Antimicrobial Magnetic Nanoparticles: A Potential Antibiotic Agent in the Era of Multi-Drug Resistance

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Abstract In the last few decades, microbes have evolved, having resistance to several drugs and antibiotics. Multiple-drug-resistant (MDR) strains have become a severe threat to human health that needs to be addressed immediately. In this context, research has led to a quest for new strategies in the development of novel antimicrobial therapies. The use of nanoparticles (NPs) has gained the attention of the research community working in the field of targeted delivery systems for drugs. Though NPs have proved their extraordinary antimicrobial activity against several disease-causing microbes, NPs with magnetic properties are found to be more efficient and effective. The unique physicochemical properties of magnetic nanoparticles (MNPs) have been proved to offer better antimicrobial activity when compared to the conventional forms. Moreover, magnetic nanoparticles have an extensive range of commercial and domestic applications in several fields, including environment, medicine, electronics, agriculture, and pharmaceuticals. This chapter provides aspects of the synthesis, use, and antimicrobial properties of MNPs along with a brief discussion of the probable mechanism involved. It also focuses on the characterization technique of MNPs, followed by the assessment strategies of antimicrobial activity. Overall, the chapter offers an insight into the antimicrobial activity of different MNPs while exploring the correlation of factors affecting the overall process.

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1 Introduction

Despite exceptional discoveries and achievements in the field of medical science, a few bacterial species have been a significant cause of chronic infections in humans that could lead to death. Antibiotics are an efficient and cost-effective solution and have been widely employed for the treatments of such diseases. However, in recent years, bacterial strains have evolved into a multi-drug-resistant (MDR) form that has become a global threat concerning severe health issues (Kruijshaar et al. 2008; Snell 2003). Moreover, only two new classes of antibiotics have been discovered and developed in the last few decades that have worsened the situation (De Vries et al. 2015). According to a report published by the World Health Organization (WHO), antibiotic resistance strains and biofilm associated infections will cost more than 300 million lives by 2050, along with the $100 trillion economic loss (Jose and Munita 2016). These severe concerns have accelerated the research towards finding and developing innovative strategies for microbial treatments (Arias and Murray 2009). An ideal antimicrobial agent should have excellent antimicrobial properties against a broader range of microbes while offering less or no toxic effect on the surrounding tissue. It should also be easy to synthesize and have no harm to the environment. Several materials have proved their potential while exhibiting antimicrobial activity against disease-causing strains. Among many, organic/inorganic polymers (nano/macroparticles), peptides, cationic surfactants (e.g., didodecyldimethylammonium bromide) have been assessed for their antimicrobial activities. Similarly, antibodies, phases, inhibitors (quorum sensitive), and antimicrobial NPs have been explored against several microbes in the recent past (Simões et al. 2016; Wang et al. 2017; Draper et al. 2015).

Generally, antimicrobial agents can be classified into two categories; organic and inorganic. Medicinal plants are organic agents that have proved their remarkable antimicrobial activities against numerous microbial strains, whereas NPs (usually less than 100 nm in diameter) belong to inorganic materials having superior antimicrobial activities against MDR strains (Kaviyarasu et al. 2017; Slavin et al. 2017). NPs seem to be an efficient and promising antimicrobial candidate against multi-drug resistance bacteria owing to their bio-mimicking properties similar to protein inhibitors. NPs show microbicidal nature where they confer similar size, geometries, and surface chemistry as biological agents. Typically, NPs can attack and directly affect the cell wall of bacteria without being penetrated into the cell cytoplasm that efficiently kills MDR strains. However, there are several other modes of action, including the release of toxic ions, generation of reactive oxygen species (ROS), interruption of electron transport, protein oxidation, and membrane collapse, which makes them a favorite antimicrobial candidate over others (Ali 2018). NPs have

shown antimicrobial effects against a broad spectrum of bacteria (Gram-positive and Gram-negative), mycobacteria, and fungi (Wang et al. 2017).

Moreover, magnetic nanoparticles (MNPs) offer superior features since they can be remotely monitored and directed using an external magnetic field to treat targeted sites, compared to their silica/carbon-based analogs signified for biopharmaceutical applications (Reddy et al. 2012). Additionally, magnetic fluid hyperthermia caused by MNPs enhances the overall antimicrobial effect where a fluctuating magnetic field of MNPs dissipates heat in the form of energy while elevating the local temperature around the targeted site (Laurent et al. 2011; López-Abarrategui et al. 2013). MNPs can exhibit unique physical properties allowing them to function at the cellular and molecular level and be efficiently established and employed in several pharmaceutical and biological applications (Reddy et al. 2012; Lu et al. 2007). Several metals, including zinc, silver, and copper, can be used to synthesize MNPs. Further, the nanoscale dimensions of these metals are inversely proportional to the antimicrobial activity (Seil and Webster 2012).

2   Microbial Resistance

Antimicrobial resistance in microorganisms is ancient and associated with the naturally produced antimicrobial compounds. Prolonged exposure and interactions between the microbes and antimicrobial compounds present in their natural surroundings can result in a resistant form. This type of microbes is known to be "intrinsically" resistant to one or more types of antimicrobial compounds. On the other hand, when a population of microbes becomes resistant that were initially susceptible to the antimicrobials, are known to have "acquired resistance." The following section focuses on the mechanisms of intrinsic/extrinsic factors that drive resistance at genetics/biochemistry level in bacteria, against antimicrobials.

2.1   Genetics at the DNA Level

Bacteria exhibit remarkable genetic adaptivity that helps them survive under a wide range of stressful environments. The presence of antibiotic molecules in the surrounding is a significant threat to bacteria and may trigger genetic modifications leading to an antibiotic-resistant form. Bacteria sharing the same environment as antimicrobial compound producing-strain can push them to withstand the impact of harmful antibiotic compounds, considering the intrinsic resistance that ultimately allows them to flourish in the presence of antimicrobials (Jose and Munita 2016). To survive and adapt to the antibiotic attack, bacteria can evolve through two major routes of genetic modifications. Spontaneous mutation of existing/exogenous gene (s) often allied with the action mechanics of the antimicrobial compounds representing the intrinsic resistance of bacteria, whereas acquired resistance causes

mutations through the acquisition of foreign code of DNA exercising horizontal gene transfer (HGT). The rise of multi-drug-resistant strains, in particular, is a consequence of the acquired resistance where the acquisition of multiple drug-resistance genes occurs in the same bacterial cell (Aung et al. 2016). Typically, bacteria can acquire external genetic composition via three routes: (1) incorporation of naked DNA via transformation, (2) bacterial sex via conjugation, and (3) phage mediated transduction. Further, the acquired resistance can be spread and transferred among bacteria through integrons, transposons, and plasmids (Coetzee et al. 2016; Tsutsui et al. 2015; Moghaddam et al. 2015).

2.2   Biochemistry at the Protein Level

Apart from genetic adjustments, certain antimicrobial resistance in bacteria could be a result of alterations in specific types of proteins present inside and on the surface of the cell. There are several possible mechanisms studied to assess the modifications of protein biochemistry. The resistance can be obtained by (1) altering of the target molecule that interacts with antibiotic molecule; (2) adding specific chemical moieties to the antibiotic molecule that ultimately hinders the molecule interaction with its target; (3) forming passivated/inactivated enzymes; (4) forming biofilms (Andersson et al. 2016); (5) employing activated efflux pump systems (Daury et al. 2016; Lytvynenko et al. 2016); (6) preventing antibiotic permeation inside the cell; and (7) eliminating specific proteins (e.g., KatG/BamA28) that are involved in the infection mechanism (Noinaj et al. 2013). Moreover, two or more mechanisms can be observed in one type of cell where resistance can be attained by (8) increasing production of a counteracting inhibitor that competes with the antibiotic and (9) preventing antibiotics through several metabolic pathways (Khameneh et al. 2016).

