Chapter 3
Nanomaterial-Mediated Delivery of Antimicrobial Agents: 'The Nanocarriers'

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Abstract Antimicrobial resistance (AMR) emergence has entangled the cure of health-related diseases with the existing medicines. Though several potent and novel antimicrobial agents have been identified in recent past, their safe and effective delivery is yet to be achieved fully. Nanotechnology has emerged as the continual and practical solution in the delivery of antimicrobial therapeutics using nanotechnology-based drug carriers (nanocarriers) and signifies the correlation between biological and physical sciences, by employing it in the variety of branches like nanomedicines and nanomaterial-based drug delivery approaches. Owing to their tiny size and large surface area, nanocarrier is the hotspot in the nanotechnology world. In the recent reports, biocompatibility, cost-effectiveness, controlled drug release, deep penetration, target specificity and sustainability of nanocarriers have revealed their ideal role in the drug delivery system. In this chapter, we discuss about the various nanomaterials and antimicrobial agents employed in the delivery of antimicrobials such as metals, peptides, drugs and plant resources to target drug

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determinants such as efflux pumps, cell membrane permeability, biofilms and quorum sensing in the drug-resistant bacteria with their applications in the clinical trials.

Keywords Antimicrobial resistance · Nanocarriers · Antimicrobial agents · Biosafety · Efficacy

3.1 Introduction

Since earlier civilizations, natural products have been widely employed as potent therapeutics against numerous ailments. Based on historical learning, modern medications are thus mostly developed from medicinal plant resources (Veeresham 2012). Natural substances exhibiting various molecular backgrounds provide a starting point for the development of new medications. Various approaches such as natural product-based drug development and drug delivery have been developed to cure enormous diseases caused by drug-resistant bacteria (Atanasov et al. 2021). However, incompatibility issues, availability restrictions and tedious purification techniques (Siddiqui et al. 2014) somewhat restrict their full potential therapeutic usages, and thus newer technologies are required to address these and other issues for the development of efficient drug/antimicrobial delivery systems. Nanotechnology has been demonstrated to bridge the gap between the physical and the biological sciences by employing nanomaterials in a variety of sectors, including nanomedicines and nanomaterial-based drug delivery approaches (Patra et al. 2018). Employing nanocarriers as an effective drug delivery system has lately gotten a lot of press because of their capacity to identify and cure diseases caused by drug-resistant bacteria (Yeh et al. 2020).

Antimicrobial resistance (AMR) or antibiotic resistance (ABR) is a condition where microbes or bacteria show resistance against commonly used antimicrobial drugs, especially antibiotics. The AMR has become a major public health threat making it challenging to cure health-related diseases with existing medicines (Lee et al. 2019b). The World Health Organization (WHO) has recognized AMR and multidrug-resistant (MDR) bacteria as major global public health threats humanity is facing (WHO 2021) owing to their colonizing abilities both domestically and globally (Hall et al. 2020), though there are several successful attempts of identifying potent and novel antimicrobial agents in recent years. However, effective and safe delivery of potent antimicrobial agents has emerged a major hurdle. The use of nanomaterial- and nanotechnology-based drug carriers (nanocarriers) that can carry nano- or other antimicrobial therapeutics is emerging as a sustainable and practical solution (Krishnamoorthi et al. 2021). These approaches use nanoscale materials for the delivery of antimicrobials including natural products to their target tissues (Yeh et al. 2020). Various antimicrobial agents including metals, peptides, drugs and plant resources possessing different inhibitory mechanisms have been owned in

nanocarriers. Nanocarriers or nanomaterial-based antimicrobial systems in MDR microorganisms have been shown to inhibit various drug resistance determinants such as efflux pumps (EPs), cell membrane, biofilms and quorum sensing (Baptista et al. 2018) showing their potential clinical applications.

In this chapter, we discuss the nanomaterials emerging as a nanocarrier for delivering wide-ranging antimicrobial agents. We describe the various types of nanomaterials and antimicrobial agents with their inhibitory mechanisms that act as the major components in the delivery of antimicrobials such as drugs, metals, peptides and plant resources. Further, we highlight the delivery of antimicrobial agents via nanomaterials to target the major bacterial drug resistance determinants (cell membrane, EPs, quorum sensing, biofilm formation). The potential applications of nanocarriers in clinical trials have been also discussed herein.

