Nanoparticle-Based Drug Delivery Systems: Promising Approaches Against Bacterial Infections

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Abstract

Despite the arrays of antibiotics available on the market, bacterial infections, notably those produced by multi-drug-resistant (MDR) bacteria and nosocomial pathogens, have become global concerns and are leading factors of morbidity and mortality, especially for immunocompromised and hospitalized patients. The choice of antibiotics is largely empirical and sometimes requires administration of multiple drugs. Recently, the emergence of MDR bacteria has also put pressure on researchers and healthcare experts to discover alternative antimicrobial agents. Additionally, there is growing concern related to biofilm-associated infections that generally inhibit the penetration of antimicrobial agents inside biofilms, leaving almost no therapeutic options. Hence, there is a dire need to develop effective antimicrobial agents. Nanotechnology offers promising new weapons in treating bacterial infections and overcoming resistance, given that it is believed that numerous mechanisms of action, such as multiple gene mutations within same bacterial cell, are required to develop resistance against nanoparticles (NPs). The past decade has seen a surge in the application of innovative nanotechnology-based antimicrobial drugs in fighting bacterial infections. Diverse compositions of NPs and nanocarriers containing antimicrobial drugs have been developed for the efficient treatment of bacterial infections, including those of MDR pathogens in in vitro and in vivo models. This chapter encompasses the emerging efforts in combatting bacterial infections using diverse nanoformulations, such as polymer, liposomal, solid lipid, nanoemulsion, and metal NPs carrying antibiotics, antimicrobial peptides, and other antimicrobial drugs.

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1 Introduction

Bacterial infections are major causes of morbidity, chronic infections, and death (Fauci and Morens 2012). In addition to acute illness in patients, bacterial infections can lead to chronic diseases, where bacteria can produce a biofilm, a three-dimensional microbial community that slows healing (Hall-Stoodley et al. 2004). After the discovery of penicillin in 1928, several classes of antibiotics, including the new generation of aminoglycosides and fluoroquinolones, have been designed and synthesized for the treatment of microbial infections (Appelbaum and Hunter 2000; Poulikakos and Falagas 2013). Antibiotics are the most favored drugs in the healthcare sectors for the treatment of bacterial infections owing to their cost-effectiveness and broad-spectrum antimicrobial activity. In recent years, infections caused by multi-drug-resistant (MDR) bacteria have become growing concerns for human health, imposing a huge burden on public healthcare costs. In Europe, 4 million patients are infected with MDR bacteria annually, causing cost over 1.5 billion euros and killing 25 thousand people per year, according to the European Centre for Disease Prevention and Control, and the European Medicine Agency in 2009 (European Centre for Disease Prevention and Control/European Medicines Agency n.d.). Therefore, despite the availability of antibiotics and other antimicrobial agents, bacterial infections continue to be a major challenge. Additionally, there has been a sharp decrease in the number of approved antibiotics, especially those effective against MDR Gram-negative bacteria, highlighting the immediate need for effective and long-term antimicrobial and biofilm preventing drugs in medicine.

Combining antibiotics with nonantibiotic drugs has shown promise as an alternative strategy to overcome bacterial resistance (Ejim et al. 2011; Farha and Brown 2013), and recently, outdated antimicrobial drugs in combination with current antibiotics have been proposed to combat bacterial resistance (Bush et al. 2011; Imperi et al. 2013). However, in addition to combinatorial therapies utilizing established drugs, it is vital that novel strategies for the effective prevention of deadly bacterial infections are developed, and nanotechnology-based approaches offer an array of promising new weapons.

Over the last few decades, the application of nanoparticles (NPs) for drug delivery has generated significant interest in medicine (Farokhzad and Langer 2009). Various drug delivery platforms, such as liposomes, dendrimers, polymers, and inorganic NPs, have received tremendous attention (Fig. 1). Moreover, NPs are emerging as potent antimicrobial agents, due to their unique physical and chemical

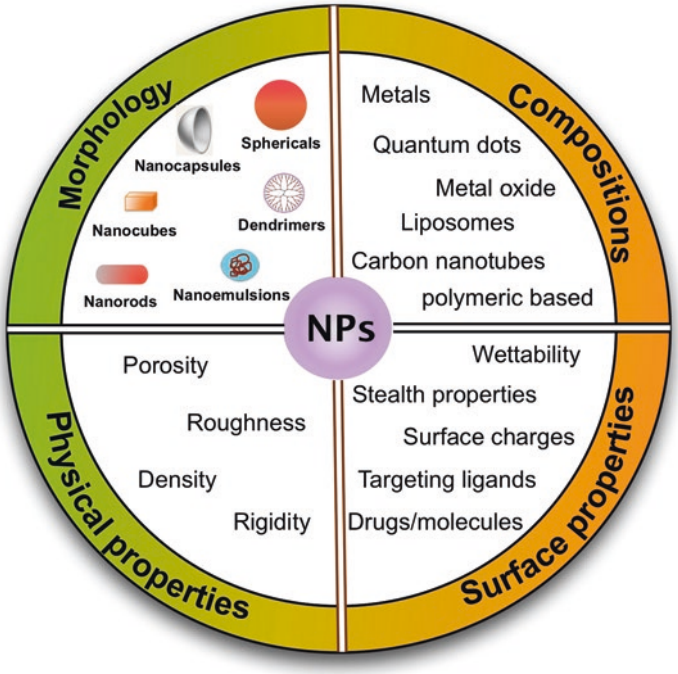

Fig. 1 Schematic representation of a number of NPs used to encapsulate/entrap or conjugate drugs. NPs show unique physicochemical properties, and their surfaces can be functionalized with appropriate molecules for antimicrobial applications

properties, and are gaining recognition as potential agents to overcome the challenges of clinical antibiotic treatments (Wang et al. 2017). For instance, the size of NPs is commensurate with drugs/biomolecules, thus NP-bacterial interactions can be fine-tuned through suitable surface functionalization of NPs with promising synergy resulting from multivalent interactions (Daniel and Astruc 2004). Importantly, NPs have superior activities, gained by the greater loads of therapeutics on their surfaces when compared to their counterparts, leading to smaller required doses of drug-loaded NPs. The combined actions of drugs and NPs make them potent antimicrobial agents against several strains of bacteria. In addition to delivering antimicrobial drugs, NPs employ multiple mechanisms, such as oxidative stress, metal ion release, inhibition of enzyme activity, damage of DNA/RNA, and photocatalysis, to kill bacteria depending on the compositions of NPs. However, the antimicrobial action of NPs is mainly through direct contact with the bacterial membrane, leading to membrane damage and leakage of bacterial content (Fig. 2) (Huh and Kwon 2011; Rai et al. 2010). Moreover, in the last few years, several NP formulations have been developed to improve the antimicrobial efficacy of antibiotics and other drugs (Miller et al. 2015; Zhao and Jiang 2013).