Pre-NP era, mainly three strategies were used to be employed to tackle the antibiotic-resistant microbes or MDR, including the development of novel antibiotics/drugs, high dosage of antibiotics/drugs (Huh and Kwon 2011), and combination of multiple antibiotic/drug compounds (Koul et al. 2011; Yount and Yeaman 2012). However, the identification and production of novel antibiotics could not keep up with the continuous evolution of bacteria through mutations. Moreover, the high dosage and application of combined drugs (two or more antibiotics) led to the intolerable toxicity that ultimately evolved highly multidrug-resistant strains than before. Therefore, NPs as an antibiotic agent can be employed to fight against resistant strains and must be explored for the possible enhancements in the field, considering their extraordinary physicochemical properties.

3   Mode of Action of Magnetic Nanoparticles

Increased usage of NPs in medicinal applications has initiated many investigations examining potential antibacterial mechanisms of NPs (Huh and Kwon 2011). The ability of NPs to eliminate bacteria to cure several types of diseases has led researchers to explore the possible mechanism involved in the process. NPs own unique chemical, physical, and biological properties along with electronic, electrical, mechanical, thermal, dielectric, optical, and magnetic properties. Metal oxide NPs have proved their great potential considering unique electronic, optical, and magnetic properties. NPs offer electrostatic interactions with negatively charged bacteria surface where they quickly get penetrated through the membrane. Moreover, a strong positive zeta potential of NPs can promote surface interactions leading to disruption of bacterial cell membrane along with enhanced flocculation with reduced viability. However, the exact mechanisms of NPs showing antimicrobial activity are yet to be entirely understood. According to prior reports, NPs can generate toxicity in several ways, including cell membrane damage, the release of toxic ions, interruption of electron transport, protein oxidation, and membrane collapse. Also, the generation of ROS (reactive oxygen species) can confer antimicrobial activity to NPs. Possible mechanisms supporting the antimicrobial activity of NPs and MNPs are discussed in this section.

3.1   Cell Membrane Deterioration

NPs can interact with bacterial cell membrane via electrostatic attractions (Li et al. 2015), Van der Waals forces (Armentano et al. 2014), and receptor–ligand hydrophobic interactions (Gao et al. 2014; Luan et al. 2016). These interactions between NPs and cell membranes may yield toxic effects on bacterial cells (Thill et al. 2006). However, the involvement of polymyxins in the process is not yet profoundly established. Reports suggest that polymyxin antibiotics can attack cell membrane that is responsible for furnishing a protecting shell around the bacterial cell (Aruguete et al. 2013). NPs can positively alter the permeability of the cell membrane that ultimately brings toxic effects to them. Several researchers suggested that pore/hole formation on the cell membrane can damage the cell where explicit evidence of cell damage has surfaced (Leroueil et al. 2007); however, the mechanics of the same demands more clarification. Nevertheless, a literal hole in the bilayer membrane can promote the absolute destruction of the plasma membrane that eventually causes the death of the cell (Niskanen et al. 2010).

3.2 Discharge of Toxic Ions

Different types of ions (e.g., Ag^+, Zn^{2+}, and Cd^{2+}) have demonstrated their ability to react with various groups of proteins present in the bacterial cell. Among many possible mechanisms, formation and accumulation of soluble salts in the cytoplasm due to the reaction of Ag^+ ions have been widely accepted for the antimicrobial effect of silver NPs. Such accumulated salts in the cytoplasm can inhibit respiration in the affected cell. For instance, silver chloride precipitation induced by chloride ions can kill the cell by hindering its essential metabolic activities. Similarly, silver NPs can also show antibiotic activity against several Gram-negative bacterial species, including *E. coli*. Silver NPs not only offer a toxic effect by delivering silver ions but also get penetrated through the cell membrane while hindering the metabolic activities of the cell (Niskanen et al. 2010). Further, Ag^+ ions have been reported to damage DNA by blocking the replication process that ultimately leads to the death of the cell. Similarly, Zn^+ and Cd^+ ions also have shown antibiotic activity against several bacterial species through binding to sulfur-containing surface proteins. These surface proteins mainly prevent external molecules from penetrating through the cell membrane. The NP-surface protein interactions make NPs easily penetrate the cell, which is necessary to cause an adverse effect on the regular metabolic activities of the cell. Additionally, the concentration of ions required to attain the bactericidal action is evidently less and therefore makes the NPs a favorable candidate over others.

3.3 Interruption of Protein Oxidation, Electron Transport, and Membrane Collapse

Positively charged NPs can evidently interact with the negatively charged cell membrane of a bacterial cell that awards antimicrobial activity to NPs. Despite the lack of establishment of a defined mechanism of the same, it was found that ions can alter the membrane-bound respiratory enzymes via oxidation. Further, it can also influence the efflux bombs of ions leading to the death of the cell (Allaker 2010). Contact of NPs with cell membranes can also trigger a cascade reaction that inactivates crucial enzymes involved in metabolic pathways. Typically, NPs coming with the contact of bacterial cells initiate possible oxidation of respiratory enzymes along with the production of reactive oxygen and radical species that ultimately alter the physiology of the cell while promoting DNA degradation (Spacciapoli et al. 2001; Xia et al. 2008).

3.4 ROS (Reactive Oxygen Species) Generation

Despite being a potent oxidant agent and acceptor of electrons during cellular respiration, oxygen could be fatal to some bacterial species. Oxygen in its singlet (O_2) or triplet $(3O_2)$ form can be toxic to the cell. Singlet (O_2) is a strong reagent that can promote undesirable and spontaneous peroxidation of several cellular components, including lipids and proteins (Bronshteint et al. 2006). H_2O_2 formed during respiration consumes O_2 while producing free hydroxy radicals that evidently lead to oxidation of lipids, proteins, and DNA (Bronshteint et al. 2006). ROS affects the cell membranes by hindering their adhesion to the surface while unable to maintain communication with nearby bacterial cells hindering their functions and efficiency. Nevertheless, several bacterial species can fight back to neutralize oxidative stress by employing enzymes (e.g., superoxide dismutase). Further, they can cope up with the oxidative stress by responding to superoxide (SoxRS) and hydrogen peroxide (OxyR) while effectively repairing damaged cell constituents (Aruguete et al. 2013; Allaker 2010).

3.5 Magnetic Fluid Hyperthermia

Under the application of a high frequency and amplitude of the alternating magnetic field, MNPs can absorb electromagnetic radiation and converts the magnetic energy to localized heat, often referred to as magnetic fluid hyperthermia (Laurent et al. 2011; López-Abarrategui et al. 2013). The MNPs induced hyperthermia is highly useful to control infectious diseases while increasing antibiotics efficacy along with biofilm detachment (Xu et al. 2019). Ibelli et al. (2018) have shown that the magnetic hypothermia process increases the membrane permeability at elevated temperature ($>45\,°C$), where most of the bacterial pathogens become vulnerable. Rodrigues et al. (2013) also derived a similar conclusion stating, at $45\,°C$, bacterial morphology, mechanical properties, and the viability of *P. fluorescens* was significantly influenced. The detailed study showed that by applying an external magnetic field, the viability of both biofilm cells and planktonic decreases with an increase in temperature. Also, hypothermia caused by MNPs has more significant destruction of the bacterial biofilms in comparison to the direct heating method. Kim et al. (2013) have further investigated the antimicrobial effectiveness of magnetic hypothermia against *S. aureus* and reported 80% efficiency of antibody-modified MNPs under the alternating magnetic field.

