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ABSTRACT

The resistance to antibiotics in combating bacteria is a serious worldwide problem. The search for new approaches to address antibacterial resistance is therefore of crucial importance and seeking alternatives for the treatment and control of bacterial diseases associated with resistant strains, which is in need of urgent action. There is an ongoing interest in metal-based nanoparticles (MBNPs) and their usage synergy with antibiotics due to their unique properties, such as overcoming bacterial resistance, reducing acute toxicity compared to their sizes, and allowing dosage reduction of active pharmaceutical ingredients. Combining MBNPs and antibiotics not only enhances the antibacterial effect but also allows the inhibition of biofilm production. Furthermore, MBNPs and antibiotics incorporated in polymeric biomaterial matrix have been widely studied to improve their efficiency and devoid the resistance. However, these studies need to be combined in a literature review. Polymeric biomaterials offer high mechanical stability with improved biocompatibility. Moreover, their use makes a single dose of administration of the final product with extended antibiotic half-life possible while slowly releasing their reservoir, which is an advantage in continuously combating resistance. This review focuses on different promising biomedical strategies for enhancing the bactericidal efficacy of antibiotics by the synergistic use of MBNPs, antibiotics, and polymeric biomaterials together to combat the resistance of different bacterial strains. In addition, it is prospected to guide opportunities for new research for future biomedical applications.

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I. INTRODUCTION

Bacterial infectious diseases cause serious health problems that attract worldwide attention as it signals a massive human health threat. At least 700 000 people die annually because of resistant infections globally.[1] Antibiotics have been the preferred methods to prevent and treat these infections due to their strong effectiveness. Nevertheless, many studies have reported that commonly used antibiotics are the primary causes of critical multidrug-resistant microorganisms.[2,3] There are numerous species, which are resistant to almost all available antibiotics that develop advanced drug resistance mechanisms to prevent them from being killed by antimicrobial molecules, which is a result of millions of years of evolution.[4,5] Pharmaceutical companies and researchers are trying to discover novel antibacterial agents and chemically displace existing antibiotics because of increasing resistant infections caused by different pathogenic bacteria.[6] A total of eight modern antibiotics developed against the World Health Organization (WHO) priority pathogens, many of which are derivatives of known traditional antibiotic classes, have been approved by the U.S. Food and Drug Administration (FDA) between 2017 and 2019.[7] However, there is no guarantee that the development of novel antibiotics to cure severe infections will be able to catch the resistance development of the

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pathogen in the time required, as they show insufficient clinical benefit over existing therapies, and these pathogens are continually evolving. Furthermore, they are more expensive than existing treatments that make them challenging to foretell their place in the current treatment landscape. Therefore, this difficult condition has led researchers to find more long-term therapeutic solutions to combat bacterial resistance development.[8,9]

Nanotechnology is an attractive area in current biomedical applications and recognized as the usage of nanoscaled (1–100 nm) materials. Due to their properties, these materials can provide enhanced physicochemical and biological properties. Metal-based nanoparticles (MBNPs) are naturally sourced materials that have been used against infectious pathogens since ancient times because of their therapeutic and blocking effects. They include monometallic and intermetallic (bimetallic, trimetallic, and quadrometallic) forms. Monometallic NPs and their oxides mainly gold (Au), silver (Ag), copper oxide (CuO), iron oxide (Fe_3O_4 or Fe_2O_3), titanium dioxide (TiO_2), and zinc oxide (ZnO) consist of a type of metal. These forms of MBNPs have been reported to be more useful than the antibiotics due to their stability in the case of infections caused by intracellular germs.[10–12] Intermetallic NPs, on the other hand, are formed by combining different metal NPs (e.g., Ag-ZnO, Au-(Platinum(Pt)-Ag), and these combinations can display better synergistic antibacterial properties compared to their monometallic forms.[13] Thus, MBNPs have gained interest in biomedical applications in recent years to enhance the antibacterial effect of antibiotics or to fight against infections when existing agents have not enough efficacy to kill resistant bacteria species.[14] Compared to traditional antibiotics, both monometallic and intermetallic NPs can increase solubility and stability of drugs,[15] while offering many advantages in cost reduction, easy synthesis, and use.[16,17] Moreover, their usage in nanoformulations allows dosage reduction of antibiotics with minimized side effects while improving the biocidal properties of NPs with different mechanisms of action in bacterial cells.[18]

Polymeric biomaterials are sourced for various biomedical applications, particularly as three-dimensional tissue scaffolds, drug carriers, and medical implants. Apart from that, researchers have also been investigating the effects of synthetic or naturally sourced polymeric biomaterials and their combinations in a system with MBNPs and antibiotics for the successful treatment of antibiotic resistance.[19] Several methods under two general approaches (*in situ* and *ex situ*) can be applied to prepare MBNPs-antibiotic/polymeric biomaterial composites to be used in medical applications. *In situ* methods use the matrix of the polymeric biomaterial as the reaction medium (under UV radiation conditions or microwave assistance), while nanoparticles are synthesized before combining with the polymeric biomaterials, which serve as a dispersion medium in *ex situ* methods (melt compounding or solution blending).[20] The most commonly used natural polymeric biomaterials for these studies are collagen, gelatin, chitosan, alginate, hyaluronic acid, and carboxymethyl cellulose, while synthetic polymeric biomaterials are polycaprolactone (PCL), polymethyl methacrylate (PMMA), polylactic acid (PLA), polyvinyl alcohol (PVA), polyglycolic acid (PGA), polyethylene glycol (PEG), and poly(lactide-co-glycolide) acid (PLGA).[21–23] These materials can retain their structure and prolong the residence time of agents for a slow release from the matrix at a desired anatomical site and extended absorption time while providing a safe transition through inhospitable physiological environments.[24] In addition, they are excellent candidates for biomedical applications since they have essentially adjustable morphology, high mechanical stability, and nontoxic features and they can provide their own therapeutic benefits while supporting cell function in combination with MBNPs and antibiotics.[25] Antibiotics can be covalently attached to a polymeric biomaterial backbone or physically combined into a polymeric biomaterial matrix. While decreasing the side effects of antibiotics and further improving economic and social impacts with a single-dose administration of the final product, they have an important part in the development of the drug delivery systems to carry agents and deliver sustained-release doses over a long time.[26,27] Moreover, they can extend the half-life of antibiotics while slowly releasing their reservoir and enhance the stability of labile antibiotics from enzymatic degradation.[28] After successfully completing their actions, the vast majority of these polymeric biomaterials can be efficiently metabolized and excreted from the body while providing superior biocompatibility over time.[25]

This review provides an overview of the literature on the synergistic activity of various MBNPs-antibiotic/polymeric biomaterial combinations to improve the bactericidal efficacy of antibiotics to combat antibacterial resistance in biomedical applications such as drug delivery, wound healing, implantable medical device coating, and vaccines. It focuses on monometallic NPs and their oxides although it must be mentioned that these are ceramic and intermetallic NPs, which are at an earlier development stage.

II. THE RISE OF ANTIBIOTIC RESISTANCE

After being nominated for Nobel Prize for discovering the first antibiotic penicillin in 1945, Alexander Fleming said: "Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug, make them resistant." As predicted, resistance appeared only a few years after introducing antibiotics into clinical use and is increasing day by day and expected to rise to 10 million annual deceases by the year 2050, while the cumulative global cost is expected to surpass US$100 trillion due to the antibiotic resistance if the current trend does not change.[29]

Clinicians were on alert for the presence of sulfa drug resistance that existed during the Second World War and that antibiotic resistance that could follow it.[30] *Staphylococcus aureus* was the first resistant bacteria found in the late 1940s by Mary Barber in Great Britain, and it was implicated with the origin of hospital outbreaks and deceases during the 1950s.[31] Since then, *S. aureus* has become the most well-known antibiotic-resistant microbe and has caused significant morbidity and mortality together with other resistant strains.[32] Unfortunately, improper stewardship of antibacterial agents, excessive consumption by both humans and animals and incorrect prescribing or usage of non-prescription antibiotics, high bacterial genome plasticity, and permanent changes between three major resistant gene reservoirs, including the environment, animals, and humans, can be listed as factors contributing to the long-standing phenomenon of antibiotic resistance.[33] The WHO has recently classified the top 12 deadliest antibiotic-resistant strains as the biggest threats to global public health and urged researchers to seek new therapies to combat these pathogens (Table I).[1]

Whenever a new antibiotic is introduced and used extensively; some bacteria develop resistance to the bactericidal effect of the drug.[34] These resistant bacteria, which are viable in the presence of

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TABLE I. List of priority pathogens.[1]

Priority	Bacteria	Resistance
Critical	*Mycobacterium tuberculosis* - Multidrug-resistant tuberculosis (MDR-TB) -Extensively drug-resistant tuberculosis (XDR-TB)	Isoniazid, rifampicin, fluoroquinolones and injectable second-line anti-TB medicines
	Acinetobacter baumannii	Carbapenem-resistant
	Pseudomonas aeruginosa	Carbapenem-resistant
	Enterobacteriaceae	Carbapenem-resistant, third-generation cephalosporin-resistant
High	*Enterococcus faecium*	Vancomycin-resistant
	Staphylococcus aureus	Vancomycin-resistant, methicillin-resistant
	Helicobacter pylori	Clarithromycin-resistant
	Campylobacter species	Fluoroquinolone-resistant
	Salmonella species	Fluoroquinolone-resistant
	Neisseria gonorrhoeae	Third-generation cephalosporin-resistant, fluoroquinolone-resistant
Medium	*Streptococcus pneumoniae*	Penicillin-non-susceptible
	Haemophilus influenzae	Ampicillin-resistant
	Shigella species	Fluoroquinolone-resistant

drugs, are capable of developing gene mutations or resistance genes and can also transfer their newly acquired resistance genes to other bacteria through conjugation (Fig. 1).

In 1978, Bill Costerton and his team pioneered the theory of biofilms, which involves the growth of bacteria inside a self-produced glycocalyx matrix that can provide protection and attachment to solid surfaces for the bacterial community.[35] Since then, it has been found that the bacterial ability to form biofilms is an important microbial survival mechanism, but unfortunately they serve a major role in infection persistence and the decrease in antimicrobial susceptibility due to the biofilm's resistance against antibiotics. Biofilms cause almost 80% of bacterial infections, resulting in ineffective antibiotic treatment, increased hospitalization, and higher mortality rates.[36] During periods where environmental conditions are outside the optimal for the bacteria, for example, presence of antibiotics, the biofilm formation is a response to the changes to ensure the survival of the species. As the biofilm protects the bacteria from the antibiotics, it can reduce antibiotic susceptibility and induce antibiotic resistance.[37] In general, biofilm formation occurs in three phases as described below and schematically illustrated in Fig. 2.