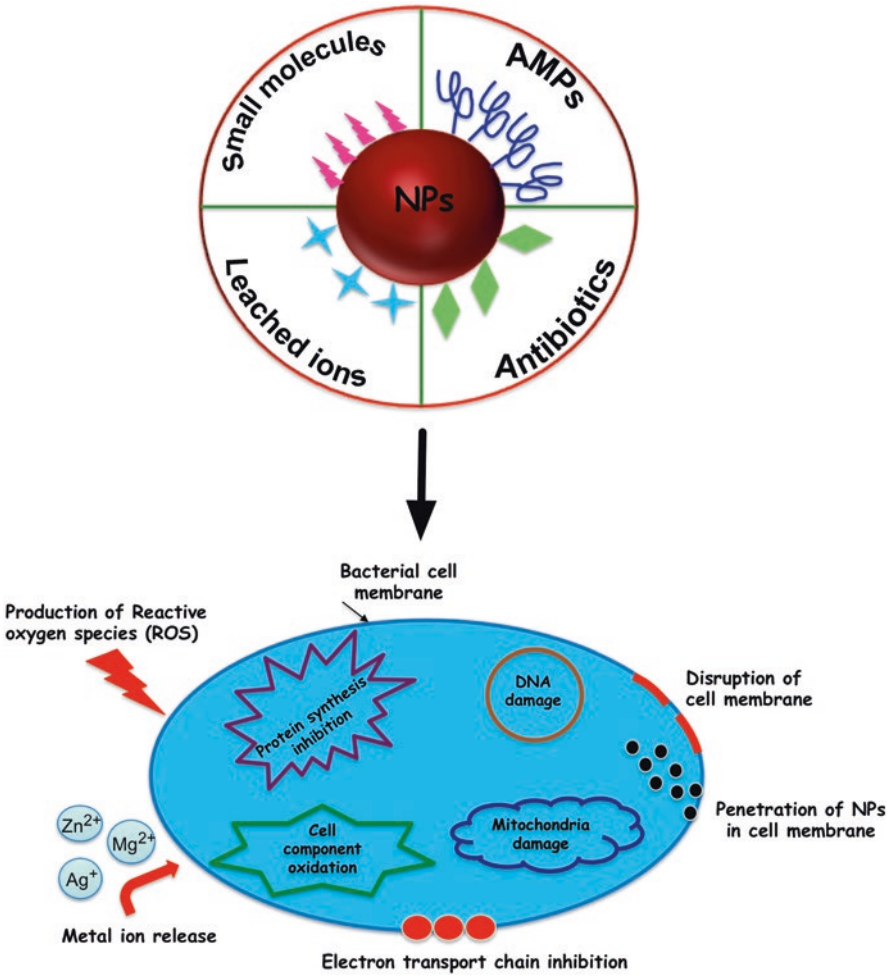

Fig. 2 Representative schematic diagram showing antimicrobial mechanisms of NPs functionalized with different antimicrobial agents

2 Development of Nanoparticles as Drug Vehicles

During the 1950s and 60s, Peter Speiser's group developed polyacrylic beads (Khanna et al. 1969), microcapsules (Merkle and Speiser 1973), and nanocapsules (Birrenbach and Speiser 1976) to achieve prolonged drug release in the blood. Following this discovery, several NP-based drug delivery platforms have been developed for pharmaceutical and biomedical applications. Importantly, NPs above 200 nm in size are not deeply pursued, and nanomedicines often refer to NPs below 200 nm. The advantage of NP-based systems is that they can use lower concentrations of highly toxic drugs in order to reduce side effect, improve drug solubility, prolong systemic circulation, and employ targeted delivery and concurrent delivery of multiple drugs (Singh and Lillard

2009). Drugs of interest loaded into, or onto, NP systems through physical encapsulation/entrapment, adsorption, or chemical conjugation, exhibit improved pharmacokinetic indexes as compared to their free drug counterparts (Singh and Lillard 2009). Additionally, after finding that polyethylene glycol (PEG)-conjugated NPs had prolonged circulation life span and reduced liver uptake (Illum et al. 1987), several studies have been performed on the ability of NPs to cross the blood-brain barrier for the targeting of deep brain tumors or infections (Borchard et al. 1994; Ramge et al. 2000). As the ability to precisely engineer multifunctional NPs continually advances, innovative approaches have emerged to improve the therapeutic efficacy of NPs for treating various diseases. A number of antimicrobial NPs has been approved for clinical use to treat infectious diseases, and several others are currently in the various stages of preclinical and clinical trials (Zhang et al. 2010).

3 Role of Nanotechnology in the Treatment of Bacterial Infections

Due to growing concerns related to bacterial resistance against antibiotics, researchers have turned their attention to nanotechnology-based approaches to produce potent antimicrobial materials to which bacteria may be less likely to develop resistance. Nanotechnology-based approaches have been widely used in a variety of biomedical applications, such as drug-conjugated NP delivery systems for the long-term inhibition of bacterial growth in medical device-related infections, and in the general control of infectious diseases (Huh and Kwon 2011; Gao et al. 2014; Muzammil et al. 2018). Synthesis of metal, metal oxide, and polymeric NPs with different physiochemical properties, such as size, shape, porosity, and surface functionalities, have led to continued evaluation of novel antimicrobial systems (Miller et al. 2015). Various NPs are available to efficiently deliver antibiotics and other antimicrobial drugs to the targeted sites, thus improving their pharmacokinetics and bioaccumulation, while minimizing side effects (Miller et al. 2015). Importantly, local release methods allow the reduction in systemic toxicity and antibiotic dosage. The ability to control the release rate of antibiotics and antimicrobial agents offers consistent therapeutic dosing, and enables the safe delivery of antibiotics over a much longer time span. Importantly, antimicrobial NPs employ multiple pathways to attack microbes, and therefore several mutations at the same time would have to occur in microbes to acquire the resistance against them (Fig. 2).

4 Challenges in Treating Bacterial Infections Using Nanotechnology Approaches

Bacterial resistance has become a serious public healthcare issue, due to the rampant usage of antibiotics, inappropriate drug selection, and the frequent switching between antimicrobial treatments. The emergence of vancomycin-resistant *Enterococcus* (VRE), for example, is a serious clinical threat. VRE has intrinsic resistance to several antibiotics and the capability of acquiring resistance to all

commercially available antibiotics (Gold and Moellering 1996). Likewise, treating vancomycin-resistant *Staphylococcus aureus* (VRSA) infections is one of the most challenging tasks of the twenty-first century, given that vancomycin is a last-resort antibiotic that is assumed to be highly effective in treating *S. aureus* infection (Chakraborty et al. 2010; Perichon and Courvalin 2009).

An attractive alternative to antibiotics is NPs that can cause physical damage to the membranes of the resistant bacteria (Pelgrift and Friedman 2013). However, it is reported that antimicrobial NPs can also induce bacterial resistance in certain cases (Qiu et al. 2012). Biofilms, having unique compositions and structures, provide protection to the resident microorganisms, helping them to escape from antibiotics and antimicrobial NPs, and are a breeding ground for frequent resistance mutations (Khameneh et al. 2016). Moreover, the highly complex structure of biofilms hinders diffusion of NPs to reach the resident microorganisms. Physiological and genetic complexities of biofilms for instance the hydrophobicity of bacterial cell walls control diffusion of NPs inside biofilms (Habimana et al. 2011). A key criterion in the preparation of NPs intended to diffuse inside biofilms is their size and surface charge. Recent studies have shown that the size of NPs governs their diffusion ability inside biofilms, owing to small pore sizes, electrostatic interactions and the uniformity of charges across the biofilms (Peulen and Wilkinson 2011; Stewart 1998; Takenaka et al. 2009). Therefore, understanding the interactions between NPs and biofilm matrices is a fundamental issue in developing effective nanotherapeutics for biofilm treatment.

The search for advanced and effective strategies to combat MDR bacterial infections and biofilms is a top priority in healthcare sectors, and there have been considerable efforts in discovery and synthesis of antimicrobial drugs and nanomaterials with improved efficacy. Challenges to the development of NP-based drug delivery systems include the need to scale-up processes to produce a large quantity of therapeutic materials and multifunctional NPs to meet biological and pharmaceutical requirements.

5 Internalization of Nanoparticles and Delivery of Drugs in Infected Cells

Therapeutic success of NPs or antibiotic/drug-loaded NPs against intracellular microbes is related to their ability to transverse the cellular membrane. Each class of antibiotics, depending on their polarities, has a different propensity to penetrate and be retained by mammalian cells (Briones et al. 2008). Despite rapid intracellular internalization of antibiotics, some of them are cleared from cells via the activation of efflux pumps (Webber and Piddock 2003). On the other hand, the internalization of NPs by cells is governed by various mechanisms, and can be controlled by fine-tuning the physiochemical properties of NPs (Chou et al. 2011). For instance, NPs are opsonized by blood plasma and internalized by the reticuloendothelial system (RES) of cells when administered through the intravenous route. However, the modification of NP's surface governs the interaction with the cell membrane through receptor-mediated, nonspecific, electrostatic or hydrophobic interactions (Chou et al. 2011). Importantly, cells can internalize NPs through several mechanisms at the

same time. Once internalized, NPs are mostly accumulated in endosomes or phagosomes, which further undergo maturation processes involving a number of fusion and fission events. After complex trafficking processes, NPs can translocate to other intracellular compartments or exocytose to the extracellular environment. In most cases, NPs become trapped in endosomes, which mature into lysosomes, where an acidic environment can lead to the degradation of NPs, triggering drug release. This is a challenge to developing suitable NPs that can escape endosomes. NPs that escape the endosomes via endosomal membrane fusion or permeabilization could result in the delivery of drugs to bacteria located in cytoplasm (Peetla et al. 2014). In another approach, NPs can be functionalized in such a way that a caveolin-mediated process internalizes them, thereby bypassing the lysosomes entirely.