To intensify the antibody interactions (immobilization) at conjugation sites, antibodies conjugated with MNPs surface have been employed in the separation and selective targeting of several bacteria (Kim et al. 2016). For the separation of *Salmonella typhimurium*, MNPs were functionalized with O-or H-antibodies. The polysorbate 80-coated MNPs (PCMNC) were prepared in two steps. Firstly, the hydrophobic ligands (oleic acid) coated MNPs were synthesized by thermal
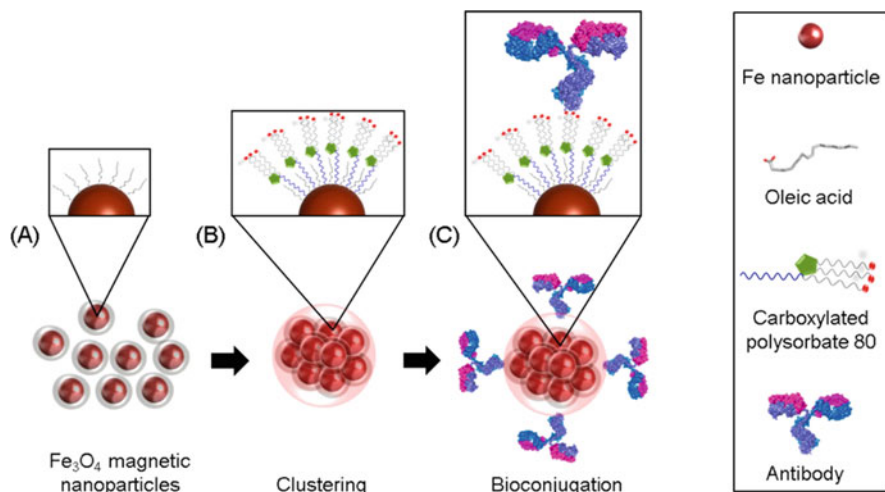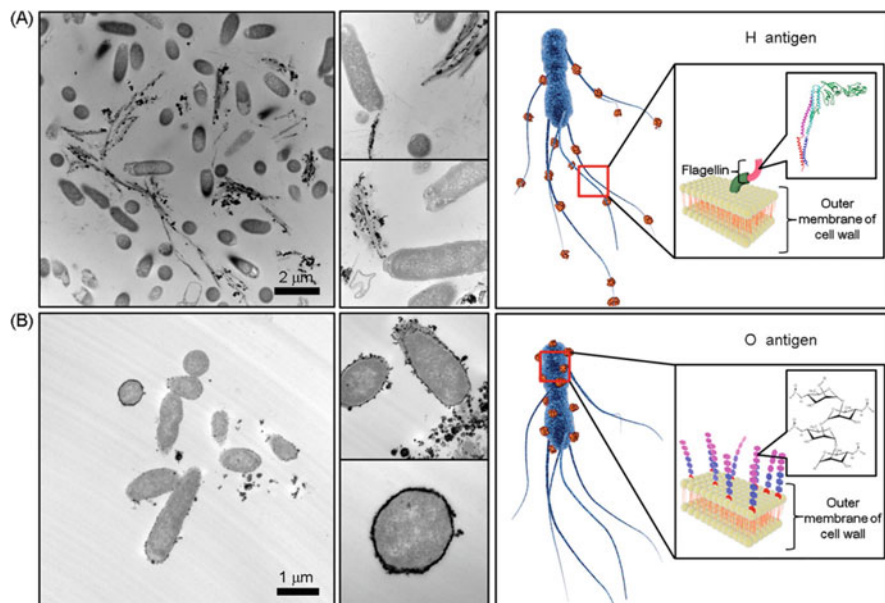
Fig. 1 Schematic of preparation of bioconjugated MNPs with antibodies (Copyright © 2016, American Chemical Society, All rights reserved, reprinted with permission) (Kim et al. 2016)

decomposition of iron (III) acetyloacetonate and oleic acid in benzyl ether (Fig. 1a). The surface of prepared material was then modified by using carboxyl group containing polysorbate 80 (Fig. 1b). The prepared PCMNC was then conjugated with amine group of antibodies to get magnetically separable nanocomposite (Fig. 1c). The MNPs nanocluster showed an effective capturing of *S. typhimurium* with 57 and 99% cell separation efficiency of H- and O-antibody modified MNPs nanocluster, respectively. The transmission electron microscopic (TEM) analysis of the *S. typhimurium* decorated MNPs cluster showed that O-antibody modified nanocluster is accumulated in flagella while H-antibody modified nanocluster is accumulated in salmonella body (Fig. 2).

Furthermore, modification of MNPs with cationic polymers or antibiotics can increase the antimicrobial activity due to the supporting action of magnetic hypothermia (Wang et al. 2018a; Pu et al. 2016; Nguyen et al. 2015; Zomorodian et al. 2018). Nguyen et al. (2015) have studied the combined effect of hypothermia induced due to MNPs along with gentamicin, against the biofilm formed by *P. aeruginosa*. Poly ((oligo (ethylene glycol) methyl ether acrylate)-*block*-poly (monoacryloxy ethyl phosphate)-stabilized iron oxide NPs (POEGA-*b*-PMAEP@IONPs) can produce local heating in biofilms when exposed to the magnetic field while promoting the detachment of biofilm cell. The combined treatments of nanocomposite, along with gentamicin, showed an increase in the efficacy against planktonic and biofilm in comparison to gentamicin alone. Fang et al. (2017) have combined the magnetic hypothermia with vancomycin to see the bacterial killing efficiency against *S. aureus*. The MNPs conjugates were heated (up to 75 °C) under the exposure of external magnetic field, which ultimately enhanced the antibacterial efficacy of vancomycin. Similarly, Chudzik et al.

Fig. 2 Selective binding of *Salmonella typhimurium* for different antigens (Copyright © 2016, American Chemical Society, All rights reserved, reprinted with permission) (Kim et al. 2016)

(2016) have described the antifungal activity of magnetic fluid hyperthermia against *C. albicans*. The composite material was prepared by functionalizing antimicrobials (anti-*C. albican*) on Meso-2,3-dimercaptosuccinic acid (DMSA) coated MNPs. The hyperthermia-induced under the exposure of external magnetic field with DMSA coated MNPs and functionalized MNPs have shown higher toxicity against the *C. albicans* cells in comparison to the static heating.

4 Synthesis of Magnetic Nanoparticles

The specific activity of the nanomaterials is the function of the structure, and the phase it exists in. The selectivity, antimicrobial activity, and overall performance of these nanomaterials are often correlated with their structure (Zhou et al. 2018). The effect of different precursors and methods of preparation results in varied activity, shape, size, and distribution of NPs. In a bottom-up approach, several methods are reported for the synthesis of NPs, which can be broadly categorized into conventional, green, and advanced synthesis.

4.1 Conventional Methods

In a typical nanoparticle synthesis, the metal precursor is reduced to the metal nanoparticle, either physically or chemically (Park 2014). In a physical method, high temperature is used to breakdown the precursor. This method gives uniform distribution and shape, though it takes a long time with harmful operating conditions. On the other hand, chemical synthesis is the most widely practiced method, which involves the use of three main components: a metal precursor, organic/inorganic reducing agents, and stabilizing agent. The most common reducing agents are sodium borohydride and hydrazine hydrate. Chemical synthesis methods are further categorized into the microemulsion, photo-induced reduction, UV-assisted photoreduction, electrochemical reduction, and different irradiation methods. The chemical methods have the upper hand in terms of the yield of NPs compared to physical methods (Fernando et al. 2018).