Initial attachment of planktonic bacterial cells to surfaces is reversible, and bacteria are still susceptible to antibiotics.[38] Cells can produce an extracellular polymeric substance (EPS) that generates the biofilm matrix and results in irreversible attachment to the surface.[39] In maturation, bacterial cells adapt inside the biofilm and increase the production of EPS; biofilms can grow up to 50 μm in thickness and becomes resistant to antibiotics.[38] Finally, during dispersion planktonic bacteria are released from the biofilm. The release of planktonic bacteria can result in biofilm formation at other sites, but planktonic bacteria do not have biofilm antibiotic resistance.[40]

As mentioned above, biofilms can protect bacterial cells from antibiotics; thus, the cells are resistant to antibiotic treatment, can tolerate the presence of antibiotics, and can cause persistence in infection. Biofilm mechanisms of resistance to antibiotics include physical barriers, enzyme production, and physiological challenges. Enzymes within the EPS can attach to antibiotics and prevent their antibacterial activity.[41] In addition, the EPS matrix can prevent or reduce the contact between antibiotics and bacterial cells; for example, the diffusion rate of beta-lactam is significantly reduced by the EPS.[42] Furthermore, cells with biofilms can become dormant, leading to impaired activity of antibiotics that target processes within active cells.[43] Moreover, Moskowitz *et al.* found the minimal inhibitory concentration (MIC) of antibiotics against biofilms were up to 64 times higher than planktonic bacteria.[44] These mechanisms of resistance results in inadequate available treatment as antibiotics, including a cocktail of antibiotics, are ineffective toward the protection and resistance provided by biofilms. Therefore, MBNPs-antibiotic/polymeric biomaterial combination is a possible solution as they challenge antibiotic resistance by providing alternative mechanisms of action.

III. MBNPS FOR COMBATING ANTIBIOTIC RESISTANCE

With current developments in nanoparticles, different kinds of monometallic NPs and intermetallic NPs are available to use in combating microbes. Monometallic NPs (e.g., Au, Ag) and their oxides (e.g., cerium oxide (CeO_2), iron(II) oxide (FeO), superparamagnetic iron oxide nanoparticles (SPIONs), nitric oxide (NO), TiO_2, and ZnO) have been proved as essential materials in numerous biomedical applications from drug delivery to antibacterial coating.[45–49] Intermetallic NPs have found a place later yet, are now an impressive research area as they offer enhanced properties by combining two metal NPs into a single material form.[50] They can be divided into two main divisions as mixed and segregated, which can be further categorized according to their arrangement of atoms, for example, alloy, intermetallic, subclusters, and core-shell types.[13] Ag-Cu, Ag-Au, Au-Pt-Pd, and many other types have been used as intermetallic NPs in biomedical applications and are often produced via many synthesis methods, that is, oxidation–reduction, micro-emulsion, and sol-gel processes.[51]

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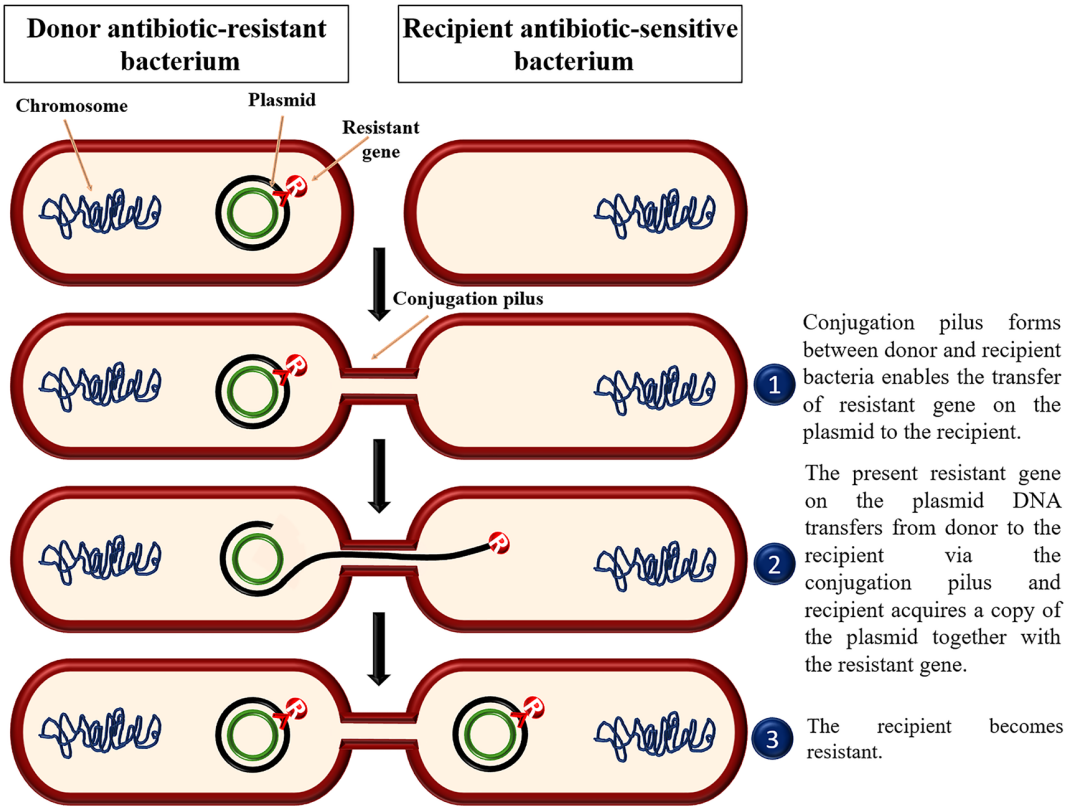

FIG. 1. Transfer of antibiotic resistance between bacteria via conjugation.

Using various synthesis methods (Fig. 3), different shapes (spherical, rod, plate, cube, etc.) and sizes of MBNPs can be obtained as desired.[52] In general, resistance to MBNPs among bacteria appears to be less common than other traditional antibiotics.[53] The size of

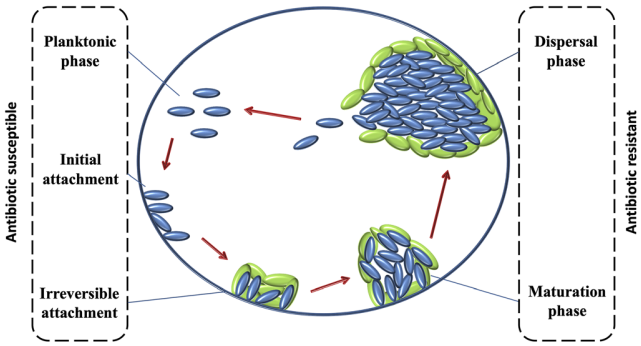

FIG. 2. Biofilm Cycle. Free planktonic phase bacteria form an initial attachment with the surface. Irreversible attachment occurs through the formation of extracellular polymeric substance (EPS). Bacteria are susceptible to antibiotics during these stages. Inside the matrix, bacteria continue to produce EPS during the maturation phase; this matrix protects the bacteria and makes them antibiotic-resistant. Planktonic bacteria are released from the biofilm during the dispersal phase due to a variety of reasons such as overpopulation or lack of nutrients.

MBNPs seems to have a significant influence on the antibacterial mechanism and action with smaller sized particles having a lower MIC. Smaller sized MBNPs are more able to diffuse through the bacterial cell wall and interact with bacteria.[54,55] Similarly, wide surface area and the shape of MBNPs can contribute to the antibacterial efficacy and mechanism of action.[56] Nanocubes and nanorods have been reported to have a higher antibacterial activity than other forms, due to the exposed planes and oxidation levels of the metals.[57] Moreover, Cha *et al.* stated that ZnO nanopyramids produce the highest antimicrobial activity by inhibiting essential enzymes due to their shape compatibility with the enzyme active site.[58]

MBNPs can provide alternative mechanisms to combat antibiotic resistance in bacteria, including bacteria protected by their biofilms. In addition, some MBNPs have been found to inhibit biofilm formation, penetrate biofilms because of their small size, and can transport drugs to deliver into biofilms.[59] The interaction between MBNPs and biofilms is a process that involves the transfer of bulk MBNPs in close vicinity to the biofilm, adhesion to the biofilm surface, and penetration and migration into the biofilm, all driven by various factors.[60] After reaching the biofilm frontier, the initial adhesion of MBNPs to the biofilm surface depends on their charge and surface properties, and hydrophobicity is determined by the physicochemical properties of the EPS. Following the adhesion, MBNPs can penetrate the biofilm and begin internal migration as a whole or as ions through diffusion to

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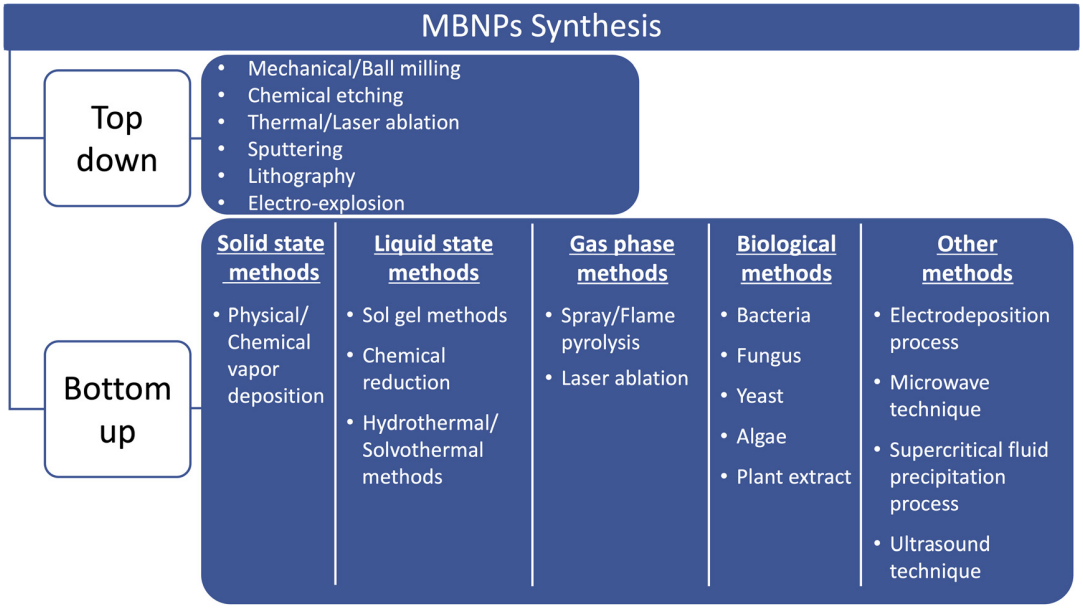