6 Antimicrobial Peptides as Promising Therapeutics

Due to the increasing development of antibiotic resistance in bacteria (French 2005), antimicrobial peptides (AMPs) have been attracting considerable attention as potential therapeutics in recent years (Elsbach 2003; Hancock and Sahl 2006). AMPs isolated from bacteria, insects, plants, and vertebrates can kill microorganisms or inhibit their growth (Koczulla and Bals 2003). AMPs are considered as small molecules containing less than 50 amino acid residues. AMPs are mostly positively charged, hydrophobic, and amphipathic in nature (Kang et al. 2017). However, a few AMPs are negatively charged and highly active, but they are less frequent and their mechanisms of action remain elusive (Falcao et al. 2014). AMPs are classified into four major groups based on their composition and secondary structure: (1) amphipathic, α-helical linear peptides, such as cecropin, histatins, magainins, and human ubiquicidin; (2) β-sheet peptides such as β-defensin; (3) peptides with the predominance of one amino acid, such as the indolicidin rich in tryptophan and PR39 peptide rich in proline-arginine residues; and (4) loop structures containing peptides, such as gramicidin (Koczulla and Bals 2003; Peters et al. 2010; Salditt et al. 2006). Cathelicidins and defensins produced by immune cells and histatins produced by salivary glands are the most prominent AMPs in humans (Peters et al. 2010). These AMPs are normally produced at sites of potential pathogen entry in the skin, providing a chemical barrier to keep human skin healthy.

AMPs have potent activities against Gram-positive and Gram-negative bacteria, fungi, and viruses, and thus represent essential players of innate immunity system (Shai 2002). Interestingly, many natural AMPs have been synthetically modified to improve upon their bioactivity, purity, and yield (Gomes et al. 2018; Zasloff 2002). To date, small biotech companies, in association with larger pharmaceutical companies, have studied the biological activities of different AMPs in animals and humans to evaluate their potential as useful drugs for several infectious diseases. Currently, there are numerous AMPs under clinical development for the treatment of infected diabetic foot ulcers, venous leg ulcers, oral mucositis, and skin infections, among other conditions (Mahlapuu et al. 2016). So far, no AMPs have reached the drug market, though many pharmaceutical companies remain enthusiastic about the

prospect of understanding the AMP molecular processing, their mechanisms of action, and their regulation, in the hope for the future use of these novel agents as a new generation of medications, especially for skin therapy.

7 Nanoparticle-Based Antimicrobial Drug Delivery Systems

NPs-based therapeutic approaches have been adopted to combat infections particularly in wounds and other bacterial infections. Antimicrobial NPs can lead to improved outcomes for bacterial infections. Unlike many antibiotics being used in clinics, antimicrobial NPs generally do not cause any acute adverse effects. Antimicrobial NPs can be broadly classified into inorganic and organic NPs that act as carriers to deliver antimicrobial agents.

7.1 Biodegradable Nanoparticles

7.1.1 Polymeric Nanoparticles

Polymeric NPs can be prepared via self-assembly of chitosan (CS), curcumin, poly lactic-co-glycolic acid (PLGA) etc. of different shapes, including nanomicelles (NM), dendrimers, and hydrogels (Kalashnikova et al. 2015). Polymeric NPs have been extensively used in healthcare sectors for the enhanced drug delivery and reduced clearance by the RES of cells (Soppimath et al. 2001). Polymeric NPs containing antimicrobial drugs offer several advantages, including (1) tunable properties (size, shape, surface charge, and controlled drug release) by manipulating polymer lengths, functional groups, and solvents, (2) versatile surface functionalization for conjugating antibiotics and drugs, and (3) structural stability during preparation and storage.

CS NPs (150–300 nm) made of pristine, soluble CS, can be used as prophylactic agents that inhibit infections and promote a significant acceleration of wound healing (Dai et al. 2009; Shrestha et al. 2012, 2014). CS is a positively charged polymer, and has an inherent antimicrobial property. CS has been frequently used as an antimicrobial agent in wound dressings to prevent bacterial infections (Burkatovskaya et al. 2006; Dai et al. 2011). It has been shown that CS NPs, in combination with alginate, can be employed to deliver silver sulfadiazine (SSD) cream to treat infections in open wounds (Huang et al. 2011). Curcumin, a natural product isolated from the root of *Curcuma longa*, has been used as a traditional medicine for centuries. Curcumin-loaded CS NPs have strong antimicrobial activities against *S. aureus* and *Pseudomonas aeruginosa* in murine skin infections (Mirnejad et al. 2014). Also, biomolecules such as lectin-conjugated gliadin-NPs selectively adhered to the carbohydrate receptors of *Helicobacter pylori*, and released antimicrobial agents inside bacterial cells (Umamaheshwari and Jain 2003). For the treatment of lung infection, an antimycobacterial drug, *E-N*2-3,7-dimethyl-2-*E*,6-octadienylidenyl isonicotinic acid hydrazide (JVA), loaded on 180 nm PLGA NPs, exhibited high activity against extracellular

and intracellular mycobacteria (de Faria et al. 2012). Additionally, nebulization of PLGA NPs, loaded with three different antitubercular drugs (i.e., rifampicin, isoniazid, or pyrazinamide), showed superior activity, reduced dosing frequency, and greater drug bioavailability to treat *Mycobacterium tuberculosis* when compared to either oral or intravenous administrations of the parent drugs (Pandey et al. 2003). In another example, ampicillin encapsulated in poly(isohexyl cyanoacrylate) (PIHCA) had greater activity in treating *Salmonella typhimurium* (Fattal et al. 1989) and *Listeria monocytogenes* (Forestier et al. 1992) infection in mice. In another case, penicillin (Turos et al. 2007a) and N-thiolated-β-lactam antibiotics (Turos et al. 2007b) entrapped in polyacrylate (PAA) NPs retained potent antimicrobial activity against methicillin-resistant *S. aureus* (MRSA) in the presence of high concentrations of β-lactamase. Similarly, the potential application of gentamycin entrapped in PLA/PLGA NPs was demonstrated for the treatment of *Brucella* infections, due to the suitable sizes of NPs for phagocytosis (Prior et al. 2000).

In the last few years, advanced techniques using near-infrared (NIR) light has been explored for the spatial-temporal release of cargo molecules from light-triggerable NPs. In the same line, using an antimicrobial photodynamic therapy (PDT) approach, chlorin e6, a photosensitizer, loaded on charge-conversion polymeric NPs, were used to kill pathogens in weakly acidic urinary tract infections under laser irradiation (Liu et al. 2015) (Fig. 3). In recent approach, vancomycin encapsulated in surface charge-switchable NPs (poly(D, L-lactic-co-glycolic acid)-*b*-poly(L-histidine)-*b*-poly(ethylene glycol) (PLGA-PLH-PEG)) demonstrated enhanced antimicrobial activity at a mild acidic condition (pH 6) when compared to physiological condition (pH 7.4) due to their strong binding affinity of positively charged PLGA-PLH-PEGNPs with negatively charged bacterial membranes via electrostatic interactions, and release of vancomycin (Radovic-Moreno et al. 2012).