3.2 Nanocarriers as Emerging Drug Delivery Systems

The significance of nanocarriers as drug delivery systems was discovered around a century ago for the delivery of therapeutic drugs and other natural agents to the site of microbial infections (Patra et al. 2018). Nanocarriers are defined as the nanoparticles that can be employed to carry antimicrobial agents or other chemical agents to the target location for their effective treatment of infections caused by the pathogenic microbes including drug-resistant bacteria (Chamundeeswari et al. 2019). Nanocarriers mainly consist of many small-sized nanoparticles (1–100 nm range) such as nanomaterials, dendrimers, lipid-based nanoparticles and liposomes that effectively transport the antimicrobial agents to the target tissue (Lombardo et al. 2019). The property of enhanced stability, improved drug serum solubility, pharmacokinetics, sustainability, longer systemic circulation duration and reduced toxicity make them excellent choice as drug delivery systems (Zhang et al. 2010). Further, deep penetration abilities of nanomaterials into the host cells, controlled drug release and endocytosis for treating drug-resistant pathogens make them ideal drug carriers with their potential clinical applications against wide range of infectious diseases (Fatima et al. 2021). To enhance the pharmacokinetics and therapeutic effects of drugs, antimicrobial agents are loaded into nanomaterials via adsorption, chemical conjugation and physical encapsulation (Patra et al. 2018).

Nanocarriers are designed in a wide range of materials with different chemical compositions to transport diverse bioactive compounds in a regulated, systemic and targeted manner, making them highly effective drug delivery agents (Manju and Sreenivasan 2010). Various nanomaterials such as metal, non-metals, semiconductors, quantum dots, dendrimers, biopolymers and organic and inorganic nanomaterials have been successfully used as nanocarriers in medical applications. Interestingly, the organic nanomaterials including liposomes, ferritin and micelles have been reported to enhance the drug bioavailability and thus improved antimicrobial activity (Yetisgin et al. 2020). Besides, other metallic and non-metallic nanomaterials combined with drugs and other antimicrobial agents have also been

widely used for the drug delivery applications (Mba and Nweze 2021). Recently, nanostructured lipid-based carriers (NLCs) have emerged as novel drug delivery systems for the delivery of chemotherapeutic agents because of their excellent physical stability, good drug-loading capacity and biocompatibility (Haider et al. 2020). The development of amoxicillin- and clarithromycin-loaded magnetic nanostructure lipid-based carriers (AMO-CLR-Fe_3O_4@NLCs) with enhanced and prolonged drug delivery with 3.13 μg/mL minimum inhibitory concentration (MIC) value against *Staphylococcus aureus*, *Bacillus subtilis* and *Bordetella pertussis* resulted in deterioration of bacterial cell morphology and ultimately led to cell death (Sharaf et al. 2021). Nano-drug carriers are also being explored in diagnosis and treatment of brain infections (Barani et al. 2021). *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Neisseria meningitidis*, *Haemophilus influenza* and *Listeria monocytogenes* are found to invade the brain causing bacterial infections in the endothelial barrier and inflammation in meninges called meningitis (Al-Obaidi and Desa 2018). The intranasal route for delivering the drugs to the brain for overcoming the blood-brain barrier and central nervous system (CNS) is considered the most viable method. The nanocarriers for drug delivery are transferred to the brain via receptor-mediated transcytosis (Sharma et al. 2021). In vivo and in vitro studies on levofloxacin-/doxycycline-loaded solid lipid nanoparticles against bacterial meningitis (Abdel Hady et al. 2020), gentamicin-loaded polymeric nanoparticles against *Pseudomonas aeruginosa* (Abdelghany et al. 2012), ansamycin-loaded polymeric nanomaterials (Nair et al. 2020b) and ofloxacin-loaded nano-transfersomes against bacterial meningitis (Eid et al. 2019), recombinant protein OmpAVac-loaded chitosan-modified poly(lactic-co-glycolic acid) (PLGA) nanoparticles against *E. coli* K1 in neonatal meningitis-infected mice (Zhang et al. 2021) and bacitracin A and brain-targeting peptide (BTP)-loaded polymeric nanoparticles against *Pneumococcal* meningitis (Hong et al. 2018) have been investigated as drug delivery systems for their biocompatibility, controlled drug release and longer systemic circulation duration for treating brain bacterial infections.