FIG. 3. Top-down and bottom-up methods of MBNPs synthesis.

interact and then destroy the biofilm and bacterial components. Even though the detailed interaction remains to be determined, all processes depend on the properties and concentration of MBNPs, the maturity, surface composition, and chemistry of the biofilm and physicochemical properties (mainly electrostatic, hydrophobic, hydrogen-bonding, and Van der Waals attraction) of both MBNPs and the biofilm.[61]

Both metal ions and NPs influence biofilms. First, the formation of biofilms has been reported to be reduced by the presence of metal ions and NPs. For example, Lange *et al.* found Ag, Cu, and Ag-Cu NPs to inhibit the production of biofilms of pathogens that commonly cause bovine mastitis disease, with 100% inhibition from Ag and Ag-Cu against several microbes at 200 ppm.[62] It has been hypothesized that the NPs damaged signaling molecules and as a result inhibited the gene expression responsible for biofilm development and modification. Similarly, metal ions Cu^{2+} and Zn^{2+} have been reported to reduce the expression of biofilm matrix promoting genes in *Bacillus subtilis*.[63] While the treatment did not report inhibition of biofilm formation, after the ion treatment, the formed biofilms were more susceptible to antibiotic solutions and had less hydrophobicity. Second, the treatment of metal ions and NPs on mature biofilms has also been investigated. The treatment of mature biofilms by metal ions was found to have similar results to that of biofilm formation. After treatment, the biofilm had reduced cell survival and reduced hydrophobicity leading to higher susceptibility to antibiotics.[63] In contrast, the treatment of nanoparticles on mature biofilms was dependent on the EPS.[64] Removal of the EPS on microbial biofilms showed a higher susceptibility to Ag NPs.[65] Subsequently, as EPS is continued to be produced as the biofilm matures, biofilms were more susceptible to nanoparticles during the early maturation stage compared to the later stages.

Common mechanisms of action of MBNPs include interaction with the cell membrane, causing oxidative stress, and the release of ions. Oxidative stress is one of the most common contributors to MBNPs antibacterial mechanisms; it is induced by reactive oxygen species (ROS) made by MBNPs. Bacterial cells can establish a ROS equilibrium within the cells, however, with excess production, it leads to cell death via damage (to membrane, DNA, ribosome, and proteins) and inhibition (of the electron transport chain, enzymes, and DNA transcription and translation). While it has been found that most MBNPs can enter the cell and induce the release of ROS, the extracellular release of ROS has also been reported.[66,67] Electrons dissociated from Ag NPs embedded in Ti were found to directly react with O_2 in the liquid culture medium, leading to ROS generation and increased oxidative stress on the microbial membrane.[68] Although NPs can elevate ROS levels in bacteria, bacterial species have a defensive mechanism called hormesis, which is stimulated by sublethal concentrations of ROS and can respond against ROS.[69] Hormesis has a short term (activated by a sudden increase in ROS concentration, resulting in the expression of ROS scavenger enzymes) and a long-term (upregulated in the transcriptional level) mechanism to protect the bacteria from ROS.[70] Therefore, hormesis must be considered while developing MBNPs-antibiotic/polymeric biomaterial systems. Furthermore, MBNPs can attach onto the cell membrane and cause damage, which may result in the leakage of cellular content or blockage of transport channels. In addition, MBNPs can form ions in suspension, which can be transported through the cell membrane. Ions can bind to functional groups and interfere with protein and DNA synthesis.[5,71] Although their action mechanisms are not fully understood, it has been theorized that they have many mechanisms of action, and multiple mechanisms can occur simultaneously. Antibacterial mechanisms of some MBNPs stated in the literature are summarized in Table II.

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TABLE II. Summary of the mechanism of action of some MBNPs.

Mechanism of Action	Description	MBNPs	Reference
Oxidative stress	• Generation of oxidative stress from increased ROS disrupting the cell membrane	Ag	72
	• Generation of ROS causing loss of membrane integrity	Al_2O_3	73
	• Increased oxidative stress from the generation of ROS leading to vacuole formation	Au	74
	• Increased intracellular oxidative stress from the attachment of NPs to bacterial cells	CuO	75
		$CuCl_2$	76
	• Oxidative stress created by ROS with releasing Fe^{2+} ions	Fe_3O_4	77
	• Simulating a burst effect of ROS which is certain was to tackle the integrity of the cell membranes, damage the DNA, proteins, and other molecules while suppressing the metabolic activity of the bacteria cells	TiO_2	78
	• Generation of ROS leading to DNA damage and protein oxidation	ZnO	79
Interaction with cellular membrane	• Increased inner membrane permeability but undamaged outer membrane	Ag	80
	• Causing photocatalytic reactions on the cell wall membrane and provide bactericidal effects	TiO_2	81
	• Membrane damage and increased permeability of membrane resulting in the accumulation of particles in cells	ZnO	79
Release of ions	• Ions can bind to thiol and prevent DNA replication	Ag	82
Enzyme inhibition	• Inhibition of enzymes [nicotinamide adenine dinucleotide (NAD) + hydrogen (H) (NADH) dehydrogenase, glutathione reductase, peroxidase)]	ZnO	79
	• Inhibition of the β-galactosidase enzyme	ZnO	58
	• Inhibition of urease and DNA polymerase enzymes	Ag, ZnO	83

Membrane disruption in mammalian cells is considerably lower than that of bacterial cells when equal concentration MBNPs is used. This is thought to be due to the differences in cell membrane structures between mammalian and bacterial cells, the presence of endocytic machinery (internalizes the nanosized particles), and multiple intracellular compartments in human cells that prevent MBNPs from easily penetrating membranes to interact directly with important molecules within the cell.[84]

IV. MBNPS IN MEDICAL APPLICATIONS

A. Antibacterial drug delivery

MBNPs have been found promising in antibacterial drug delivery system development for decades to enhance the antibacterial efficacy of drugs in challenging resistance. They have a strong defense line for combating multidrug-resistant bacterial strains that are getting stronger each day as the antibacterial resistance rises continuously.[85] These MBNPs also offer drug delivery systems for systemic, oral, transdermal, or further application ways when combined with antibiotics and polymeric biomaterials. The system can also sustain the antibiotic release to prolong the half-life and bioavailability while shielding the drug from a possible enzymatic attack. Moreover, possible troubles like toxicity caused by some MBNPs, such as Ag NPs and FeO NPs, can be eliminated when combined with polymeric biomaterials.[86] These combinations have been prepared using several production methods from an easy one-step synthesis to complex electrospinning.[87,88] Various MBNPs and their therapeutic outcomes, when combined with antibiotics and polymeric biomaterials, are given in Table III.

It can be stated that the Ag NPs are one of the best MBNPs that can be used in biomedical applications due to their adjustable toxicity levels depending on surface properties and particle sizes, significant bacteria inhibition potential in parallel with its ability to tackle the factors related to antibiotic resistance.[104,105] At first glance, this might be seen as a downside while evaluating the future of the Ag NPs in antibacterial drug delivery applications. However, when it is about multidrug-resistant bacteria related diseases, the treatment concept is a delicate and continuous journey in which maintaining the balance between the bactericidal efficiency of the vectors used and their side effects is a crucial requirement. In addition, compromising from one to another to preserve the necessity, namely, health, of each individual might be required. Many kinds of research elucidate the drug delivery applications of Ag NPs-antibiotics/polymeric biomaterial combination. Kora and Rastogi combined Ag NPs with different antibiotics individually (streptomycin, ampicillin, and tetracycline) in the

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TABLE III. Combinations of some MBNPs-antibiotic/polymeric biomaterial systems for drug delivery applications.

MBNPs	Antibiotic	Polymeric biomaterial	System production method	Bacteria strains tested against	Key findings	References
Ag	Streptomycin, ampicillin, and tetracycline	PVP	*In situ*	*E. coli* *S. aureus*	Enhanced bactericidal effect and antibacterial activity.	89
	Vancomycin and amikacin	PVP	*In situ*	*E. coli* *S. aureus*	Augmented synergistic antibacterial effect. Conjugates containing amikacin were more potent against *E. coli*, while conjugates containing vancomycin were more efficient against *S. aureus*.	90
	Azithromycin, levofloxacin, and tetracycline	Chitosan	*In situ*	*E. coli* *K. pneumonia* *S. aureus* *E. faecalis*	Synergistic antibacterial effect. Promoting the internalization of the adsorbed drugs. MIC of the drugs was observed to be diminished by 37–97%.	87
Au	Penicillin-G(Peni)	Polycobaltocenium homopolymer (PCo)	*In situ*	*S. aureus* *E. coli* *K. pneumonia* *P. vulgaris*	Increased antibacterial efficacy.	91
	Ampicillin	Chitosan	*In situ*	*E. coli* *S. aureus* *K. mobilis*	Increased antibacterial efficacy. Reduced side effects of antibiotics and decreased antibiotic dose by almost 50%.	92
	Ampicillin	PEG-functionalized rosette nanotubes (RNT)	*In situ*	*S. aureus* Methicillin-resistant *S. aureus* (MRSA)	Improved antibiotic efficacy.	93
	Colistin	PCL	*Ex situ*	*E. coli*	Increased antibacterial efficacy.	88
	Doxycycline	PEG	*In situ*	*S. aureus* *E. coli* *K. pneumoniae* *P. aeruginosa* *A. baumannii*	Increased bactericidal activity toward major human pathogens.	94
CuO	Tetracycline hydrochloride	Hyperbranched polyglycerol (HPG)	*Ex situ*	*S. aureus*	Slow and gradual release of antibiotic. Enhanced killing activity against *S. aureus* in comparison of tetracycline hydrochloride alone.	95
FeO	Tobramycin	Alginate	*In situ*	*P. aeruginosa*	Enhanced biofilm inhibition caused by *P. aeruginosa*. Having a potential to beat the biofilms in cystic fibrosis caused by *P. aeruginosa*.	96
	Erythromycin	PEG	*In situ*	*S. pneumoniae*	The usage of the ternary combination improved the antibacterial effect by decreasing	97