4.2 Green Methods

Recently, the paradigm of using chemical reducing agents has shifted to green and sustainable methods (Park 2014). The biological synthesis methods offer an excellent solution to develop environment-friendly methods. The ability of bacteria, fungi, and plants to biosynthesize the metal NPs by an environmentally friendly process offers an exciting prospect (Prasad et al. 2016, 2018). In this method, the plant extract is utilized to reduce the metal precursor to obtain NPs (Park 2014; Rafique et al. 2017; Prasad 2014; Joshi et al. 2018). The plant extract, as a reducing agent coming from multiple parts of the plant (e.g., leaves, flowers, bark, root fruits, etc.) is used. The antimicrobial property of such NPs can be correlated to their enhanced stability. Thus, cationic and anionic surfactants are employed to stabilize the NPs (Andersson et al. 2016).

4.3 Advanced Synthesis Methods for Functionalization of Nanoparticles

The physical properties and the stability of each metal vary concerning the structure, activity, and application. This demands the development of new strategies to synthesize advanced functional materials. Several metal NPs, including Ag, Cu, Zn, Ti, Au, and carbon-based, have been investigated for their antimicrobial activity. Among others, silver NPs have shown a broad spectrum of applications, and several methods are reported for the synthesis of Ag NPs. Ag NPs supported on SiO_2 were prepared using the co-condensation method to enhance the antimicrobial activity (Tian et al. 2014). Multi-functional nanocomposite supported on graphene oxide was prepared by the co-precipitation method. The graphene as support helps to grow the

NPs and gives them stability. Functionalized gold particles with antimicrobial activity can be obtained by chemical processes such as Turkevic, brust, and seeded growth. Similarly, the biological method can also be employed where functionalization can be obtained using plant extracts, microorganisms, and biomolecules (Shah et al. 2014).

Some of the advanced methods for the synthesis of antibacterial MNPs are mentioned below. Ag NPs with antimicrobial activity were incorporated with iron oxide to provide magnetic properties. One-pot hydrothermal synthesis of porous core–shell structure was developed by embedding the Ag in Fe_3O_4 shell. The synthesized structure helped the sustained release of silver ions that prolonged the antibacterial activity (Fang et al. 2014). Moosavi et al. (2015) have prepared the magnetic nanocomposite made of Fe_3O_4 as a core, the graphene oxide as a shell, and Ag as supported metal. The graphene oxide sheet was first incorporated with iron oxide to provide magnetic properties. This magnetic graphene sheet was then supported with silver NPs using cinnamon extract (Moosavi et al. 2015). Recyclable MNPs were prepared by inducing a controlled living radical polymerization technique wherein the Fe_3O_4 NPs' surface was functionalized with the atom transfer radical polymerization (ATRP) (Dong et al. 2011). The synthesis consists of multiple steps, and the resulting material showed excellent reusability with sustained antimicrobial activity for eight multiple cycles (Dong et al. 2011). In another example, silver MNPs were prepared by forming a silver ring and the magnetic core with ligand sandwiched in between, which facilitated a promising increase in antibacterial properties of the material (Mahmoudi and Serpooshan 2012). Multifunctional polyester fabric with antibacterial and magnetic properties was prepared by in-situ grafting of Fe_3O_4 NPs on the surface of a fabric. Chloride and sulfate precursor of Fe in specific ratios were used to treat the polyester fabric by the co-precipitation method using NaOH as a base (Harifi and Montazer 2014). The pulsed laser ablation technique synthesized Fe_3O_4 NPs by dispersing iron target in dimethylformamide and sodium dodecyl sulfate (SDS) solution (Ismail et al. 2015). Bomila et al. (2018) have prepared La-doped ZnO MNPs by the wet chemical method, which showed a varied antibacterial activity with different doping concentrations. The various methods for the preparation of antibacterial nanomaterials are summarized in Table 1.

5 Characterization of Magnetic Nanocomposites

The characterization of prepared nanocomposites can be divided into two parts. The physical and chemical properties of prepared MNPs can elaborate on the advancements in the field. On the other hand, the antimicrobial assessment of synthesized MNPs can help in assessing the biological responses associated with their physicochemical properties.

Table 1 Methods for the preparation of antibacterial magnetic nanomaterials

Sr. No.	Magnetic nanoparticles	Method of preparation	Antibacterial activity	Reference
1.	Ag and Fe core shell	Solvothermal	*Escherichia coli* and *Bacillus subtilis*	Fang et al. (2014)
2.	Ag, Fe, graphene oxide	Co-precipitation and ultra-sonication	*E. coli* and *S. aureus*	Moosavi et al. (2015)
3.	Fe	Co-precipitation	*E. coli*	Dong et al. (2011)
4.	Au and Fe core shell	Chemical reduction	Pathogens	Mahmoudi and Serpooshan (2012)
5.	Fe	In-situ co-precipitation on fabric	*S. aureus*	Harifi and Montazer (2014)
6.	Fe	Pulsed laser ablation	*S. aureus*, *E. coli*, *Pseudomonas aeruginosa*, and *Serratia marcescens*	Ismail et al. (2015)
7.	La-doped Zn	Co-precipitation	Gram-positive: *Bacillus subtilis*, *S. aureus*, Gram-negative: *Proteus mirabilis*, *Salmonella typhi*	Bomila et al. (2018)

5.1 Physicochemical Techniques

Several methods and techniques are proposed to understand the physical and chemical structure of MNPs and nanomaterials.

5.1.1 Microscopy

The stability and magnetic properties of nanocomposites mainly depend on their shape and size (Allafchian and Hosseini 2019). The several microscopic techniques used include scanning electron microscopy (SEM), field emission scanning electron microscopy (FESEM), transmission electron microscopy (TEM), and HRTEM. The detailed microscopic characterization gives the information on shape, aggregate state, size, and core–shell structure of NPs (Ali et al. 2016; Hurley et al. 2015; Ansari et al. 2019). FESEM and HRTEM usually analyze the NPs of less than 20 nm in size. Moreover, atomic force microscopy (AFM) provides information about shape heterogeneity, dispersion for a wide range of analyzing conditions such as liquid, air, or vacuum. Besides, AFM is useful for the simultaneous analysis of a biological system to gather data on their morphology, elasticity, deformation, energy dissipation, and adhesion (Ansari et al. 2019).

5.1.2 Spectroscopy

Spectroscopy techniques such as Raman, Fourier Transform Infrared (FTIR), Energy dispersive X-ray (EDS), UV-visible (UV-Vis), X-ray photoelectron (XPS) are used for the structural confirmation of NPs (Ali et al. 2016; Hurley et al. 2015; Ansari et al. 2019; Arakha et al. 2019). Raman spectra can confirm the formation of a certain material phase in the sample. FTIR investigates the surface chemical group of samples and various chemical bonds formed. EDS provides the electron mapping of the sample and hence give information on the composition of the nanomaterial. UV-vis spectroscopy provides information on the optical absorption rate of suspension. XPS examines the surface layer, which is generally highly oxidized that helps to assess the chemical state of the components.