Recently, AMPs have been considered to be alternatives to antibiotics, given that AMPs mostly perturb the integrity of the bacterial membrane. Temporin B AMPs, derived from frog skin, encapsulated in CS NPs, exhibited enhanced and long-lasting antimicrobial activity against clinically relevant *S. epidermidis*, and a reduced cytotoxicity profile compared to free peptides (Piras et al. 2015). However, in vivo/ex vivo studies are needed to fully evaluate the ability of these AMP-conjugated CS NPs to prevent/treat infections occurring at mucosal/skin surfaces, and in increasing the translational potential of promising AMPs. For example, in ex vivo study, plectasin AMPs, classified as defensins, were encapsulated in PLGA NPs for the treatment of airway *S. aureus* infections with high encapsulation efficiency (71–90%) and continuous release of AMPs over 24 h in infected bronchial epithelial cells (Water et al. 2015). In another work, LL37-capped PLGA NPs were explored to promote wound healing and fight infections (Chereddy et al. 2014). Results showed that the administration of LL37-capped PLGA NPs promoted rapid wound closure due to the sustained release of both LL37 and lactate when compared to PLGA or LL37 administered alone in a full-thickness excisional wound model. In vitro, LL37-capped PLGA NPs induced cell migration and displayed antimicrobial

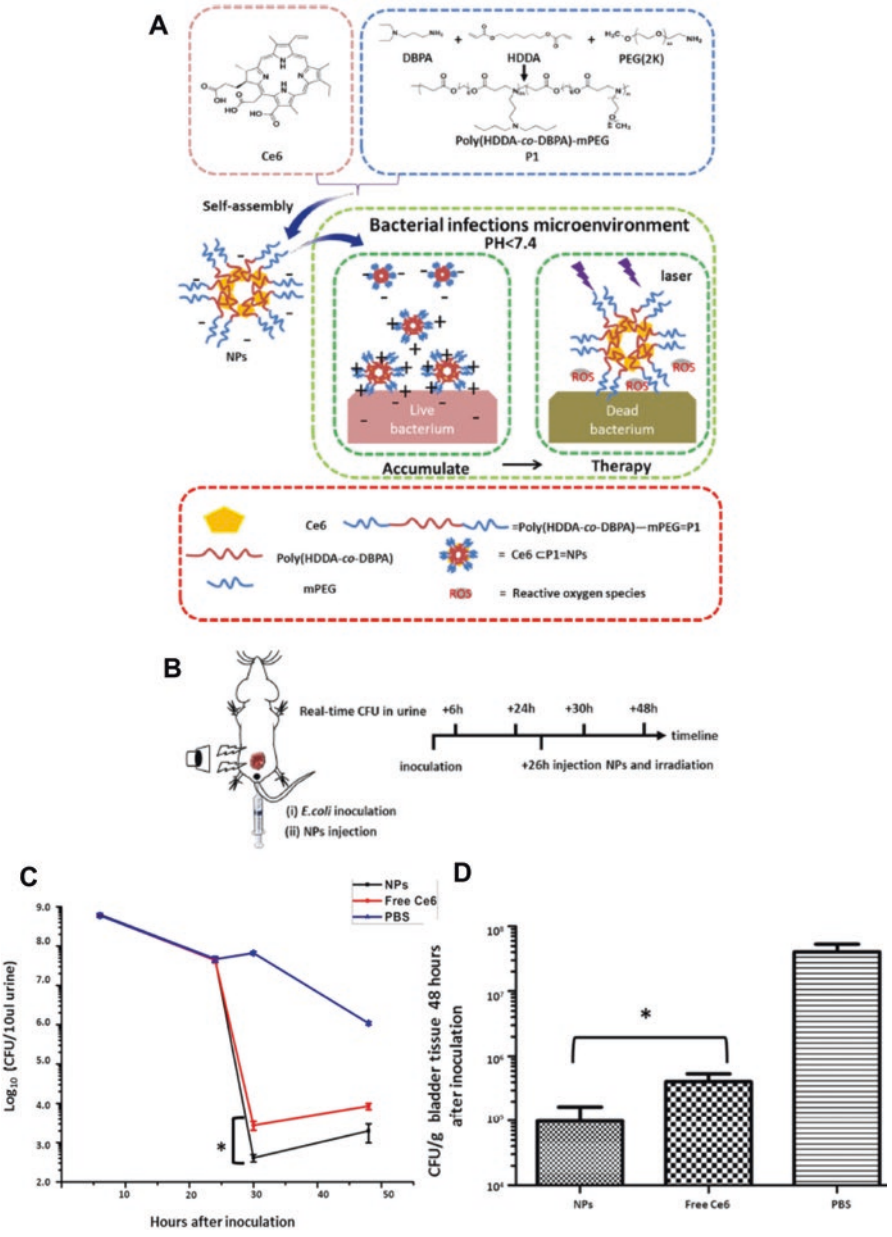

Fig. 3 (**a**) A schematic representation of surface charge-conversion NPs for the recognition and killing of bacteria in the infected site. (**b**) Time-dependent protocol for bladder infection induction and photodynamic therapy. (**c**) Time-dependent reduction of bladder infected *E. coli* in urine after treatment. (**d**) Estimation of *E. coli* in the bladder after treatment. (Reproduced from Turos et al. (2007b) with permission)

activity against *E. coli* (Chereddy et al. 2014). Similarly, nisin immobilized on phytoglycogen (PG)-NPs through electrostatic and hydrophobic interactions showed prolonged antimicrobial efficacy against *L. monocytogenes*, along with minimum loss of peptide activity during storage (Bi et al. 2011).

7.1.2 Dendrimers

Dendrimers are hyperbranched polymers in the nano-scale size range (1–10 nm) with precise nanoarchitecture and monodisperse structures. They are synthesized via a layer-by-layer approach around a core unit, allowing the control of surface functionalization and branching points for conjugation of either hydrophilic or hydrophobic drugs (Svenson 2009). Dendrimers have shown promise as antimicrobial agents in multiple studies. One example is that of dendrimers functionalized with high densities of quaternary ammonium molecules on their surfaces, which displayed greater antimicrobial activity than free antibiotics, due to their ability to destroy bacterial membranes or disrupt multivalent interactions between bacteria and host cells (Chen and Cooper 2002). Additionally, water-insoluble antibiotics, such as nadifloxacin and prolifloxacin, loaded on polyamidoamine-based dendrimers showed enhanced antimicrobial properties (Kalomiraki et al. 2016). In another approach, silver-loaded dendrimers were found to have synergetic anti-inflammatory and antimicrobial properties, allowing them to kill microorganisms and accelerate wound healing (Liu et al. 2014).

7.1.3 Liposomal Nanoparticles

Liposomal NPs are spherical vesicles consisting of phospholipid bilayers with hydrophilic core. Liposomes have been extensively used as clinically acceptable carriers of antimicrobial agents and antibiotics for treating several diseases, given that their lipid bilayer structure mimics cell membranes, allowing them to rapidly fuse with infectious microorganisms (Nisini et al. 2018). Delivery of antimicrobial drugs using liposomal NPs such as liposomal amphotericin-B (Abelcet®, Amphotec®, AmBisome®), approved by the Food and Drug Administration (FDA), have been used in the treatment of aspergillosis, cryptococcal meningitis, and visceral leishmaniasis (Torchilin 2005). For instance, AmBisome® showed improved bioactivities over free drug, including sustained circulation half-life, decreased renal clearance, and enhanced therapeutic efficacy. Another successful example is Polymyxin B-loaded lysosomal NPs, which showed excellent antimicrobial activity against *P. aeruginosa* in a rat lung infection model (Omri et al. 2002). Importantly, free Polymyxin B has limited success due to its toxic side effects, such as nephrotoxicity, ototoxicity, and neuromuscular blockade, and liposomal formulation diminishes the incidence of these side effects (Mugabe et al. 2006). It was observed that lipid molecules of liposomes reorganized in *P. aeruginosa* membranes, leading to bacterial membrane deformation and delivery of high-dose drugs, thus overwhelming the efflux pumps and suppressing the possibility of antimicrobial resistance (Mugabe et al. 2006).