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TABLE III. (*Continued.*)

MBNPs	Antibiotic	Polymeric biomaterial	System production method	Bacteria strains tested against	Key findings	References
					the MIC from 0.25 μg/mL (for only erythromycin) to 0.12 μg/mL.	
	Gentamicin	Chitosan-PEG	*Ex situ*	*S. aureus*	System supported deeper penetration into biofilm of *S. aureus* due to the superparamagnetic performance of Fe_3O_4 NPs commencing to an efficient gentamicin release for the elimination of biofilm.	98
SPIONs	Methicillin	PEG-*b*-PLA copolymer	*Ex situ*	*S. epidermidis*	Deeper penetration into *S. epidermidis* biofilm.	99
NO	Gentamicin	Poly ((oligoethylene glycol) methyl ether methacrylate)-*b*-Poly(3-vinylbenzaldehyde) copolymer	*Ex situ*	*P. aeruginosa*	Synergistic effects, reducing the viability of *P. aeruginosa* biofilm and planktonic cultures by more than 90% and 95%.	47
TiO	Norfloxacin	PLA	*Ex situ*	*S. aureus* *P. aeruginosa* *E. coli* *Salmonella* *K. pneumonia*	Enhanced antibacterial activity with adjusted release profile by altering the PLA within the ternary system.	100
ZnO	Minocycline	Carbopol 940® hydrogel	*Ex situ*	*P. intermedia* *S. oralis* *P. gingivalis* *S. sanguis*	Increased antibacterial properties.	101
	Ciprofloxacin	Humic acid	*Ex situ*	*B. cereus* *P. aeruginosa*	Enhanced bactericidal activity.	102
Ag-ZnO	Rifampicin	PLGA	*Ex situ*	*Mycobacterium tuberculosis* (*M. tb*)	Improved the efficiency of rifampicin by as much as 76% and increased the membrane disorder of intracellular *M. tb*.	103

presence of polyvinylpyrrolidone (PVP) polymer used as a capping agent to investigate whether there is an enhancement on the bactericidal potential.[89] In addition, different capping materials were also used to see the impact of the capping agent on the bactericidal effect and antibacterial activity of each sample was analyzed against *E. coli* American Type Culture Collection (ATCC) 25922 and *S. aureus* ATCC 25923. Results denoted that the antibacterial activity enhanced for each antibiotic type when combined with Ag NPs. Furthermore, the importance of the PVP capping was also highlighted in the study since the PVP capped active ingredient showed better bactericidal activity compared to other capping materials, trisodium citrate dehydrate, and sodium dodecyl sulfate. This study is promising for future research since it is a good example where antibiotics and Ag NPs combined and capped with a polymeric biomaterial for better efficiency for drug delivery applications. Kaur and Kumar reported combining Ag NPs with vancomycin and amikacin to enhance their antibacterial efficiency while using PVP to protect the drugs and regulate the release profile.[90] The antibacterial test results reported that Ag NPs did not show any antibacterial effects due to their low concentrations. However, their antibacterial effects with both antibiotics and PVP polymer conjugations increased against *E. coli* and *S. aureus*. For amikacin, the zone of inhibition was 9 mm on *E. coli* and increased to 20 with the conjugation of the Ag NPs, while for *S. aureus* the corresponding increase was from 5 mm to 10 mm. While testing vancomycin, the zone of inhibition for *S. aureus* increased from zero to 8 mm, while the bacterial inhibition was reported to be 7–11 mm for *E. coli*

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when Ag NPs were added into the antibiotic/polymeric biomaterial conjugation. In addition, it is noteworthy that the vancomycin-resistant *E. coli* also became sensitive after being in contact with the combination of Ag NPs-vancomycin/PVP.

Among all MBNPs, Au NPs are one of the most preferred options in drug delivery applications due to low toxicity, wide antibacterial performance, and biocompatibility.[106–108] They can be easily synthesized in different shapes such as spherical, rod-like, and cage-like, in sizes from 1 nm to more than 100 nm and functionalized for effective interaction with the bacterial surface to have a bactericidal effect.[109,110] These MBNPs can increase drug efficacy and be directly bonded with different active agents through ionic or covalent bonding or by physical absorption.[111] They have also demonstrated an excellent ability for application as drug delivery carriers when used with polymeric biomaterials. Rai *et al.* investigated the synergistic antibacterial mechanism of Au NPs–cefaclor conjugation prepared *in situ* and observed bactericidal activity related to interaction with the outer peptidoglycan layer.[112] Au NPs created voids in the cell walls, while cefaclor increased membrane porosity. Therefore, it has been suggested that cefaclor and Au NPs penetrate bacterial membranes and interact with DNA when used together. Furthermore, they proposed an interaction between Au NPs and DNA that inhibit DNA blocking and transcription. The use of Au NPs in the combating with various bacterial strains has different mechanisms of destruction. For example, Au NPs for *E. coli* stimulates vesicle formation that produces gaps in the membrane, while increasing the concentration of intracellular ROS species for *S. aureus*. Consequently, Au NPs bond prevent transcription in *E. coli* and *S. aureus*. To enhance the efficacy of β-lactams against different bacteria strains, Yang *et al.* developed a system using Au NPs-penicillin-G(Peni)/polycobaltocenium homopolymer(PCo).[91] After agar diffusion disk-diffusion assays, all samples showed increased antibacterial efficacy with the addition of Au NPs against different strains. Furthermore, Au NPs containing samples showed the least OD_{600} (bacterial growth) values compared to others for all strains tested (Fig. 4). According to enhanced antibacterial efficacy results in the literature, a system based on Au NPs-antibiotic/polymer combination is promising in the treatment of antibacterial resistance. More studies focusing on Au NPs should be done to increase the selectivity and effectiveness of the antibacterial system by using different antibiotics and biomaterials.

Armijo *et al.* reported combinations of Fe_3O_4 NPs-tobramycin/alginate and Fe_3O_4 NPs-tobramycin/PEG to be effective against *P. aeruginosa* biofilms to reduce morbidity and mortality of the diseases related to this strain in the treatment of biofilm lung infections in cystic fibrosis.[96] Results indicated that the capping agent plays a significant role in bactericidal efficacy since Fe_3O_4 NPs capped with PEG showed zero susceptibility. In terms of effectiveness, alginate performed better than PEG, which was explained by the biodegradation rate of the PEG compared to the alginate, may keep the iron ions from interacting with *P. aeruginosa*. After 60 days of incubation with *P. aeruginosa*, all samples treated with only tobramycin were found resistant to the drug compared to others treated with Fe_3O_4 NPs, and Fe_3O_4 NPs-tobramycin/alginate ternary system was found susceptible for the same therapeutic dose of 10 μg. At the end of the period, the Fe_3O_4 NPs-tobramycin/alginate ternary system was found ideal in biofilm

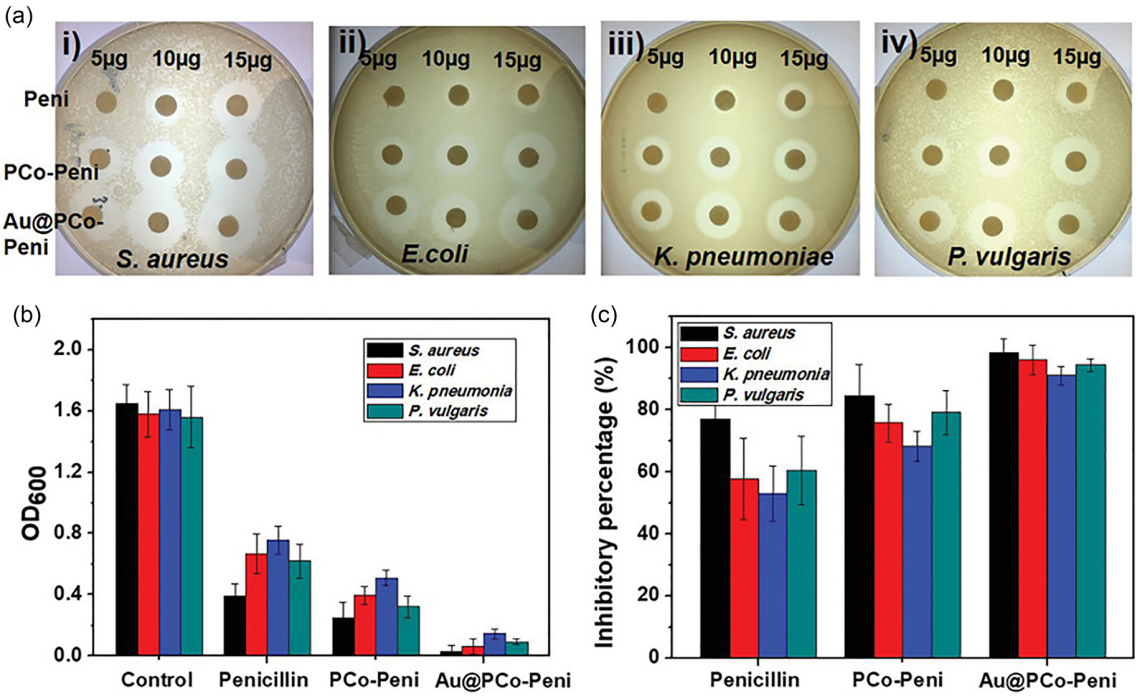

FIG. 4. (a) Disk-diffusion assay images of samples with different concentrations (5–15 μg) of penicillin-G against (i) *S. aureus*, (ii) *E. coli*, (iii) *K. pneumonia*, and (iv) *P. vulgaris*. (b) OD_{600} (bacterial growth) values and (c) the inhibitory percentage of four bacteria incubated with penicillin-G, Peni/PCo, and Au NPs-Peni/PCo, respectively. Reprinted with permission from P. Yang *et al.*, Adv. Healthcare Mater. **8**, 1800854 (2019). Copyright 2018, John Wiley and Sons.[91]

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inhibition caused by *P. aeruginosa*. Geilich *et al.* produced iron oxide-encapsulating polymersomes (IOPs) using PEG-*b*-PLA copolymer and made a ternary system by loading IOPs with SPIONs and methicillin using ultrasonication.[99] Deeper penetration into *S. epidermidis* biofilm was achieved with the ternary combination (Fig. 5). In addition, the formulation used in the study was found to be selectively toxic to methicillin-resistant biofilm cells but not to mammalian cells.