5.1.3 Magnetometric Techniques

The magnetic properties of prepared MNPs and composites can be analyzed using magnetometers such as superconducting quantum interference device (SQUID) and vibrating sample magnetometer (VSM). The critical magnetic parameters of MNPs, such as coercive field, remnant magnetization, and saturation magnetization, are measured using the above-mentioned magnetometers (Tarantash et al. 2018; Ghazanfari et al. 2016). The SQUID is considered as standard magnetization measurement technique due to its better sensitivity (up to 10^{-10} emu) in comparison to VSM (up to 10^{-6} emu) and offers the analysis of samples in various forms (Ali et al. 2016).

5.1.4 Other Conventional Techniques

Apart from the techniques mentioned above, other relevant methods, such as X-ray diffraction (XRD), contact angle measurement, and zeta potential, are employed. XRD helps to identify the phase of the NPs, crystallinity of the sample while verifying the chemical composition (Talpade et al. 2019; Tiwari et al. 2017). The surface wettability of NPs can be monitored using contact angle measurement and thus can be used for the quantitative analysis of hydrophobicity and hydrophilicity of the surface of a material (Allafchian and Hosseini 2019). Zeta potential measures the colloidal stability of NPs. The high value of zeta potential for small enough dispersed particles would resist their tendency to aggregate. The dispersed NPs having zeta potential magnitude more than 30 mV are found to be stable (Hatamie et al. 2015).

5.2 Antimicrobial Activity Test

Understanding the impact of antimicrobial agents on the viability of a microbial cell is an essential factor for the development of next-generation antimicrobial agents. Here, a brief overview of conventional methods for testing antimicrobial property of NPs is provided. The details regarding all these methods can be found in the published literature along with their limitations (Webster and Seil 2012; Hoseinzadeh et al. 2017).

5.2.1 Disk-Diffusion Method

In this method, a disc containing antimicrobial agents is placed on the microbes inoculated agar (Mueller-Hinton agar (pH 7.2–7.4). After an incubation period of 24 h, if the examined agent inhibits the growth of the microbes, a clear zone of inhibition will form around the disc. The common factors affecting the size of the inhibition zone are nanoparticle size, agars' porosity, the diffusion rate of NPs, and possible interaction between agar and antimicrobial agent (Vega-Jiménez et al. 2019).

5.2.2 Dilution Methods

Two types of processes, agar or broth dilution method, are employed to measure the antimicrobial activity against microbes (Webster and Seil 2012). Also, the dilution methods are more appropriate to determine the minimum inhibitory concentration (MIC) value. The broth dilution method is less laborious and gives better results in comparison to agar dilution, and hence is a preferable method of testing (Baker et al. 1991).

5.2.3 Minimum Inhibitory Concentration (MIC)

The MIC refers to the minimum concentration of antimicrobial agent that completely inhibits the growth of microbes and is a well-documented method to determine the antimicrobial potential of NPs (Hoseinzadeh et al. 2017). Moreover, the calorimetric methods based on the use of dye reagents are developed to determine the MIC endpoint (Balouiri et al. 2016). The most common dyes used are Tetrazolium salts, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) and 2,3-bis {2-methoxy-4-nitro-5-[(sulfenylamino) carbonyl]-2Htetrazolium-hydroxide} (XTT) are utilized to determine MIC endpoint in both antifungal and antibacterial assays (Balouiri et al. 2016; Liang et al. 2012; Al-Bakri and Afifi 2007; Monteiro et al. 2012).

5.2.4 Minimum Lethal Concentration (MLC)

Minimum bactericidal concentration (MBC) or minimum fungicidal concentration (MFC) refers to the lowest concentration of antimicrobial agents needed to kill 99.9% of bacteria or fungi (Allafchian and Hosseini 2019). MLC testing compares the germ-killing activity of the different antimicrobial agents in single experiments (Hoseinzadeh et al. 2017).

5.2.5 Time-Kill Method

The time-kill test provides the time-dependent or concentration-dependent antimicrobial effect and is a robust tool to determine the interaction between microbial strain and antimicrobial agents (Hoseinzadeh et al. 2017, 2012, 2014; Lara et al. 2010). This method is more frequently used to assess the antimicrobial activity of NPs.

5.2.6 Flow Cytofluorometric Method

In the flow cytofluorometric technique, a fluorescent dye is used to determine the cell viability after exposure to drugs or pathogenic organisms (Hoseinzadeh et al. 2017). Propidium iodide (PI), a red fluorescent nucleic acid dye, is mostly used as a DNA staining agent.

6   Applications of MNPs

6.1   MNPs as Antimicrobials

The toxicity can be influenced by the intrinsic properties of NPs, along with the composition and surface modifications. Moreover, the type of bacterial species also affects the extent of the antibacterial effect generated by NPs. In comparison to several MNPs, iron oxide NPs (IONPs) have found great importance in biomedical applications owing to their ease of preparation, surface modification, and low toxicity (Liu et al. 2013). Prucek et al. (2011) have synthesized two different types of MNPs, one having the ultra-small Ag NPs (~5 nm) supported on Fe_3O_4 (~70 nm) as a magnetic core (Ag@Fe_3O_4). The second form of MNPs (α-Fe_2O_3@Ag) was prepared by taking silver NPs (20–40 nm) as a core and surrounded by the ultra-small α-Fe_2O_3. The prepared NPs have shown vital antimicrobial activities against different bacterial strains. These MNPs are found to be useful for the transportation of targeted antimicrobial agents to the specific target while offering convenient removal of particles by applying the external magnetic field. Several parameters,

including size, shape, surface features, and functionalization play a crucial role in producing overall antimicrobial effect.

6.1.1 Size

The small size of the NPs has been a responsible factor conferring potent antimicrobial activity to these particles. IONPs (66 nm in size) were tested against different bacterial strains and found to have better antimicrobial activity against Gram-positive bacteria in comparison to Gram-negative bacteria (Behera et al. 2012). However, the prepared particles were not coated and adversely affected the antimicrobial efficacy and stability of MNPs. The antimicrobial activity of NPs is mainly due to their active surface area, which increases with a decrease in size and increase in numbers (Allafchian and Hosseini 2019). Auffan et al. (2008) have synthesized the iron-based NPs and studied their antibacterial activity against *E. coli*. The results showed that the NPs exhibited a size-dependent inhibitory effect. Gao et al. (2016) described the antimicrobial activity of MNPs in combination with H_2O_2 as an effective method to kill bacteria (*S. mutans*), causing dental caries. The catalytic nanoparticle, along with H_2O_2, has shown a high antibacterial effect (>99.9% killing in 5 min) against the biofilm. Therefore, the excellent activity of the system can be correlated with the small size of IONPs.

6.1.2 Shape/Composite

Core and shell-type of magnetic nanocomposite ($Fe_3O_4@SiO_2$/CTMP NPs) having a core of magnetic Fe_3O_4, silica as the middle layer, and antibacterial N-calamine as the outer components were prepared (Yao et al. 2016). The prepared material showed a strong antimicrobial effect against two bacterial strains (*E. coli* and *S. aureus*) while killing bacterial cells in 20 min (100% kill rate) with an oxidative concentration of Cl^+ (0.58%). Thukkaram et al. (2014) have studied the effect of IONPs on biofilm structure while assessing them with different surfaces and biomaterials. The MNPs found to have the potent antimicrobial activity against *S. aureus*, *P. aeruginosa*, and *E. coli*, while showing a significant decline in the biofilm growth for all bacterial species. The formation of biofilm results in a decrease in the effectiveness of antibiotics; hence suitable anti-biofilm therapies have been put forward using NPs (Taylor et al. 2014). In this context, Grumezescu et al. (2015) have reported the synthesis of core and shell structure of MNPs loaded with an antibiotic (as an antibiotic adsorption shell) assembled by matrix-assisted pulsed laser evaporation. The novel anti-biofilm nano-coatings consist of magnetic core (Fe_3O_4), sodium lauryl sulfate (SLS) as a shell, and encumbered with cephalosporin (cefotaxime (CTX) and cefrom (CEF)) as antibiotics. The prepared MNPs have been tested against *E. coli*, *S. aureus*, and *P. aeruginosa* and showed a significant decrease in biofilm growth. This study also revealed that the amount of MNPs required is

relatively less since iron NPs at 0.15 mg/mL showed the highest reduction in biofilm formation.

