	N/A	Bone tissue engineering	[186]
ZnO and CuO NPs	N/A	Green synthesis	20–40 nm (ZnO) and 10–25 nm (CuO)	Paints	[187]
ZnFe ₂ O ₄ NPs	Reduced graphene oxide (RGO)	Solvothermal	N/A	Battery	[188]
ZnFe ₂ O ₄ NPs	N/A	Microwave combustion	8.55 nm to 13.04 nm	Catalysis for biodiesel production	[189]
NiFe ₂ O ₄ NPs	Graphene oxide (GO)	Hydrothermal	N/A	Immobilization of lipase for biodiesel production	[190]
Zn _{1-x} Ba _x Fe ₂ O ₄ (x = 0, 0.01, 0.05, 0.10, 0.15) ferrite	N/A	Auto combustion	39.5 nm to 45.4 nm	Solar cell	[191]

Beyond the medical field, environmental biosensors that employ MNPs are creating new opportunities for the real-time detection of pollutants, poisons, and contaminants in soil, water, and air [194]. The ability of nanosensors to detect dangerous compounds, such as heavy metals and organic pollutants, at incredibly low concentrations is essential for environmental regulation and protection [195]. Moreover, “lab-on-a-chip” technologies that combine MNPs with electronics and microfluidic systems have the potential to provide portable, quick, and affordable diagnostic and monitoring tools for use in clinical settings as well as distant or resource-constrained environments [196]. To improve food safety and cut down on waste, sensors based on MNPs are being developed in the food sector to track freshness, identify pathogens, and detect spoiling [197].

In the future, developments in materials science and nanotechnology are likely to generate novel types of MNPs with even more specific characteristics, such as magnetic, quantum, or polymer-based MNPs, increasing their usefulness even more. These developments are anticipated to have a significant impact on the expanding field of nanomedicine, where MNPs can serve as vehicles for targeted drug delivery, reducing adverse effects and enhancing therapeutic efficacy. Similar to this, MNPs are being utilized in energy conversion and storage to create more effective solar panels, fuel cells, and batteries—applications that are essential to meeting the world’s need for sustainable energy [198].

Although these encouraging uses, there are challenges and moral issues to be resolved, such as the effects of disposing of MNPs on the environment and human health, the scalability of producing them, and the regulatory frameworks for safe use [199]. The potential uses of MNPs in a wide range of industries are promising if scientists continue to develop novel techniques for their synthesis, functionalization, and control. MNPs are anticipated to be crucial in forcing the fields of science and technology into a more sustainable and health-conscious future with continuous innovation.

8 Conclusion

Antibiotic resistance poses a serious threat to world health since it reduces the effectiveness of traditional antibiotics and calls for creative ways to treat infections that are resistant. MNPs are a good alternative to traditional antibiotics because of their unique physicochemical properties, which include high surface area, magnetic responsiveness, and functionalization potential. The stability, bioavailability, and specificity of MNPs are further improved by surface modifications using substances like citric acid, chitosan, and olive oil. This allows for targeted antimicrobial applications and lowers the possibility of negative side effects. MNPs’ manufacturing techniques and antibacterial mechanisms imply that they may play a key role in developing novel, effective treatments that not only treat bacterial infections but also get around current resistance mechanisms.

Despite their great potential, there are still challenges to be solved, such as toxicity worries, the possibility of nanomaterial resistance, and the requirement for standardized processes for MNP synthesis and testing. Future studies should concentrate on improving synthesis methods, examining long-term biocompatibility, and examining how MNPs may function in conjunction with already available antibiotics. Furthermore, regulatory frameworks need to change to accept antibacterial drugs based on nanotechnology. In other hand, MNPs have a lot of potential to improve environmental remediation, antimicrobial therapy, and other fields. Their further advancement may result in innovative, long-lasting strategies that fight antibiotic resistance and help establish a new standard for the treatment of infectious diseases.

Author contributions AE and KE drafted and wrote the manuscript. AE, KE, MO and LR prepared tables and collected data, AE, KE, MO and LR edited and corrected the manuscript. All authors reviewed the manuscript.

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Data availability The data presented in this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate Not applicable.

Competing interests The authors declare that they have no conflict of interest.

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