Mihu *et al.* showed that sustained NO-releasing PEG–chitosan NPs interfere with MRSA adhesion and prevent biofilm formation on a rat central venous catheter model of infection.[113] Thickness of staphylococcal biofilms and adherence of MRSA cells were significantly reduced with NO NPs/PEG-chitosan system treatment (Fig. 6). It was also revealed that chitosan added additional antibacterial activity to the system. The developed system was found promising for prophylactic or therapeutic use against bacterial biofilms on central venous

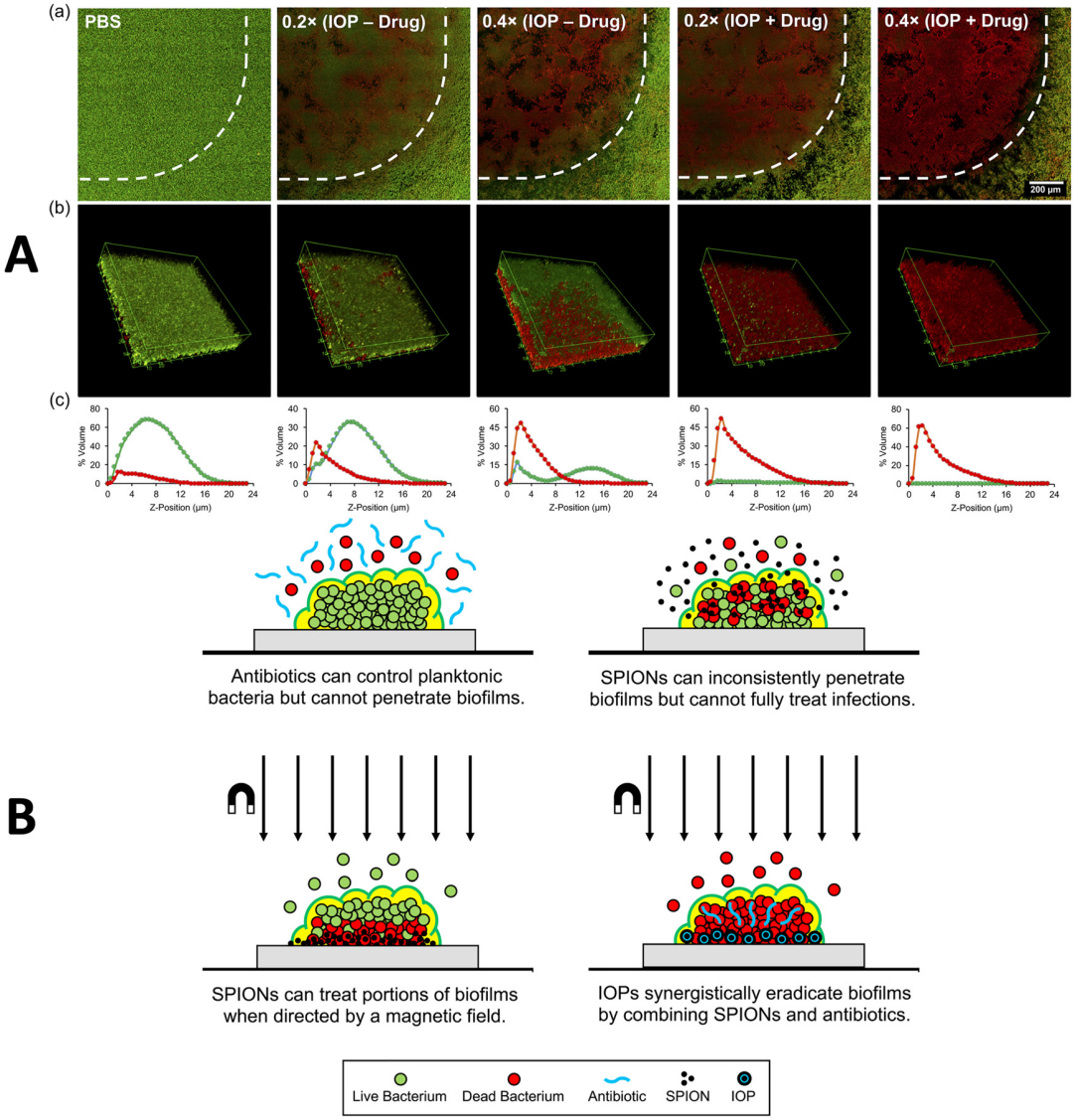

FIG. 5. Anti-biofilm activity of SPIONs-methicillin/PEG-b-PLA copolymer against *S. epidermidis*. (a) LIVE/DEAD staining of biofilms treated with different dilutions of IOPs (1x stock = 100 μg/mL SPION; 50 μg/mL methicillin) for 24h. (a) Tile scans collected halfway through the biofilm show concentration-dependent bacteria death within the boundary of the external applied magnetic field (dashed line). (b) 3D reconstructions of z-stacks collected across the biofilm thickness inside the magnetic field. (c) The percentage of biofilm volume occupied by live and dead bacteria as a function of biofilm depth (0 μm = bottom) as quantified from image slices. Viable and dead cells appeared green and red, respectively. (B) Current mechanisms for biofilm treatment using the ternary system. Reprinted with permission from Geilich *et al.*, Biomaterials **119**, 78 (2017), Copyright 2017, Elsevier.[99]

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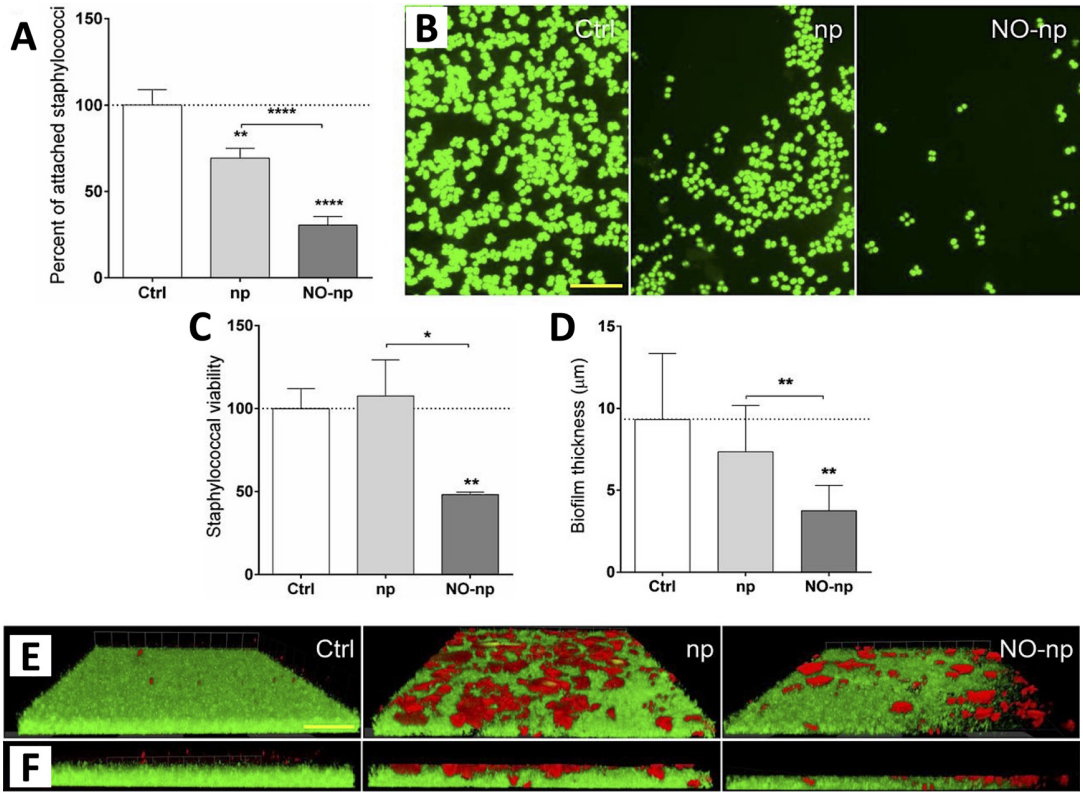

FIG. 6. (a) Percent of adhered MRSA cells to glass-bottom plates and (b) representative images of adhesion by control and NPs- or NO NPs-treated MRSA cells (Scale bar represents 10 μm). (c) The viability (percentage of control) of biofilm-associated cells and (d) the differences in biofilm thicknesses. (e) Confocal images of mature bacterial biofilms display exopolymeric matrix (red) and bacterial cells (green) after treatment with NO NPs. (f) The thickness and morphology of each biofilm can be observed in the Z-stack reconstruction (Scale bar represents 20 μm). Ctrl = nanoparticles without NO, np = only NO NPs, and NO-np = nanoparticles with NO/PEG–chitosan. Statistical significance ($^{*}P < 0.05$; $^{**}P < 0.01$; $^{****}P < 0.0001$). Reprinted with permission from Mihu *et al.*, Antimicrob. Agents Chemother. **61**, e02020 (2017), Copyright 2016, American Society for Microbiology.[113]

catheters and other medical devices. Moreover, it can be used in a ternary system with an antibiotic for increased efficacy.

Salahuddin *et al.* incorporated TiO_2 NPs and norfloxacin, a model drug used as an anti-cancer medicine and an antibiotic to treat bacterial infections.[100] Comparison of the antibacterial activity for norfloxacin/PLA and TiO_2 NPs-norfloxacin/PLA was determined using agar disk-diffusion test against *S. aureus, P. aeruginosa, E. coli, Salmonella,* and *K. pneumonia*. Different shapes and concentrations of TiO_2 NPs were used to measure the inhibition zone and assess the effectiveness. Results indicated that the addition of TiO_2 NPs successfully increased the zone of inhibition in at least one sample in each bacteria strain. The authors suggested that antibacterial activity can be increased by combining TiO_2 NPs with an antibiotic, and the release profile of the active ingredients can be adjusted by altering the polymeric material within the system.