Considering the phototoxicity and low tissue penetration, light-responsive nanomaterials are emerging with potential drug design and light-triggered controlled drug delivery systems mostly useful in photothermal therapy (PTT) and photodynamic therapy (PDT) (Zhao et al. 2019; Tang and Wang 2021). Liu et al. (2021a) developed rough carbon-iron oxide nanohybrids (RCF) for near-infrared (NIR) synergistic antibacterial therapy, resulting in increased RCF bacterial adhesion and PTT in methicillin-resistant *Staphylococcus aureus* (MRSA), proposing a facile strategy to construct antibacterial agents for designing drugs and medical applications. Further in vivo studies in MRSA rat wound models showed enhanced synergistic antibacterial effects revealing their potential role in treating drug-resistant bacterial infections (Liu et al. 2021b). Wang et al. (2018) developed *Staphylococcus aureus*-pre-treated macrophage-membrane-coated gold nanocage (Sa-M-GSNC) drug delivery system, where macrophage membrane receptors were used to achieve specific bacterial-targeted delivery under near-infrared (NIR) laser irradiation in infected mice, and this resulted in better bacterial adherence, effective delivery and retaining in infection site with prolonged blood circulation and system

biocompatibility. Other than light-responsive nanomaterials, some of the alternative strategies such as pH-responsive nanomaterials, enzyme-responsive nanomaterials and redox-responsive nanomaterials are also used as drug delivery systems (Devnarain et al. 2021). Hassan et al. (2020) developed novel chitosan-based pH-responsive lipid polymer hybrid nanovesicles (OLA-LPHVs) as a vancomycin delivery system against MRSA biofilms leading to the easy release of vancomycin at pH 6.0 and inhibition of biofilms via damaging bacterial cell membrane and showing their potentials in treating bacterial infections. Enzyme-responsive nanogels developed from alginate/peptide ciprofloxacin conjugates with enhanced stability in dispersion and aqueous environment resulted in enzyme-triggered release of ciprofloxacin by degrading the peptide linkers against *S. aureus* (Bourgat et al. 2021). Similarly, Salamatipour et al. (2019) synthesized light-reduction-/oxidation-responsive alginate nano-hydrogels loaded with the folic acid drug by reverse emulsification-diffusion method and improved water retention capacity (WRC) under UV light that resulted in antibacterial activity against *S. aureus* and *E. coli*.

3.3 Types of Nanocarriers

3.3.1 Metal-Based

Metal nanoparticles usually have non-specific broad-spectrum bacterial toxicity mechanisms where they bind to outer membrane receptors (Yuan et al. 2018) that enhance their potencies. Metal-based nanoparticles have shown their efficacy in both Gram-positive and Gram-negative bacteria with multiple biomolecule target involved in the development of resistant strains (Slavin et al. 2017).

3.3.1.1 Silver Nanoparticles (AgNPs)

Chemical methods in the production of AgNPs include three components: a metal precursor, a reducing agent and a stabilizing agent (Singh et al. 2015). Appropriate size, shape and polydispersity of AgNPs can be achieved by monitoring experimental parameters such as precursors used in the reaction, reducing agents, reagent concentration, pH and temperature in the nucleation step during the synthesis process (Solomon et al. 2007; Dakal et al. 2016; Kumar et al. 2018b). Stabilization being the critical stage, chitosan, amine derivatives, thiols and gluconic acid have been recently used as stabilizers with polymeric compounds proven advantageous (Solomon et al. 2007). Beta-D glucose as the reducing agent has emerged as with special interest of researchers for the reduction of $AgNO_3$ and green synthesis giving $AgNO_3$ up to 10 nm mean size (Kumar et al. 2018b). Pal et al. (2019) studied antimicrobial peptide (AMP)-AgNP against MDR bacteria strains (*Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Salmonella typhi*) using combinations of AY1