Several antimicrobial drug delivery system based on liposomal NPs have been developed for the treatment of bacterial infections. Ampicillin-loaded liposomes against *Salmonella typhimurium*, bezyl penicillin-loaded liposomes against *S. aureus*, ciprofloxacin-loaded liposomes against *Salmonella dublin*, and gentamicin-loaded liposomes against *Brucella* infections have been developed, and have greater stability and antimicrobial properties than free antibiotics (Gao et al. 2014; Ladaviere and Gref 2015). For example, ciprofloxacin-loaded liposomal NPs accumulate in the spleen and liver and persist in these organs for 48 h after the final administration, suggesting that these liposomal formulations can be an effective therapy for *Salmonella* infection (Magallanes et al. 1993). Recently, co-encapsulation of two or more active drugs within liposomes has become an attractive choice for treating recalcitrant bacterial infections. For example, the synergistic therapeutic efficacy of co-encapsulated gentamicin and ceftazidine show prolonged circulation time and enhanced accumulation at the infection site (Bakker-Woudenberg et al. 1995). Likewise, co-encapsulation of daptomycin and clarithromycin resulted in significant elimination of MRSA infections and increased survival of mice (Li et al. 2015). Also, the combination of levofloxacin and serratiopeptidase loaded on liposomes had improved antimicrobial and antibiofilm efficacy in treating an *S. aureus*-infected lungs in a rat infection model, along with reduced levels of inflammatory cytokines (Gupta et al. 2017). Interestingly, in another study, lipase-sensitive, singlet oxygen-producible and erythromycin-loaded liposomes (LSSPL) were developed for antibacterial therapy in skin disorders by coating erythromycin-loaded liposomes with pullulan-pheophorbide A (PU-Pheo A) in order to produce reactive oxygen species under laser exposure. *Propionbacterium acnes* infections cause skin inflammation and secrete extracellular lipases that promote the degradation of LSSPL, thereby releasing erythromycin and PU-Pheo A. The combined effect of antibiotics and singlet oxygen produced from PU-Pheo A under laser irradiation inhibited *P. acnes* infection in nude mice dorsal skin (Jeong et al. 2017).

Table 1 summarizes antimicrobial liposomal NPs encapsulated with various antibiotics.

7.1.4 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNPs) are made of solid lipids and used as drug carriers with the combined properties of liposomes and NPs (Table 2) (Mofazzal Jahromi et al. 2018; Sala et al. 2018). SLNPs are effective against skin infections, as they tend to adhere to the skin surface and continuously release drugs over long periods of time in the stratum corneum. Ciprofloxacin-loaded SLNPs exhibit the prolonged release of drugs, especially in skin and oral infections (Jain and Banerjee 2008). Likewise, Nitrofurazone encapsulated SLNPs was used for topical delivery of drugs to improve their antimicrobial activity in treating infections in burn eschar patients (Shariff et al. 2010). SLNPs have also been tested against eye infections. Tobramicin (Cavalli et al. 2002; Chetoni et al. 2016) and levofloxacin (Baig et al. 2016) -encapsulated SLNPs provided significantly superior bioaccumulation in the aqueous humor, and can be used for treating Pseudomonal keratitis and conjunctivitis, respectively.

Table 1 Liposomal nanoparticles for the delivery of antibiotics

NP composition	Encapsulated molecules	Target bacteria	Therapeutic activity
DPPC and chol liposome	Polymyxin B	*P. aeruginosa*	Decreased bacterial load in the lungs and increased bioavailability (Omri et al. 2002)
PHEPC, chol, and PEG-DSPE liposome	Gentamicin	*Klebsiella pneumoniae*	Increased survival rate of animals infected with bacteria (Schiffelers et al. 2001)
SPC and chol liposome	Ampicillin	*Salmonella typhimurium* and *Micrococcus luteus*	Enhanced stability of encapsulated antibiotics and activity against extracellular bacteria (Schumacher and Margalit 1997)
EPC, DCP, and chol liposome	Vancomycin and Teicoplanin	MRSA	Enhanced intracellular antimicrobial effects due to increased drug uptake by macrophages (Onyeji et al. 1994)
DPPC and chol liposome	Ciprofloxacin	*Salmonella dublin*	Bioaccumulation of NPs to all organs and decreased mortality of infected animals (Magallanes et al. 1993)
PG, PC, and chol liposome	Streptomycin	*Mycobacterium avium*	Targeted delivery of antibiotics to the infected site (Fielding et al. 1998)

Abbreviations: *Chol* cholesterol, *DPPC* 1,2-dipalmitoyl-phosphatidylcholine, *PHEPC* partially hydrogenated egg phosphatidyl choline, *PEG-DSPE* 1,2-disteroyl-sn-glycero-3-phosphoethanol-amine-(N)-(polyethylene glycol-2000), *SPC* soybean phosphatidyl choline, *ECP* egg PC, *DCP* diacetylphosphate, *PG* phosphatidylglycerol, *PC* phosphatidyl choline

Table 2 Lipid-based nanocarriers to deliver antimicrobial drugs

NP composition	Encapsulated molecules	Target bacteria	Therapeutic activity
SA, STC, and SPC	Ciprofloxacin	Gram-negative and Gram-positive bacteria	Drug release over long time (Jain and Banerjee 2008)
SA, STC, and SPC	Tobramycin	*P. aeruginosa*	Increased antibiotic availability (Cavalli et al. 2002)
SA	Rifampicin, isoniazid, pyrazinamide	*M. tuberculosis*	Increased bioavailability of antibiotics in infected organs (Pandey and Khuller 2005)
PC, glycerol monostearate	LL37	*S. aureus and E. coli*	Synergetic effect to kill bacteria and promote wound healing (Fumakia and Ho 2016)

Abbreviations: *SA* stearic acid, *STC* sodium taurocholate

Another advantage of SLNPs is that they can be administered using a nebulizer, and are mostly phagocytosed by alveolar macrophages in the lungs. No tuberculosis bacteria were found in the spleens and lungs when isoniazid, rifampicin, and pyrazinamide-loaded SLNPs were administered via the nasal route to infected guinea pigs every 7 days (Pandey and Khuller 2005). Conversely, daily administration of the free drugs was needed to achieve the equivalent therapeutic efficiency of SLNP-loaded drugs, indicating that antimicrobial-loaded SLNPs are patient-friendly and cost-effective for tuberculosis treatment.

AMPs can also be loaded in SNLPs. Recently, LL-37, an AMP involved in the modulation of wound healing, and serpin A1, an elastase inhibitor, co-encapsulated in SLNPs, were developed for the sustained release of both molecules at specific ratios in order to promote wound closure by inducing the migration of fibroblast and keratinocyte cells, as well enhancing antimicrobial activity against *S. aureus* and *E. coli* (Fumakia and Ho 2016).

Table 2 summarizes various compositions of lipid NPs as carriers for antimicrobial agents.

7.1.5 Nanoemulsions and Nanogels

Nanoemulsions (NEs) are spherical colloidal particulates that have amphiphilic molecules. NEs have generally hydrophobic cores and hydrophilic shells. The hydrophobic core is used to load water-insoluble drugs, and the hydrophilic shell promotes NEs to be soluble in water. NEs made of NB-201, a novel antimicrobial compound (Cao et al. 2017), and chlorhexidine acetate-encapsulated NEs (Song et al. 2016), showed effective and rapid activity against MRSA-infected wounds in a skin burn wound model and hindered the formation of biofilms due to increased leakage of proteins, Mg^{2+}, K^{+}, DNA, and alkaline phosphate from the bacterial cells. NB-201 NEs reduced epidermal and deep dermal inflammation by inhibiting the secretion of pro-inflammatory cytokines in the infected wounds. In another study, NEs containing eucalyptus oil impregnated in CS films exhibited significant antimicrobial activity against *S. aureus*, likely through bacterial membrane damage (Sugumar et al. 2015). Intriguingly, self-assembled cationic peptide micelle NPs containing TAT peptide (a membrane translocation peptide), conjugated with 6 arginine residues and cholesterol, crossed the blood-brain barrier and suppressed *S. aureus* and *Cryptococcus neoformans* infection in a meningitis-infected rabbit model (Fig. 4). These nanoparticles have a broad spectrum of potent antimicrobial activities; much stronger than soluble peptides (Liu et al. 2009; Wang et al. 2010).