Mou *et al.* produced a ZnO NPs-minocycline/Carbopol 940® hydrogel ternary system for the treatment of periodontitis disease.[101] ZnO NPs and minocycline together in the microspheres showed remarkable synergistic effects with increased antibacterial properties after 24h after cultivation with different pathogen strains. For topical and site-targeted delivery, Murugesan and co-workers investigated a ternary system of ZnO NPs-ciprofloxacin/humic acid prepared by simple emulsification techniques.[102] After the *in vitro* antibacterial test, the complete death of *B. cereus* and *P. aeruginosa* cells was observed within 2–3h of incubation with the ZnO NPs-ciprofloxacin/humic acid sample and 4–5h with the ciprofloxacin alone. They stated that ZnO NPs loaded carriers are much more effective than ZnO NPs-free carriers in combating various microorganisms.

Intermetallic NPs coupled polymeric biomaterials have also shown promising results in bacteria inhibition. Ag-Cu NPs and Ag-Au NPs have been reported to display antibacterial effect against *S. aureus*, *K. pneumonia, P. aeruginosa, B. subtilis,* and *E. coli*.[114,115] Gulam Mohammed *et al.* reported high antibacterial efficacy of Ag-Cu bimetallic NPs against *B. subtilis*.[116] Ag-ZnO NPs displayed a synergistic effect against *S. aureus* by reducing the MIC.[117] Baker *et al.* studied the synergistic effect of Ag-Au bimetallic NPs with different antibiotics.[118] They observed significant antibacterial activity against drug-resistant pathogens when Ag-Au NPs coupled with bacitracin, chloramphenicol, erythromycin, gentamicin, kanamycin, and streptomycin. Ellis *et al.* developed a pulmonary drug delivery system with Ag-ZnO bimetallic NPs-rifampicin/PLGA to compromise membrane stability, increase bacterial permeability of rifampicin, and allow a simultaneous

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release to *Mycobacterium tuberculosis* (*M. tb*) within alveolar macrophages.[103] The release of Ag and ZnO NPs improved the efficiency of rifampicin by as much as 76% and increased the membrane disorder of intracellular *M. tb* (Fig. 7). The authors stated that by enhancing *M. tb* membrane permeability, this system can also affect the treatment of drug-susceptible tuberculosis in addition to drug-resistant *M. tb* strains.

Since the intermetallic NPs have proven their synergistic antibacterial effects toward various gram-positive and gram-negative bacteria strains, the development of new drug delivery systems focused on using these intermetallic NPs in combination with antibiotics and polymeric biomaterials would be helpful in combating resistance.

B. Wound dressing

Antibiotic usage on wound dressings is a highly adopted method in wound therapy. However, the emerging antibiotic resistance cannot

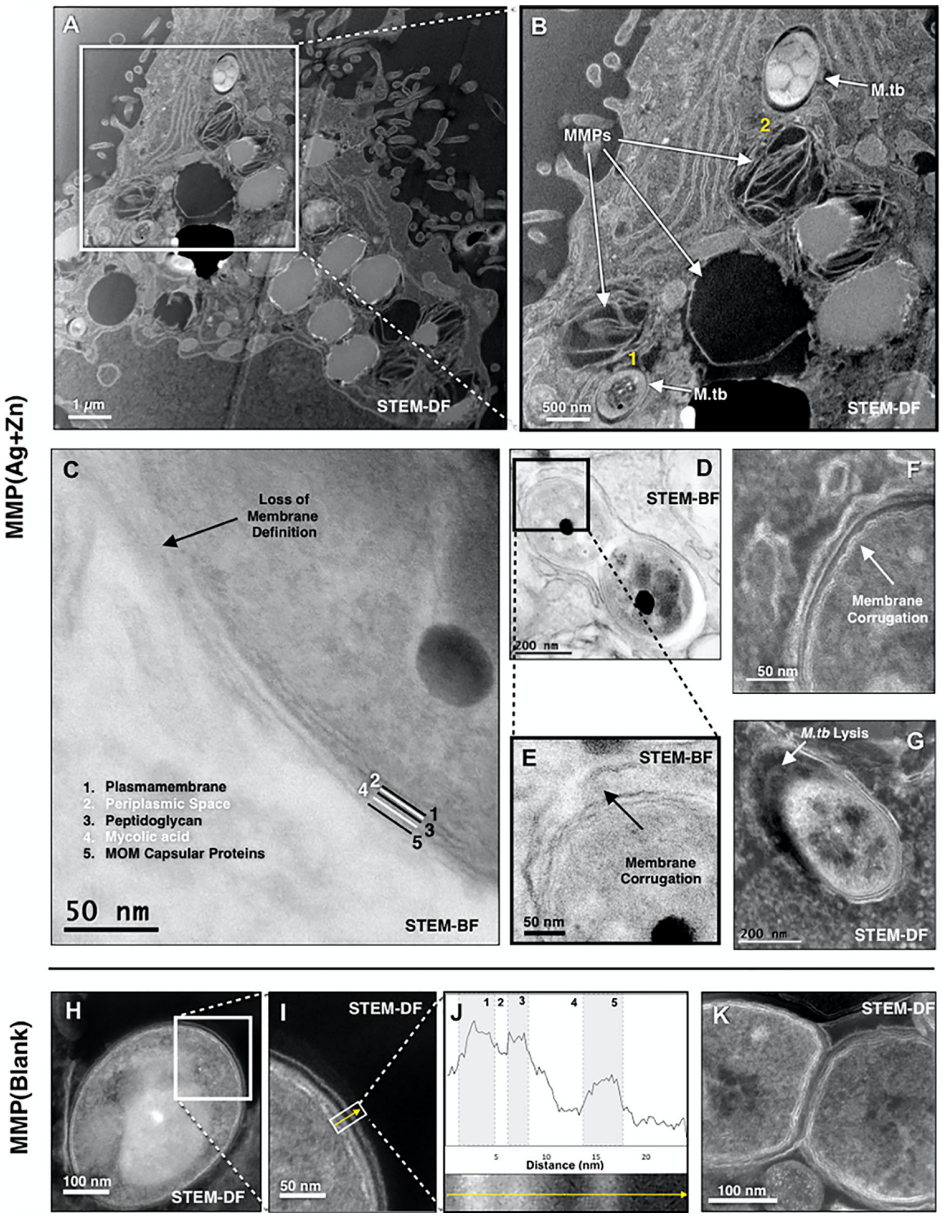

FIG. 7. Membrane disorder of intracellular *M. tb* is increased with the application of Ag-ZnO NPs while increasing rifampicin penetration. (a)–(g) High-angle annular dark-field imaging (HAADF)-STEM analysis images to determine the effect of the system application to *M. tb*-infected THP1 macrophages compared to the control samples (h)-(k). Reprinted with permission from T. Ellis *et al.*, ACS Nano **12**, 5228 (2018). Copyright 2018, American Chemical Society.[103]

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be easily controlled in current medical approaches and is a significant financial burden to society.[119]

The assortment of MBNPs with polymeric biomaterials like cellulose, chitosan, and others showed remarkable inhibition of bacterial growth while amplifying the healing progression of burns and chronic wounds.[120,121] The early stage of inflammation is considered as a critical period of the wound healing process, especially for chronic wounds, essential for clearing contaminating bacteria and creating an environment conducive to subsequent tissue repair and regeneration events. However, scarring is correlated with the intensity and duration of inflammation during healing. Moreover, a prolonged or excessive inflammatory environment increases ROS production, which damages extracellular matrix proteins and causes cell damage. Therefore, for the reduction of inflammatory process related to wound healing, many dressings have been designed to subdue the inflammatory response allowing wounds to heal and improve the final scar appearance ultimately.[122]

Zhou *et al.* manufactured an antibacterial wound dressing with Au NPs–gentamicin sulfate/silk fabric via a facile two-step conjugation approach to increase the antibacterial efficacy by reducing the drug dosage through wound healing (Fig. 8).[119] The study revealed an enhanced antibacterial effect with minimal drug use due to the presence of Au NPs in the system. In addition, the product offered better and faster performance than those commercial dressings (e.g., Aquacel Ag®).

Gentamicin has also been electrospun together with TiO_2 and PCL to produce a nanofibrous wound dressing showing enhanced MRSA inhibition with a synergistic act of composite materials.[123] In another study, ZnO NPs and gentamicin were incorporated with chitosan to maintain a moist level at the wound interface while slowly releasing the antibiotic.[124] This ZnO NPs–gentamicin/chitosan combination increased the inhibition zone from 11 mm (gentamicin control) to 17 mm for *S. aureus* and from 13 mm (gentamicin control) to 17 mm for *P. aeruginosa*. Rath *et al.* evaluated the efficacy of ZnO NPs–cefazolin/gelatin nanofiber mats against *S. aureus*.[125] The study revealed that ZnO-cefazolin/gelatin samples had more inhibition zone diameter compared to those of only cefazolin-loaded gelatin and ZnO NPs-loaded gelatin samples. Furthermore, ZnO-cefazolin nanofibers showed a sustained release profile after 24 h, while the release behavior was regulated by the addition of ZnO NPs in the composite. *In vivo* tests also demonstrated that ZnO–cefazolin/gelatin samples provided enhanced wound healing than those loaded with only cefazolin or ZnO NPs. Again, to be used on wound dressing applications, Fazli *et al.* used electrospinning for fabricating ZnO NPs–hydrocortisone– imipenem–-cilastatin/chitosan–Poly(ethylene oxide) (PEO) nanofiber mats.[126] The combination displayed enhanced hydrocortisone release (82%) within the first 12 h while slowing release, due to the presence of ZnO NPs, of imipenem–cilastatin (20%) during this period of time. The authors stated that this nanofiber mat is very well suited to be used mainly as a wound dressing since it inhibits both excessive inflammation (with hydrocortisone) and infection (using imipenem–cilastatin antibiotics and ZnO NPs). To design a hydrogel film for wound dressing applications, Rakhshaei and Namazi made a ternary blend of ZnO modified tetracycline/mesoporous silica (MCM-41)-carboxymethyl cellulose