6.1.3   Surface Features

Apart from the size of the nanoparticle, surface features also play an essential role in the efficiency of antimicrobial agents. Javanbkht et al. (2016) have evaluated the interaction of superparamagnetic iron oxide NPs (SPIONs) on the bacterial biofilm (*S. mutans*) based on their surface feature. Two different SPIONs, one with a positive charge and second with a negative charge, were prepared and tested to show that surface feature determines the diffusion of nanoparticle through biofilm. The positive charged SPIONs showed better activity in killing bacteria than negative charged MNPs. Arakha et al. (2015) have also studied the effect of the surface potential of MNPs on their antimicrobial activity against *E. coli* and *Bacillus subtilis*. The results showed that MNPs with negative surface potentials have significant antimicrobial activity against both the Gram-negative and Gram-positive bacteria. Bhosle et al. (2018) have prepared the $NiFe_2O_4$ NPs by two different methods. The prepared NPs were tested against different bacterial strain and fungal species. The antimicrobial activity of prepared NPs was mainly controlled by the surface properties such as lesser agglomeration leading to high crystalline structure formation. Similarly, Konwar et al. (2016) have described the antimicrobial activity of graphene oxide coated iron oxide nanomaterial with the chitosan matrix. The prepared nanocomposites have shown substantial antimicrobial activity against *Candida albicans* along with different bacterial strains due to the specific surface properties of MNPs. The above results confirmed that the surface characteristic of NPs is one such parameter that needs to be tuned in order to enhance the overall efficiency of antimicrobial agents.

6.1.4   Surface Functionalization

The surface functionalization of MNPs also results in enhanced antimicrobial activity. Glycerol-iron oxide NPs with an average size of ~4.2 nm were prepared by the co-precipitation method (Iconaru et al. 2013). The prepared MNPs have shown the inhibitory effect against the biofilm formation of *P. aeruginosa* at a lower concentration (ranging from 0.01 to 0.625 mg/mL). In recent, Farouk et al. (2020) have used an aqueous extract of *Citrullus colocynth* (CTC) to produce MNPs with enhanced antimicrobial activity. The produced MNPs showed a comparable antimicrobial activity against two Gram-positive (i.e., *B. subtilis* and *S. aureus*) and two Gram-negative (*E. coli* and *P. aeruginosa*) bacteria along with yeast (*Candida albicans*). Sandhya and Kalaiselvam (2020) have also reported a similar kind of result where the MNPs were synthesized using the seed coat extract of *Borassus flabellifer*. The prepared MNPs have shown enhanced microbial activity against *E. coli*, *B. subtilis*, *Shigella*, *S. aureus*, *A. niger*, and *Candida albicans*. Khan et al. (2020) have

synthesized the citric acid-functionalized MNPs with different concentrations of citric acid. The prepared functionalized MNPs showed an increase in the antibacterial activity against *E. coli and B. subtilis*, in comparison to the native form of MNPs. Cyanoethyl cellulose (CEC)/Fe_3O_4 composite was prepared by in-situ blending techniques (Dacrory et al. 2020). The prepared nanocomposite found to have significant antimicrobial properties against both Gram-positive (*S. aureus*) and Gram-negative (*E. coli*) bacteria, yeast (*C. albicans*), and fungus (*Aspergillus niger*). The prepared particles have shown higher antimicrobial activity in comparison to CEC alone. The Fe_3O_4 particle produced ROS that ultimately is responsible for the antimicrobial activity of MNPs.

Further antifungal nano therapies based on the MNPs were also studied (Konwar et al. 2016; Chifiriuc et al. 2012; Anghel et al. 2013; Franco et al. 2016). Parveen et al. (2018) have prepared the IONPs using tannic acid as a reducing and capping agent. The prepared MNPs have shown significant antifungal activity against several fungal species. Citric acid-modified $MnFeO_4$ NPs of 5 nm diameter in size were tested against *C. albicans*, *S. aureus*, and *E. coli* (Franco et al. 2016). The results showed that the prepared MNPs have an inhibitory effect on the growth of *C. albicans* but were not effective against the tested bacterial strains. The results also showed that the antimicrobial action of these MNPs is specific to a yeast cell mainly due to the electrostatic connection among yeast plasma membrane and MNPs.

However, the bare iron oxide NPs can lead to an increase in bacterial growth. The MNPs of different sizes showed no inhibition against the biofilm growth of *P. aeruginosa* (Haney et al. 2012). The MNPs of smaller size (2 nm) were found to be responsible for an increase in the formation of biofilm significantly in comparison to the larger NPs (540 nm) (Balouiri et al. 2016). The hypothesis behind the increase in bacterial growth could be associated with the release of Fe^{3+} ions from MNPs that help in the growth of bacteria. Haney et al. (2012) have also reported that similar results for three different sets of MNPs assessed against *P. aeruginosa* biofilm growth. The concentration of MNPs up to 200 µg/mL was found to have no inhibition ability against the biofilm formation that supported the hypothesis mentioned above.

6.2 MNP-Based Antibiotic Delivery Systems

MNPs of different structures have shown excellent antibacterial activity to kill bacterial species of wide range, including multidrug-resistance bacteria and bacterial biofilms (Dacrory et al. 2020). Various antibiotics such as vancomycin, gentamycin, methicillin, and cephalexin (Lai and Chen 2013; Bhattacharya and Neogi 2017; Geilich et al. 2017; Rayegan et al. 2018) supported on MNPs and their derivatives (Co-doped, cationic polymer-modified, Au coated, or Ag coated) have been widely investigated to explore their potential to penetrate biofilms and inactivate

antibiotic-resistant strains (Pu et al. 2016; Zomorodian et al. 2018; Dhanakotti et al. 2015; Car et al. 2014; Chen et al. 2016).

MNPs have also been used as a vehicle for the controlled release of a different drug (López-Abarrategui et al. 2013). MNPs based drug delivery system has a primary aim of drug accumulation in a specific organ or tissues using drug loaded on the magnetic carrier while applying an external magnetic field (Chomoucka et al. 2010; Wu et al. 2016; Rodrigues et al. 2019). The use of MNPs based drug delivery system minimizes the systemic side effects since it requires relatively less drug concentration to be administrated. The low activity, stability, and inhibitory effect of drugs is mainly due to the hindrance that occurred during drug transportation across cellular membranes. This has promoted research towards the quest for novel strategies to enhance the overall antimicrobial effect (López-Abarrategui et al. 2013; Chudzik et al. 2016; Ulbrich et al. 2016). The use of NPs as a drug carrier can be one of the possible solutions for the existing shortcomings. The various materials like mesoporous silica and polymers (chitosan, PAA, PEG, etc.) can be used as a coating material for bare MNPs before employing in drug delivery (Wu et al. 2008, 2016). The choice of coating material is a crucial factor and depends on the release behavior and tailored drug loading.