Nanogels are three-dimensional nano-sized hydrogels formed by cross-linked, swellable polymer or biopolymer networks. Hyaluronic acid nanogels encapsulated with the LL37 analog, LLKKK18, demonstrated superior killing efficiency against mycobacteria, when compared to the peptide alone, in both

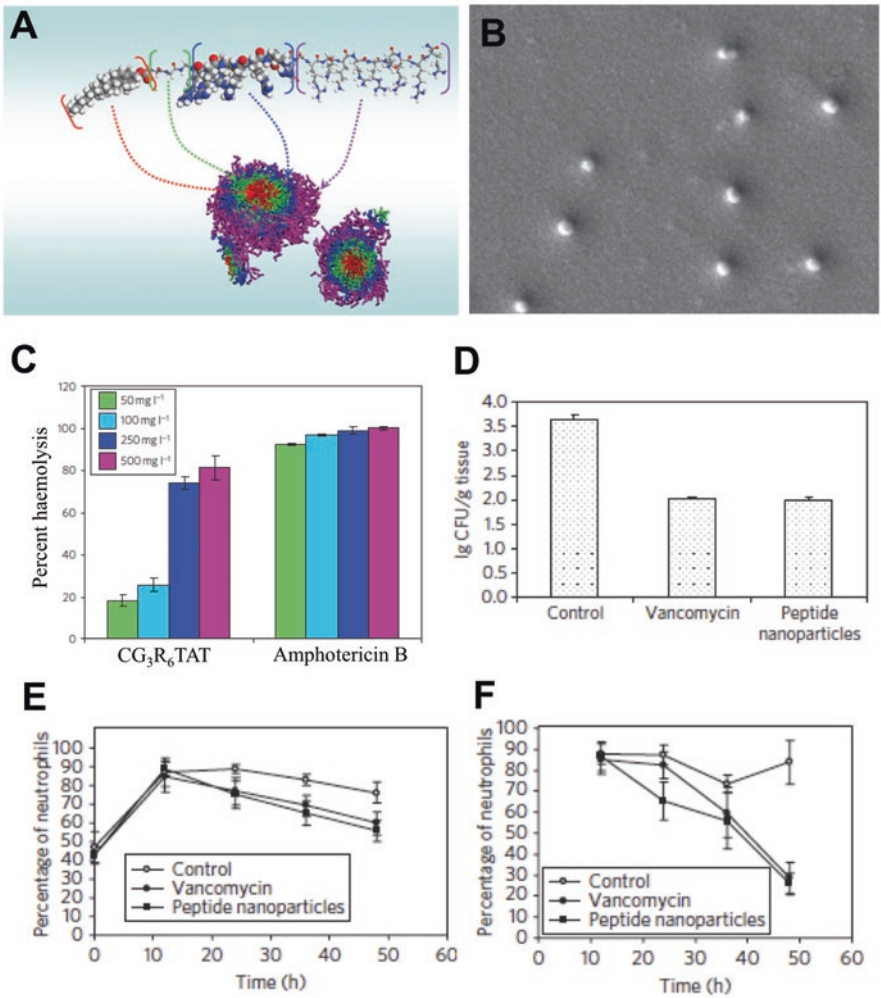

Fig. 4 (**a**) Formulation of micelles simulated through molecular modeling using Materials Studio software. (**b**) Scanning electron microscopy (SEM) image of peptide NPs. (**c**) Dose-dependent hemolytic activity of peptide NPs compared with that of amphotericin-B. (**d**) CFU of *S. aureus* in brain tissues. Percentage of neutrophils in blood (**e**) and CSF (**f**). (Reproduced from Song et al. (2016) with permission)

in vitro and in vivo models, demonstrating their potential to treat tuberculosis. It was found that the hyaluronic acid nanogels were able to protect the peptide from proteolytic degradation and reduce host toxicity (Silva et al. 2016).

7.2 Nonbiodegradable Nanoparticles

7.2.1 Nonantibiotics and Antibiotic-Conjugated Gold Nanoparticles

Typically, gold is considered biologically inert, but gold nanoparticles (Au NPs) exhibit unique physiochemical and biological properties that have triggered tremendous interest for fundamental research and the development of industrial products. For example, Verigene® composed of Au NPs were approved by the FDA in 2012 (Nanosphere) for an in vitro blood infection test for Gram-positive bacteria. Several nonantibiotic molecules conjugated to Au NPs have been explored as potent antimicrobial agents with low induction of bacterial resistance. Jiang's groups have developed a library of amino-substituted mercaptopyrimidine compounds, which have been conjugated to Au NPs (3 nm) in order to test their antimicrobial potency against MDR clinical isolates (Zhao et al. 2010). Out of several compounds, 4,6-Diamino-2-pyrimidinethiol-capped Au NPs (Au-DAPT) showed the best activity when compared with the other two pyrimidine-capped Au NPs. Importantly, Au-DAPT showed very slow induction of resistance compared with gentamicin, with resistance increasing the MIC by 1.3-fold after 50 passages for NPs and tenfold after only 10 passages for gentamicin (Zhao et al. 2010). Recently, Au-DAPT covered in bacterial cellulose (BC) showed excellent physiochemical characteristics, such as water uptake capability, mechanical strain, and biocompatibility, along with inhibition of bacterial growth (*E. coli* and *P. aeruginosa*) in wounds, while promoting wound repair (Li et al. 2017). Similarly, Au NPs capped with a mixture of small molecules can exhibit an antibacterial effect against MDR strains without inducing resistance. For example, 2 nm Au NPs capped with p-mercaptobenzoic acid (pMBA-Au), 3-mercaptopropylsulfonate (MPS-Au), and 2-mercaptoethylamine (MEA-Au) completely inhibited the growth of *E. coli* with an MIC of 0.5 μM, indicating that these NPs could be useful in the treatment of infected wounds (Bresee et al. 2014). 3-mercaptopropylsulfonate and p-mercaptobenzoic acid are inactive against bacteria, while 2-mercaptoethylamine is antimicrobial at high concentrations (2 mM) (Bresee et al. 2014).

Au NPs incorporated in polymeric matrix can accelerate wound closure and aid in fighting infections. In one work, intermediary antibiotic components, such as 6-aminopenicillanic acid (6-APA), 7-aminocephalosporanic acid (7-ACA), and 7-aminodesacetoxycephalosporanic acid (7-ADCA)-coated Au NPs were electrospun with poly(ε-caprolactone) (PCL) and gelatin to produce biocompatible wound dressings to fight MDR infection (Yang et al. 2017). Wettability and tensile strength of Au NP-embedded fiber was similar to PCL/gelatin fiber. Importantly, antibiotic intermediate Au NP-coated fiber significantly decreased the MDR bacterial load in wounds with enhanced wound healing when compared to PCL/gelatin fibers or Ag mat (Fig. 5) (Yang et al. 2017). Similarly, Au NP-chitosan nanocomposites showed improved