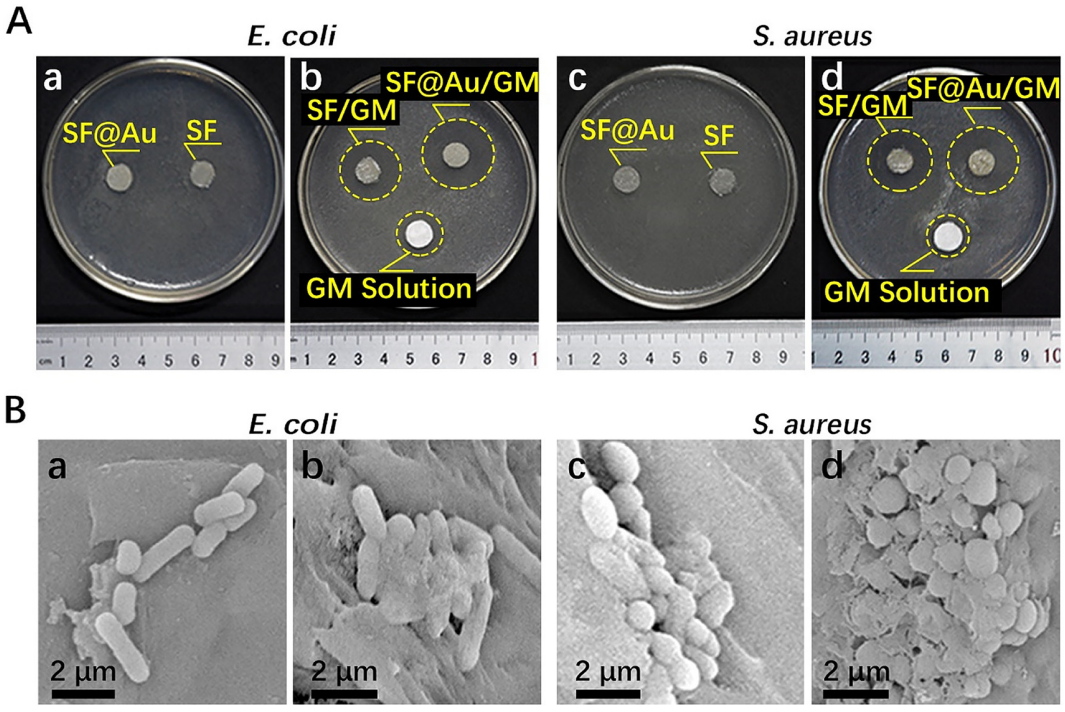

FIG. 8. Antibacterial behavior of fabrics. (A) Inhibition zones of fabrics: Gentamicin sulfate (GM)-free (a and c) and GM-containing (b and d) samples in the bacterial medium; (B) morphology of bacteria prior to (a and c) and following (b and d) 3-h incubation on Au NPs-GM/silk fabric (SF). Reprinted with permission from L. Zhou *et al.*, J. Clean. Prod. **243**, 118604 (2020). Copyright 2020, Elsevier.[119]

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hydrogel and studied antibacterial properties of the film.[127] ZnO NPs had a synergistic effect with tetracycline, and the film showed enhanced antibacterial efficacy while the polymeric carrier improving the erosion, gas permeability, and swelling properties. To increase the antibacterial efficacy and lower the risks of antibacterial resistance, antibacterial electrospun nanofibers were produced by Abid *et al.* in combination with ZnO–ciprofloxacin/PEO–chitosan.[128] Addition of ZnO NPs maximized the bactericidal activity for both *E. coli* and *S. aureus* strains. Moreover, ZnO NPs and ciprofloxacin loaded samples exhibited nontoxicity against human dermal fibroblasts (>82.5%) and human keratinocytes (>85.60%), which justifies the biocompatibility of the samples. Also, ZnO–ciprofloxacin/PEO–chitosan combination was found to have the ability to kill or inhibit infection in burn wounds with fewer side effects.

Several studies have reported products containing different intermetallic NPs and polymeric biomaterials for antibacterial wound dressing use. Ag-ZnO bimetallic NPs were conjugated with polyurethane via electrospinning by Jatoi.[129] Produced nanofibers presented a complete kill of *E. coli*, *S. aureus,* and *B. subtilis* strains and inhibited the growth of all for up to 72 h in liquid media. Cu-Zn bimetallic NPs were dispersed in carbon nanofibers via the chemical vapor deposition method.[130] The final product showed excellent prolonged antibacterial efficacy by inhibiting the growth of the *E. coli*, *S. aureus,* and MRSA strains instantly and is promising for use as an antibiotic wound dressing. In another study, Ashfaq *et al.* produced a composite film consisting of Cu-Zn bimetallic NPs dispersed activated carbon micro/nanofiber with PVA and cellulose acetate phthalate.[131] As the study reports, the material was able to suppress the growth of *P. aeruginosa* strains isolated from the burning, surgical, and traumatic injury wounds. Moreover, PVA and cellulose acetate phthalate were found thriving in encapsulating the Cu-Zn bimetallic NPs while providing a slow release of them and increasing the hemostasis during wound healing. In addition, activated carbon micro/nanofiber helped the Cu-Zn bimetallic NPs offering mechanical and thermal stability. Li *et al.* incorporated Ag-Au NPs with egg white and chitosan by the freeze-drying method for wound dressing applications.[132] The dressings produced exhibited low cytotoxicity against L929 cells (mouse skin fibroblast cells) while promoting wound healing and provided improved antibacterial activity against *S. aureus* and *E. coli* compared to samples containing only monometallic Ag NPs or Au NPs.

Altun *et al.* produced antibacterial bacterial cellulose–PMMA fibers with pressurized gyration method for epidermal wound dressing applications using two different intermetallic NPs blends (UHNP-1 and AVNP-2) (Fig. 9).[133] The cellular response and the accompanying bactericidal efficacy to the dressings having the highest NPs concentrations (1 wt.%) for both blends were investigated by the *in vitro* co-culture of *S. aureus* and keratinocytes. Higher antibacterial efficacy and increased keratinocyte cell viability were observed with the samples containing AVNP-2 intermetallic NPs compared to those containing UHNP-1 intermetallic NPs. The fibers were found promising to be used as epidermal wound dressing materials.

According to the studies mentioned above, intermetallic NPs–polymeric biomaterial systems can effectively destroy diverse bacteria strains in wound dressing applications. However, intermetallic NPs-antibiotic/polymeric biomaterial systems as an antibacterial wound dressing are still a mystery. Research in this area would reduce antibiotic dosage with intermetallic NPs while enhancing their prolonged bactericidal effect with polymeric biomaterial.

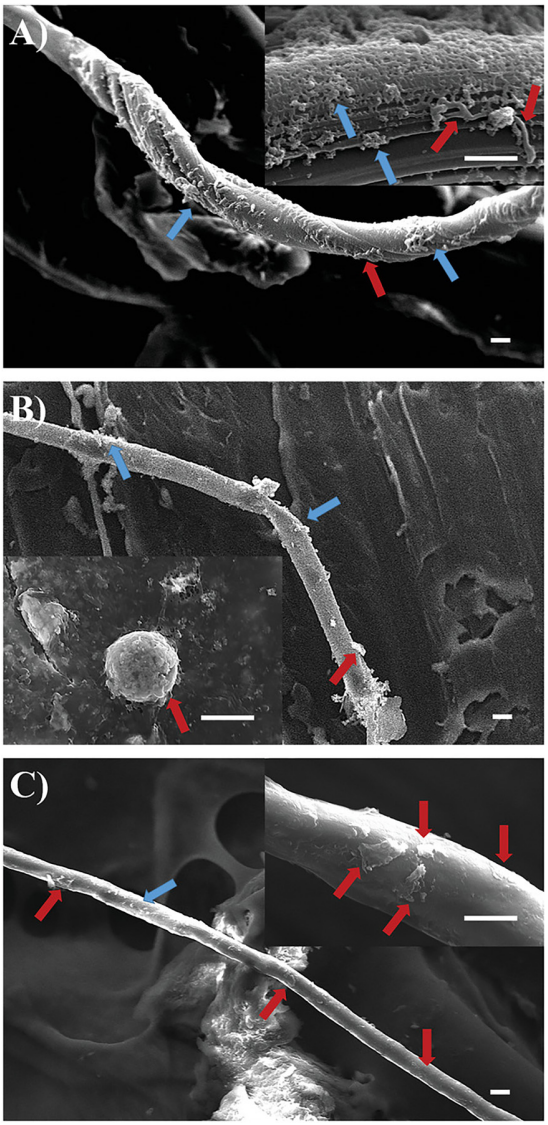

FIG. 9. SEM images of wound dressing samples after cell viability (indicated with red arrows) and bacterial colony counts (indicated with blue arrows) following co-culture. (a) Control material (bacterial cellulose–PMMA), (b) bacterial cellulose–PMMA-1 wt.% combination of Cu-Ag-Zn/CuO NPs (UHNP)-1, and (c) bacterial cellulose–PMMA-1 wt.% combination of Cu-Ag-Tungsten carbide NPs (AVNP)-2. (Scale bars indicate 10 μm). Reprinted from E. Altun *et al.*, Macromol. Mater. Eng. **304**, 1800537 (2019). Under a CC BY License, Copyright 2018, the Author(s).[133]

C. Implantable medical device coating

Medical implant devices are a frequently used concept and a significantly popular way of treating tissue related diseases where a specific part of a particular tissue is lost or suffering from damage. As those

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implant surfaces are mainly designed to host native cells of the body and allow the formation of the tissue structure onto them, the most significant competitors, namely, microorganisms, are also finding these surfaces intriguing. Therefore, a competition emerges for surface adhesion, which is the race of both natural cells and microorganisms to overcome each other.[134] To support medical requirements in treating tissue-related diseases by eradicating the antimicrobial activity on implant surfaces, scientists have adopted various aspects to support cell growth while inhibiting bacterial growth. As antibiotic usage can generate specific and well-known problems like resistance, scientists worldwide are constantly seeking alternatives while practicing MBNPs.[135] Monometallic NPs, intermetallic NPs, ceramic–metallic NPs combinations, and even polymeric biomaterial added, or antibiotic enhanced metallic mixtures can create various material combinations and help to combat microorganisms while allowing native cells to easily attach to implant devices and increase the success rate of treatments.

Many studies have already proven that MBNPs can be used in coatings of medical implant devices with polymeric biomaterials and are excellent sources for increased antibacterial activity, as summarized in Table IV.