To increase the antimicrobial properties of different molecules, they can be chemically and physically bonded with MNPs (Rodrigues et al. 2019; Ragelle et al. 2017). Several studies have demonstrated the enhanced antimicrobial activity of antimicrobial peptides (AMP) and antibiotics in conjugation with MNPs (Chudzik et al. 2016; Franco et al. 2016; Rodrigues et al. 2019). Zhang et al. (2012) have covalently immobilized bacitracin on the Fe_3O_4 NPs via Click chemistry and investigated its antimicrobial activity against both Gram-positive and Gram-negative microorganisms. The conjugated NPs showed higher activity in comparison to bacitracin itself against all tested microorganisms. The enhanced microbial activity of the magnetic nanocomposite conferred high drug efficacy while reducing the side effects largely caused by an excess dosage of antibiotics. Niemirowicz et al. (2015) have prepared core and shell-type MNPs (MNP-CSA-13) with ceragenin CSA-13 as a shell linked with iron oxide as a core through amine linkage. The pH control system was used to release the CSA-13 from the prepared nanocomposite and showed potent antibacterial activity in comparison to soluble ceragenin in killing of *P. aeruginosa*.

Similarly, MNPs based drug delivery system has been tested against fungi, bacteria (MDR), and biofilm of *S. aureus* and *P. aeruginosa* (Nguyen et al. 2015; Niemirowicz et al. 2016a). Niemirowicz et al. (2016a) have studied the effect of MNPs on the activity of AMP, i.e., cathelicidin, synthetic ceragenins, and antibiotics (colistin and vancomycin) against methicillin-resistant microorganisms. Three different core and shell structure MNPs, i.e., gold-coated (MNP@Au), amino silane coated (MNP@NH$_2$), and quaternary ammonium derivatives coated (MNP@PQAS) NPs were synthesized and tested as combined therapy against the microorganisms. The results were calculated based on the fractional inhibitory concentration index and fractional bactericidal concentration index using the microdilution method. In most cases, a synergistic effect of the combination of MNPs with AMP or classical

antibiotics was observed. The core–shell MNPs, along with antibacterial agents, also found to restrict biofilm formation. The prepared MNPs interact with cellular membrane or bacterial cell wall, which enhances the antimicrobial molecule penetration resulting in an increased activity of the combined system. The similar type of synergistic effect of combining MNPs and antibiotics (polypeptides, B-lactams, aminoglycosides, and macrolides) have been reported (Istrate et al. 2014). The prepared nanosystem increases the interaction of antibiotics with the cellular membrane by increasing the membrane fluidity. Grumezescu et al. (2014) have also reported the 5 and 8-fold MIC reduction of amoxicillin against *S. aureus* and *E. coli*, respectively, when combined with MNPs. Geilich et al. (2017) conducted a similar study of anti-biofilm activity assay of biocompatible multicomponent nanocarrier made up of superparamagnetic iron oxide coated with methicillin and obtained identical results. The penetration depth and antibacterial property of MNPs loaded with methicillin against bacterial biofilm was also studied by using a laser scanning confocal microscopy. Wang et al. (2018b) have investigated the antibacterial activity of the MNPs based material coated with multilayer films containing antibiotic gentamicin, tannic acid, and silver nanoparticle. Further biodegradable hyaluronic acid was capped on the outer surface as a responsive shell to improve biocompatibility while getting control over drug release. The prepared nanocomposites have shown satisfactory antibacterial capacities against Gram-positive *S. aureus* and Gram-negative *E. coli*. The probable mechanism of biofilm treatment was presented based on the confocal laser scanning microscopy (CLSM-3D) images of the biofilms (Fig. 3). With the application of a magnetic field, a selective and fast penetration in a biofilm of *S. aureus* was achieved. In the absence of the magnetic field, the nanocomposites showed an insufficient antibacterial activity due to their incapability to penetrate the dense and intact biofilm (Fig. 4). Though the treatment with nanocarrier increased the number of dead bacteria, in absence of a magnetic field, a high number of live bacteria were observed. However, the application of the magnetic field showed a dramatic decrease in viable bacteria and biofilm thickness. The results confirmed that the use of MNPs based drug delivery system could help to attain deep penetration while delivering high concentrations of antibiotics into the targeted multilayers of biofilms.

Streptomycin-coated chitosan MNPs (Strep-CS-MNP) released a 100% antibiotic over 350 min (Hussein-Al-Ali et al. 2014a). The prepared nanocomposite showed an enhanced antibacterial activity against *S. aureus*. The results confirmed that the nanocomposites activity depends on the antibiotic only, as the bare MNPs have no antimicrobial activity at all (Hussein-Al-Ali et al. 2014a). Hussein-Al-Ali et al. (2014b) have studied the antibacterial and antifungal activity of nystatin incorporated on the chitosan-coated MNPs (Nyst-CS-MNP). The prepared nanocomposites released a 100% Nyst in 1800 min. The prepared nanocomposites showed high activity against *Candida albicans*, *P. aeruginosa*, and *E. coli* while showing a weak activity against *S. aureus*. In another study, Niemirowicz et al. (2016b) have prepared polyene (amphotericin (AMF) and nystatin (NYS)) attached to the surface of MNPs and used against the clinical isolates of Candida species. The synthesized nanosystem showed a synergistic activity due to a combination of NPs and polyene
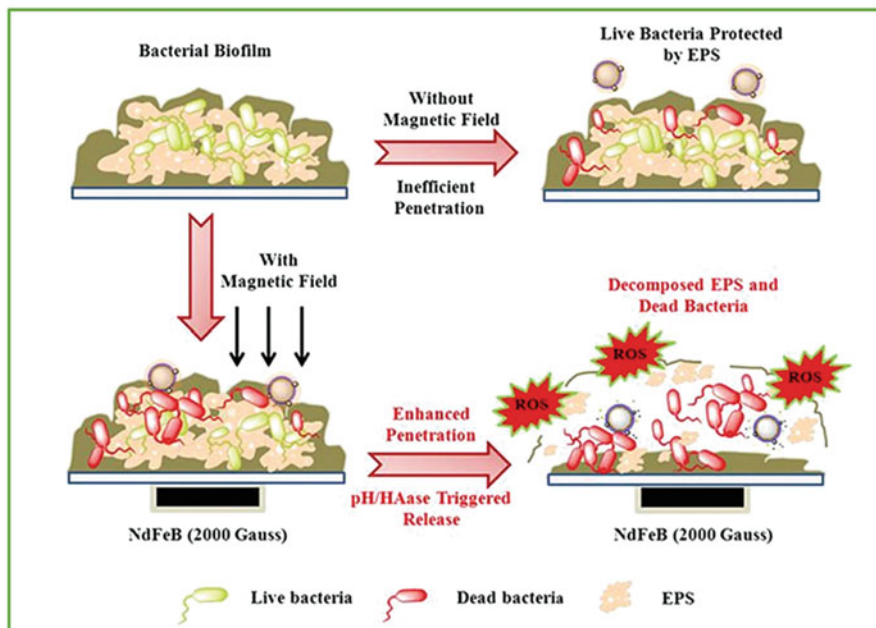
Fig. 3 Illustration for inactivation of embedded bacteria using MNPs nanocomposite (MNPs@Ag@HA) under magnetic field (Copyright © 2018, American Chemical Society, All rights reserved, reprinted with permission) (Wang et al. 2018b)
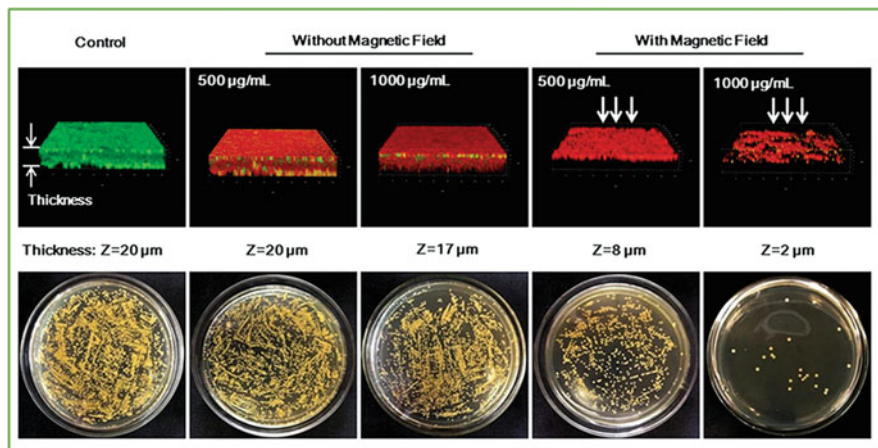
Fig. 4 Live/dead staining of 3D reconstructions of biofilm of *S. aureus* and bacterial colonies of surviving *S. aureus* in biofilms after treatment of MNPs@Ag@HA with and without applied magnetic field, respectively (Copyright © 2018, American Chemical Society, All rights reserved, reprinted with permission) (Wang et al. 2018b)