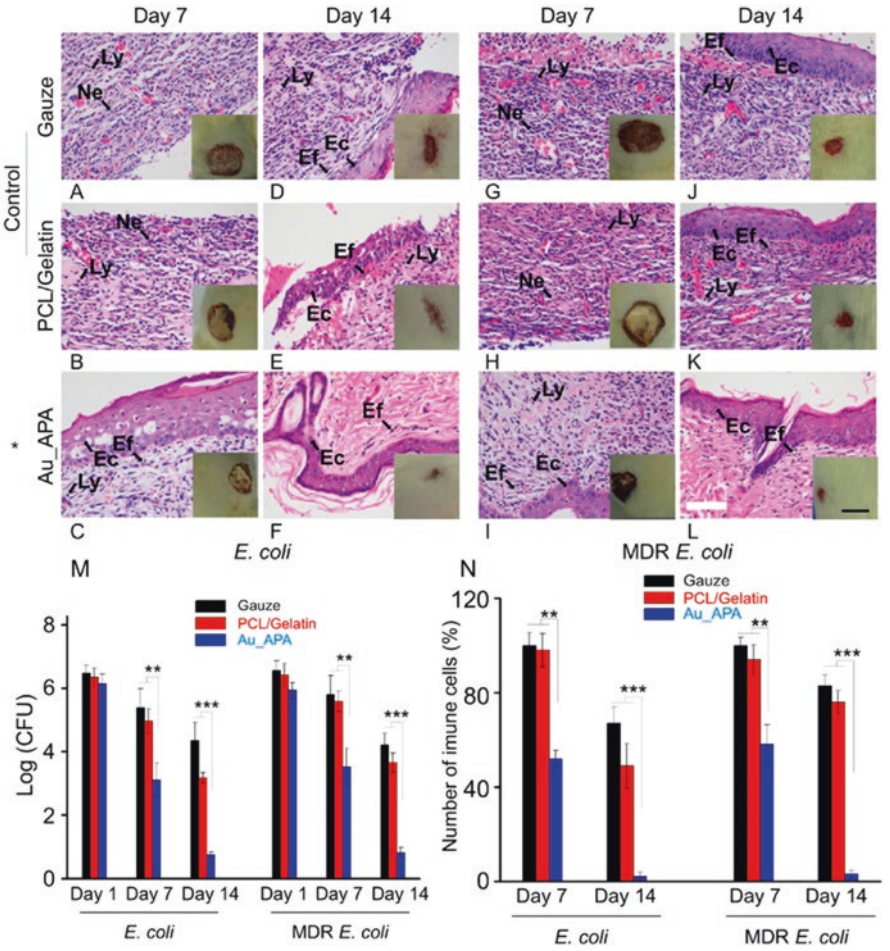

Fig. 5 Animal models of wounds infected with *E. coli* or MDR *E. coli*. Histological images of skin tissues stained by H&E dissected on postoperative day 7 (**a**–**c**, **g**–**i**) and day 14 (**d**–**f**, **j**–**l**). (**m**) Local bacteria count in the wound area and (**n**) relative number of immune cells compared with control group (gauze). Inserted photos show the macroscopic morphologies of wounds. The control groups were treated with wound dressings of gauze (**a**, **d**, **g**, **j**), and PCL/gelatin nanofibers (**b**, **e**, **h**, **k**), and the experimental group was treated with Au-APA electrospun nanofibers as wound dressings (**c**, **f**, **i**, **l**). The presence of Ly and Ne indicates an inflammatory response. Ec and Ef signal reepithelization, and are beneficial for the formation of matured fibrous granulation tissue; ** and *** represent two levels of significant statistical differences (**$P < 0.05$, ***$P < 0.01$). White and black scale bars are 100 μm and 1 cm, respectively (*Ly* lymphocyte, *Ne* neutrophil, *Ec* epithelial cells, *Ef* elongated fibroblasts). (Reproduced from Li et al. (2017) with permission)

wound healing in comparison with Tegaderm (a commercially available wound dressing containing chlorhexidine gluconate) by promoting wound epithelialization and hemostasis (Hsu et al. 2011). In another study, Au NP-embedded collagen scaffolds (AuNPs-SCs) were designed as a skin substitute with good biocompatibility, high

mechanical strength, reduced hydrolytic activity, and stability against enzymatic degradation. AuNP-SCs improved granulation tissue generation, inhibited inflammation, and induced angiogenesis in order to rapidly heal wounds (Akturk et al. 2016).

Several works based on antibiotic-loaded Au NPs have been developed as potent antimicrobial agents (Zhao and Jiang 2013). However, these works showed only in vitro antimicrobial efficacy against bacteria, with none of them having yet been tested in vivo infection models for clinical efficacy. In one report, it was showed that when gentamicin-loaded Au NPs were administered intravenously in mice having intramuscular infections of *S. aureus* in the thigh, most of the NPs were accumulated in the kidneys and blood, with a small amount in the infected thigh but more than in a normal thigh within 60 min postinjection. However, the antimicrobial efficacy and the selectivity of the Au NPs between normal and infected thighs were not studied (Ahangari et al. 2013).

7.2.2 Antimicrobial Peptide-Conjugated Gold Nanoparticles

Several formulations of AMPs conjugated to inorganic NPs have been recently proposed for wound-healing and infection treatments. We have developed a one-step methodology to generate small, homogenous Cecropin-Melittin (CM)-conjugated Au NPs with high loading of the peptide. CM-SH-conjugated Au NPs demonstrated potent antimicrobial activity against both Gram-positive and Gram-negative bacteria in human serum, and in the presence of high concentrations of proteolytic enzymes, than soluble CM-SH, as well as low cytotoxicity to human endothelial and fibroblast cells (Rai et al. 2016). Moreover, CM-SH-conjugated Au NPs demonstrated high antimicrobial activity in chronic wound and systemic infection models. Using the same strategy, Comune et al. immobilized LL37 on Au NPs and demonstrated higher wound-healing properties in comparison to soluble LL37 in both in vitro and in vivo models (Fig. 6) (Comune et al. 2017). The LL37-Au NPs showed antimicrobial activity against *E. coli* and high promigratory activity and low cytotoxicity toward keratinocytes. The LL37-Au NP formulation developed in this work may have great potential to treat chronic wounds, which are often infected by bacteria (Comune et al. 2017). Importantly, the developed nanoformulation is effective in treating wound healing at multiple stages, such as fighting bacterial infection and inducing the migration of keratinocytes to facilitate re-epithelialization in wound with superior efficacy and lower cytotoxicity than LL37 peptide alone.

In another study, the frog skin AMP, esculentin-1a (Esc), chemically conjugated to Au NPs via a PEG linker showed remarkably improved antibacterial activity when compared to the activity exhibited by the same concentration of the free peptide (Casciaro et al. 2017). The developed nanoformulation showed potent anti-Pseudomonal activity of the membrane-active Esc (1-21) approximately 15-fold without keratinocyte toxicity and increased the peptide's re-epithelialization activity on the keratinocyte monolayer (Table 3). These findings make NP attractive candidates for the topical treatment of skin infections. Additionally, Chen et al. prepared gold nanodots (Au-NDs) conjugated with surfactin (SFT; an AMP) and 1-dodecanethiol (Chen et al. 2015). SFT-conjugated

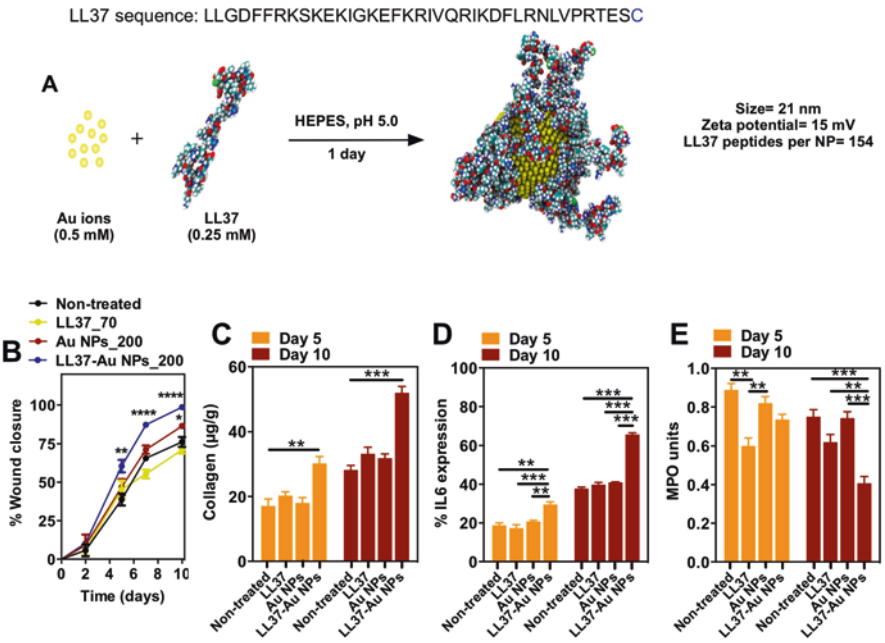

Fig. 6 (**a**) Schematic representation of the synthesis process of LL37-conjugated Au NPs. (**b**) Wound closure in wounds treated with vehicle (0.9% NaCl), LL37 peptide (70 µg per wound), Au NPs (200 µg per wound), or LL37-Au NPs (200 µg per wound). The formulations were administered intradermally at several sites around the wound. Ten animals (therefore 20 wounds) were used per each group. Wound areas were quantified by a high-definition camera. Results are average ± SEM, $n = 20$. (**c**) Quantification of collagen at days 5 and 10 by a sircol assay. Results are average ± SEM, $n = 10$. (**d**) Quantification of IL6 by qRT-PCR at days 5 and 10. Results are average ± SEM, $n = 10$. (**e**) Quantification of myeloperoxidase (MPO) activity at days 5 and 10. Results are average ± SEM, $n = 10$. (Reproduced from Rai et al. (2016) with permission)

Au-NDs showed more pronounced antimicrobial activity against MDR bacteria, and lower cytotoxicity and hemolysis when compared to SFT alone. In vivo MRSA infection studies showed faster healing, improved re-epithelialization, and the efficient collagen fiber production for the SFT-loaded Au-NDs incorporated in a dressing material (Chen et al. 2015).