Tian *et al.* used Ag NPs doped hydroxyapatite coatings to support osteoconductivity and obtain bactericidal effect simultaneously.[139] Results indicated that an increased bactericidal effect occurred against *S. aureus* and *E. coli*. In another research, Hazer *et al.* coated titanium pedicle screws with polypropylene-based PEG grafted Ag NPs.[140] After testing against MRSA, results indicated that the coating material combination increased antibacterial properties and inhibited biofilm formation. A previous study published by Abdulkareem *et al.* is an excellent example of enhanced antimicrobial activity achieved by merging ceramic and metallic materials.[141] A coating material consisted of hydroxyapatite and ZnO NPs was used to coat on titanium dental implants. The study reported that the biofilm formation capacity of the bacteria was reduced along with the antimicrobial growth while helping the bone tissue regeneration mechanism with the proposed combination. Nevertheless, ZnO NPs are not the only ones tried together with hydroxyapatite since implantable medical devices are attractive in dental studies. The role of Zn derivative have to be analyzed with caution as the underlying chemistry of Zn compounds can induce misleading results.

As previous studies revealed, biocompatible magnesium implant devices suffer from a high degradation rate, which compromises the integrity of the medical device and coating material used and its necessary duties, Rezk *et al.* proposed another approach to coat magnesium alloys to provide antibacterial effects while improving the implant device properties in different aspects.[142] They prepared a bimetallic Ag-Au NPs/polydopamine combination and reported that the antibacterial efficacy of coated medical implant devices was increased against *E. coli* and *S. aureus* compared to the uncoated samples used. In another study, azithromycin and clarithromycin antibiotics were incorporated with biologically synthesized colloidal Au NPs and a better bactericidal property against oral pathogens was achieved with the combination.[143] Due to its significant antibacterial effect against oral pathogens, the suggested study can also be an attractive candidate to crate coating surfaces with polymeric biomaterials for oral implant devices.

The antibacterial efficacy of these implantable medical device coatings can be further expanded by combining them with antibiotics. The polymeric phase would enhance the surface properties of the coating material while being used as stabilizing agents and tuning the ion release by anchoring MBNPs depending on the application type, and MBNPs would improve antibiotics to provide sufficient antibacterial activity. In contrast, the usage of less amount of antibiotics due to antibacterial MBNPs would lower the risk of developing antibacterial resistance. Hence, studies in this area are highly recommended for further research.

D. Antibacterial vaccine adjuvants

Vaccine adjuvants are used to induce the immune response by enhancing the effects of vaccines.[144] Most vaccines need an adjuvant,

TABLE IV. Some MBNPs for coating of medical implant devices.

MBNPs type	Biomaterial	Tested microorganisms	Coated surface	Notes	References
Ag	Polyelectrolyte	*S. aureus* *E. coli*	Titanium alloy	Improved biocompatibility and reduced infection risk for the titanium implant used.	136
	Calcium phosphate	*S. aureus*	Titanium substrate	Enhanced antimicrobial activity.	137
	Chitosan and bioglass	*S. aureus*	Stainless steel 316	Increased antibacterial properties.	138
	Hydroxyapatite	*S. aureus* *E. coli*	Titanium alloy	Enhanced bactericidal effect.	139
	PEG and polypropylene	MRSA	Titanium pedicle screw	Increased antimicrobial effect and inhibited biofilm formation.	140
ZnO	Hydroxyapatite	*Streptococcus spp.* *Anaerobes spp.* *Aerobes spp.*	Titanium dental implant	Enhanced antimicrobial effect, prevention of biofilm.	141
Ag-Au	Polydopamine	*S. aureus* *E. coli*	AZ-31 Magnesium alloy	Increased antibacterial properties.	142

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while some do not require them since their protein forms into a particle. Polymeric biomaterials can entrap or encapsulate these adjuvants along with substances like antigens and MBNPs can deliver controlled and sustained release up to months as a carrier while offering tunable surface properties, low toxicity, favorable biocompatibility, and biodegradability. Moreover, they have found to be more stable as compared to other colloidal vectors such as liposomes.[145]

Although the essential roles of vaccine adjuvants have already proven themselves, researchers around the globe are still searching for safer and effective adjuvants to prepare more effective vaccines to cure emerging and existing pathogens.[146] Among others, MBNPs found themselves a vital place in the vaccine adjuvant concept. As stated by Gregory *et al.*, MBNPs are more suitable for being used as a vaccine adjuvant than non-MBNPs having similar activity in terms of particle size optimizing and tracking the migration of NPs to tissue.[147] There are many examples of MBNPs that increase the effectiveness of vaccines to provide better treatments due to their variety of sizes, shapes, and compositions. Au NPs, a pioneering example that has been included in various vaccines, have been shown to have protective activity against other bacterial infections, enhancing antibody response and extending the protection of.[148,149] Zhou *et al.* stated that Au NPs/chitosan conjugation could generate an augmented serum antibody response tenfold more effective than naked DNA vaccine.[150] Safari *et al.* proposed a study allowing Au NPs as a vaccine adjuvant against *S. pneumoniae*.[151] Results indicated that specific antibodies to react against the micro-organism were successfully induced, and Au NPs are extraordinarily effective and promising to be used as vaccine adjuvants. Au NPs have also been used against *Burkholderia mallei*, a gram-negative infectious bacterium that causes glanders disease.[152] Torres *et al.* used Au NPs in a study where a nanoparticle glycoconjugate vaccine was developed using E264 liposaccharides taken from *B. thailandensis*.[153] Authors reported that this was the first study using nanoparticle glycoconjugate vaccine turning to be immunogenic and showing successful outcomes in non-human primate subjects where the vaccination has been made before the contact with the pathogens.

SPIONs also have been used in vaccine adjuvant studies by Al-Deen *et al.*[154] They developed a malaria DNA vaccine system based on SPIONs/polyethylenimine (PEI)–hyaluronic acid against *P. yoelii*. An injection site focused external magnetic field was applied in combination with the system to maintain a stabilized local SPION concentration in the targeted area. The developed vaccine system improved the immunity by inducing antibody production in *in vivo* studies and found beneficial in malaria vaccine developments.

Aluminum-based composites remain dominant as adjuvants for their licensed use in human vaccines since they have the strongest safety history of any human adjuvants.[155] In a study, aluminum-based NPs have been implemented by Orr *et al.*, using polyacrylic acid (PAA) as a stabilizing agent.[156] Antigen-specific immune response was prompted with the proposed adjuvant model and found promising for improved protection against severe pathogens causing infections like tuberculosis and pertussis.

β-lactamase inhibitors, efflux pump inhibitors, and outer membrane permeabilizers are antibiotic adjuvants developed to enhance the efficacy of antibiotics and protect them from a bacterial inactivation while blocking microbes' resistance mechanisms when used in combinations.[157] Although they have demonstrated fruitful results in clinical studies, these antibiotic adjuvants in combination with an antibiotic approach also represent the risk of adverse outcomes from possible drug–drug interactions.[158] Hence, using MBNPs in combination with an antibiotic can successfully be used in vaccine adjuvant applications, potentially lowering the amount of current antibiotic usage and maintaining prolonged bactericidal efficacy in combating antibiotic resistance with the help of polymeric biomaterials.

One important factor to keep in mind while developing these MBNPs-antibiotic/polymeric biomaterials for vaccine applications is that MBNPs must be carefully monitored as they can migrate to different parts of the body and cause toxicity. Therefore, despite significant advances, *in vivo* properties, biodistributions, and excretion pathways of administered MBNPs need to be understood as each type demonstrates different behaviors.[159] The *in vivo* functioning such as interactions with biological components, cellular uptake, *in vivo* destiny, and toxicity of MBNPs is believed to be significantly correlated and influenced by their physicochemical properties (size and shape), degree of aggregation, and surface chemistries.[160] Upon introduction to the bloodstream, MBNPs are subjected to several physiological behaviors, including opsonization (the process of protein shell creation to remove foreign agents from the blood), detection, and uptake by phagocytic cells existing in the organs of the reticuloendothelial system, and removal from the blood circulation and the body.[160] It has been stated that MBNPs >10 nm in diameter are immediately entrapped in the reticuloendothelial system via macrophage phagocytosis. In contrast, those <10 nm in diameter are likely to undergo rapid distribution in the body, then cleared efficiently by renal mechanisms and finally leave the body via the urine.[161,162] Synthesizing of smaller and uniform MBNPs would benefit their slower opsonization and excretion from the reticuloendothelial system while positively affecting their *in vivo* pharmacokinetics and biodistribution by lowering their polydispersity index.[161] Surface coating of MBNPs using polymeric biomaterials can also affect their *in vivo* fate and biological properties. PEGylated MBNPs, for instance, are reported to have stabilized properties with reduced opsonization, slowed down reticuloendothelial system organs uptake, and prolonged blood circulation time while moderately excreted into bile and feces via hepatic clearance.[161] Despite this, the precise mechanisms defining the full clearance of MBNPs are not yet fully clarified due to their complex nature, clearly further evaluation is needed in this area before implementing MBNPs as an antibacterial vaccine adjuvant.

V. CONCLUSIONS AND FUTURE PERSPECTIVES

As emphasized in this review, a remarkable volume of research has already been done to find an appropriate MBNPs-antibiotic/polymeric biomaterials system to combat critical, high, and medium priority antibiotic-resistant bacteria. Based on the existing literature, each of the MBNPs discussed above has demonstrated potential synergistic activities for this purpose when used in a system with different conventional antibiotics and polymeric biomaterials. Moreover, usage of MBNPs in a MBNPs-antibiotic/polymeric biomaterials system not only enhances the delivery of the agent but also increases the antibacterial effectiveness of antibiotics and offers sustained release while reducing the side effects related to the vast usage of traditional antibiotics. In addition, the synergy of a MBNPs-antibiotic/polymeric biomaterials system for the inhibition of resistant strains provides the use of antibiotics available in clinical practice more effectively, which promises to overcome the restrictions associated with the

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bioavailability of those agents. Although there are promising results obtained from studies on MBNPs-antibiotic/polymeric biomaterial system, there is no existing product approved by the FDA for human use. Therefore, future research should focus on clarification of the detailed features of various MBNPs, routinely used antibiotics, including the effect of their storage times, and different polymeric biomaterials systems to produce safe and effective products to combat antibiotic resistance and perform as the next-generation therapeutics. This comprehensive review is expected to guide those future studies.

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AUTHOR DECLARATIONS

Conflict of Interest

The authors declare that they have no known competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

Author Contributions

E.A. performed conceptualization, resources, and visualization, and wrote original draft. M. O. A. wrote original draft. E. C. wrote original draft. G. R. involved in conceptualization and supervision. S. H.-V. involved in conceptualization and supervision. M. E. involved in conceptualization and overall supervision, reviewed, and edited the manuscript.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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