against all tested candida strains in comparison to unbound AMF and NYS. Similarly, Saldanha et al. (2018) have prepared the nanocomposite consisting of amphotericin B drug loaded on the MNPs. The prepared nanocomposite showed an enhanced antifungal activity against *Paracoccidioides brasiliensis*.

Nevertheless, the use of MNPs does not always have a positive effect on the antimicrobial activity, and some uncertainty has been observed associated with the delivery systems of antimicrobial agents (Amirnasr et al. 2012; Masadeh et al. 2015). Borcherding et al. (2014) have studied the synergistic effect on antimicrobial activity of a combination of antimicrobial molecules (lactoferrin, lysozyme, and human neutrophil peptide (HNP) 1 and 2), in the presence of MNPs of different diameter ($2 \pm 1, 43 \pm 6, 85 \pm 25$, and 540 ± 90 nm). The experiments conducted for one-hour incubation of antimicrobial peptides (AMP) mixture at 37 °C in the presence of different MNPs, followed by centrifugation to separate the soluble molecules. Further, a soluble medium was used for the antimicrobial activity assessment. The small NPs were found to have high adsorption capacity of antimicrobial polypeptides and resulted in a decrease in the activity of AMP. The antimicrobial activity of ciprofloxacin was studied in combination with cerium oxide (CeO_2) and iron oxide (Fe_2O_3) NPs (average diameter of 45 nm) on a panel of Gram-positive and Gram-negative bacteria (Masadeh et al. 2015). The minimal inhibitory concentration (MIC) of antibiotics against different bacteria was compared between MICs of NPs (CeO_2 and Fe_2O_3) with and without ciprofloxacin. The results showed that the presence of NPs resulted in a decrease in the activity of antibiotics, whereas the NPs alone failed to inhibit bacterial growth and biofilm.

In general, the results showed that the MNPs based drug delivery system could deepen the drug penetration along with high antibiotic concentration delivery into the biofilm. This could result in high activity, unlike bare antibiotics that cannot penetrate the biofilm while only able to control the planktonic bacteria. The use of MNPs, a drug delivery platform, allows the use of the low amount of drug in comparison to traditional drug therapies while decreasing the adverse effects caused by drug toxicity. Moreover, the use of MNPs with antimicrobial molecules has a synergistic effect on the activity of prepared nanocomposite, which can be associated with the inherent antimicrobial properties of MNPs.

7 Limitations of the Current Research and Future Prospects

Understanding the precise mechanism of antimicrobial activity is still in its infant stage. Although several reports confirmed the antimicrobial activity by MNPs, the shortage of standard experimental parameters to assess the antimicrobial activity is a concerning issue. Moreover, the research also lacks a uniform method that meets all the required conditions to collect data concerning the antibacterial mechanisms of NPs. Since the efficiency of antimicrobial activity shown by different types of MNPs

varies, a general hypothesis is often suggested. Despite being employed as an antibiotic agent, an explicit mechanism of MNPs is still unclear. Many reports indicate that ROS driven oxidative stress is a primary reason for antimicrobial activity of MNPs, whereas other studies could not confirm the same. For instance, the role of MgO NPs showing antimicrobial activity could not be associated with the regulation of bacterial metabolism, unlike most of the reports. Therefore, it demands more research to understand the mechanisms involved in MNPs antimicrobial activities that could lead the research to the next level. Further, in vitro studies to assess the antimicrobial effect of MNPs have not been much practical since the in vitro model organism cannot entirely simulate the in vivo state. In vitro bacterial models may differently interact with MNPs that questions the assessment of antimicrobial activity of MNPs being considered for in vivo application.

The clarity on nano-neurotoxicity is yet to be established where several questions are open. Research in the field has not able to prove that how NPs can cross the membrane of a bacterial cell that is mainly a barrier regulating in/out movements of molecules. Typically, Gram-negative bacterial cells can allow the transport of a molecule through porins, with a specific size (up to 600 Da). However, several reports surfaced stating that porins can facilitate the transport of NPs, ranging from 1 to 9 nm diameter (Neal 2008). Though the endocytosis, a natural process that can engulf large molecules can facilitate the transport of such NPs through the bacterial cell membrane (Lai et al. 2015), an evident report on the same is yet to be reported.

Nevertheless, the most acceptable and rational explanation for antimicrobial activities of NPs could be associated with a mechanism, where NPs exposure to the bacterial cell causes damage to the cell membrane. During the NPs exposure, the entire disintegration of the cells, along with the release of the lipopolysaccharides layer, occurs in the form of vesicles. NPs present in the surrounding can interact and bind with these vesicles and enter into the cell by electrostatic attraction. However, more research should be carried in the field. Additionally, there are several limitations associated with the synthesis of MNPs. The antimicrobial activity of the metal NPs is the function of the structure. A slight deviation in the preparation method may result in loss of the activity and lead to toxicity. Extensive research has committed to developing advanced materials with enhanced stability and antimicrobial activity. However, most of the processes limit the scalable approach. To summarize, more studies should be carried out assessing the mechanisms associated with the intracellular inhibitory actions of MNPs while overcoming synthesis related challenges. Moreover, interactions of NPs with gene/protein level along with its overall effect on metabolic activities of bacterial cells deserve more consideration.

8 Conclusion

MNPs have established themselves as an efficient candidate considering the magnetic properties that make them superior to NPs. MNPs have demonstrated antimicrobial activity while having varying sizes, shapes, and surface coatings. Also,

several engineering advancements in the biomedical field have improved MNP's features, including size distribution and crystallinity, along with superior magnetic properties. Magnetic properties of NPs make them easily target specific sites that are generally difficult to address. Additionally, the synthesis of MNPs is a cost-efficient process that also offers high versatility when compared to other existing options. Moreover, the optimal physicochemical properties of MNPs have paved new opportunities in clinical research to innovate efficient ways of drug administration. However, more research should be focused on understanding the explicit mechanism of MNP's role in antibiotic activities that are essential to developing a more efficient MNPs as an antibiotic agent. Nevertheless, MNPs are promising agents offering a significant antimicrobial approach to fight against MDR and antibiotic-resistant strains causing obstacles in treating infectious diseases in humans.

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