7.2.3 Silver Nanoparticles

Silver (Ag) has been considered as an antimicrobial material for preventing bacterial infections since ancient times. Clinicians have used Ag, SSD and silver nitrate ($AgNO_3$) for the treatment of the burn wound, dental caries, and bacterial infections. In the last few decades, silver in form of NPs (Ag NPs) has been reported to be effective against several microorganisms such as bacteria, fungi, and yeast. The potent antimicrobial activity of Ag NPs is believed to be due to the release of Ag ions in acidic conditions. It is believed that Ag ions interact electrostatically with the microbial membrane, leading to accumulation on the membrane, loss of intracellular potassium ions, collapse of

Table 3 Antimicrobial NPs

NPs composition	Encapsulated molecules	Target bacteria	Therapeutic activity
CS	Temporin B	*S. epidermidis*	Long-lasting antimicrobial activity, reduced cytotoxicity (Piras et al. 2015)
PLGA	Plectasin	*S. aureus*	High encapsulation efficiency, prolonged release of AMPs over 24 h (Water et al. 2015)
PLGA	LL37	*E. coli*	Synergetic effect to of antimicrobial activity and wound closure (Chereddy et al. 2014)
PG	Nisin	*L. monocytogenes*	Prolonged antimicrobial efficacy, long-term stability (Bi et al. 2011)
Au	CM	Gram-negative and Gram-positive bacteria	High antimicrobial activity and stability in a systemic infection model (Rai et al. 2016)
Au	LL37	*E. coli*	Antimicrobial activity, prolonged cell migration, and in vivo rapid wound closure (Comune et al. 2017)
Au	Esculentin-1a	*P. aeruginosa*	In vitro higher antimicrobial activity and wound healing (Casciaro et al. 2017)
Ag	LL37	*P. aeruginosa*	Antimicrobial and antibiofilm activity (Vignoni et al. 2014)

Abbreviations: *CS* chitosan, *PLGA* poly lactic-co-glycolic acid, *PG* phosphatidylglycerol, *Au* gold, *CM* Cecropin–Melittin, *Ag* silver

the proton motive force, and a decrease in intracellular ATP levels, resulting in bacterial death (Lok et al. 2006). There are several research papers and commercial products (Acticoat® from Smith & Nephew; Aquacel® from Convatec and 3 M Ag mesh from Tegaderm® dressings) available based on wound dressings containing Ag NPs for the treatment of infections in normal and burn wounds (Mofazzal Jahromi et al. 2018; Parani et al. 2016). Recently, alkylated ε-polylysine-capped Ag NPs were synthesized, and used to target bacteria by enhanced multivalent/polyvalent interactions between polylysine and lipopolysaccharide moieties, but showed no cytotoxicity against fibroblasts. Ag nanocomposite-treated wounds had an abundance of pro-inflammatory cells, such as macrophages and $CD3^+$ T lymphocytes, thus helping to control infections and fuel immune responses in order to promote wound healing (Dai et al. 2016). In another approach, Ag NPs synthesized using deoxidizer egg white were mixed with konjac/glucomannan to prepare a composite sponge by freeze-drying. The composite Ag sponge exhibited an excellent antimicrobial activity due to the presence of Ag NPs. The sponge effectively enhanced wound-healing performance within 14 days, owing to its water adsorption properties, which helps to maintain a moist wound environment, and its suitable mechanical strength, which promotes the migration of cells in the wounds (Chen et al. 2018). Beside gold, LL37 peptides have been conjugated to Ag NPs to provide synergetic antimicrobial against *P. aeruginosa*, and have antibiofilm formation activity (Table 3) (Vignoni et al. 2014). Ag NPs functionalized with Polymyxin B peptide showed potent antibacterial activity against MDR *Vibrio fluvialis* and nosocomial

P. aeruginosa. The results of antibacterial assays and live-dead staining showed the peptide-conjugated Ag NPs to display ~threefold higher antimicrobial effects than citrate-capped NPs, due to damage of bacterial membranes. Furthermore, the peptide-conjugated Ag NPs inhibited the biofilm formation and efficiently removed endotoxin (Lambadi et al. 2015).

Ag-related products could cause permanent pigmentation in the skin (argyria) and may induce toxic effects in the kidney and liver, as well as irritation in eyes, skin, and respiratory tract (Drake and Hazelwood 2005). However, Ag NPs are considered to be less toxic than Ag ions, though some reports have shown adverse effects on the mitochondrial activity of cells, and induction of Ag resistance in bacteria, and therefore aggregative clinical use of Ag-based products must be done with caution (Parani et al. 2016; Hussain et al. 2005).

Table 3 summarizes various biodegradable and nondegradable NPs conjugated with AMPs.

8 Future Prospective and Conclusion

Microbial infections, coupled with the emergence of antimicrobial resistance, pose highly complex problems to healthcare systems. The high susceptibility to microbial infections during illness, in addition to the need to achieve rapid and satisfactory treatments, demands the discovery of innovative biomedical technologies. Although topical and intravenous administrations of antimicrobial agents are the most common clinical practice, alternative approaches, including targeted NPs, AMPs, antimicrobial phototherapy, therapeutic microorganisms, and immune-based antimicrobial molecules have also been explored. A range of sophisticated NPs has been developed to control infections and simultaneously promote healing. However, in the future, it is expected that multicomponent and multifunctional NPs will be developed that can deliver drugs on demand. Another challenging task in this area is to target bacteria residing in non-phagocyte cells localized outside the RES using smart NPs loaded with antimicrobial agents. For example, *Salmonella, S. aureus, B. besnlae, chlamydia, L. monocytogenes*, and others mostly accumulate in non-phagocytic cells, such as fibroblast, endothelial, hepatocyte, and enterocyte cells. One possible approach to improve the internalization of antimicrobial NPs within these non-phagocytic cells is to increase the circulation lifetime of NPs by decreasing RES uptake in order to achieve maximum accumulation at infection foci by enhanced retention effects and permeation. Modification of the surface of antimicrobial NPs with specific ligands can also improve the active targeting of infection sites. The most critical issues with NPs are stability during storage, and during their transport from the administration site to the infection site, as well as drug inactivation and premature release. To address these issues, covalent conjugation of drugs and targeted ligands within the same NPs should be explored to reach the infection loci. To tackle notorious MDR infections in wounds, innovative NPs must be developed that not only penetrate and damage the biofilms, but also deliver antimicrobial agents and drugs to

effectively kill MDR bacteria and heal wounds respectively. In the future, smart nanomaterials combined with biotechnologically related advances, such as gene-editing techniques, including CRISPR-Cas systems, will be key players in treating several infectious diseases by suppressing MDR pathogens.

Given the immense research efforts that are currently being invested in developing nanotechnology-based therapies for the treatment of bacterial infections, future progresses in multifunctional and smart antimicrobial nanomaterials are expected to be achieved in the next few years. Importantly, scientific knowledge on the long-term toxicity profile of antimicrobial NPs is desired in order to ensure their successful clinical applications.

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