(CAY1-AgNP and AY1C-AgNP) showing increased stability and antimicrobial activity. Recent investigations on tragacanth gum, N-isopropyl acrylamide and 2-(vinyloxy) ethanol-based stimuli-responsive silver nanocomposites (TGIAVE-Ag) resulted in controlled release of 5-fluorouracil against MDR bacteria (Nagaraja et al. 2021). Similarly, selective delivery of AgNP-responsive microparticles incorporated into dissolving microneedles against *Staphylococcus aureus* and *Pseudomonas aeruginosa* biofilms resulted in controlled release of AgNPs and eradication of biofilms with improved antibiofilm activities in ex vivo biofilm-infected rat skin model (Permana et al. 2021).

3.3.1.2 Gold Nanoparticles (AuNPs)

Gold nanoparticles are colloidal particles consisting of gold as a core substance with good biocompatible property. The synthetic versatility of these NPs allows them to control particle solubility, stability and interaction with the environment. Further, studies on gold nanospheres conjugated with gentamicin have shown great activity against *S. aureus* than gentamicin alone (Ahangari et al. 2013). Reduction of chloroauric acid followed by agglomeration in the presence of the stabilizing agent is the basic synthesis process of all chemical, biological and physical pathways (Newman and Blanchard 2006). Pathogen-specific antibodies or photosensitizing molecules for photothermal and PDT conjugated with AuNPs have also been proven to promote antimicrobial activity (Savas et al. 2018; ElZorkany et al. 2019). Flavonoid-coated AuNPs with enhanced antibacterial effects of chrysin, kaempferol and quercetin against Gram-negative *E. coli* bacteria resulted in bacterial cell membrane penetration and their ablation, hence making them good drug delivery candidates (Alhadrami et al. 2021). Similar to this, *Punica granatum* extract delivering chitosan-gold hybrid nanoparticles (CS-AuNPs) exhibited high synergistic effects against MRSA (Hussein et al. 2021).

3.3.1.3 Ceramic Nanoparticles

Ceramic nanoparticles constitute oxides, carbides, phosphates and carbonates of metals and metalloids such as calcium, titanium, silicon, etc. The favourable property of heat resistance and chemical inertness makes them suitable for their wide variety of applications in medicine where they are structured by heat and pressure (comprising of solid core and a combination of metal/non-metal, at least two non-metallic elemental solids, at least one metal and a non-metallic elemental solid or a non-metal) (Wu and Zreiqat 2010). Depending upon architectural differences, they are further categorized into ceramic nanoparticles, ceramic nano-scaffold and nano-clay and are made up of ceramic compounds such as silica-titania and alumina (Rawat et al. 2008). Nano-scaffolds are defined as a structure that allows interactions of cells and extracellular matrices with microporosity (pore size >50 nm), whereas nano-clay resembles thin layers having a thickness of few nanometres.

These ceramic nanoparticles can be synthesized with microemulsion preparation, hydrothermal synthesis, sol-gel process, aerogel method, pechini-citrate gel method and low-temperature combustion (LCS) methods (Singh et al. 2016). In a recent study on biphasic calcium phosphate (BCP), a biocompatible and non-immune-responsive biphasic ceramic was used to synthesize silver-doped BCP/alginate (AgBA) microcluster stating their inhibitory action on *S. aureus* and *E. coli* (Nie et al. 2021). In one of the studies, the in vitro release profile of vancomycin-loaded hydroxyapatite compared with the pure vancomycin-HCl with increased antibiotic-loaded hydroxyapatite release rate and antibacterial activity (zone of inhibition 11.5 ± 0.5 mm and 15 ± 0.4 mm) in *S. aureus* and *E. coli*, respectively, when compared to antibiotic alone (Ain et al. 2020). Similarly, zirconia nanoparticle green synthesized using *L. nobilis* were found to be more effective against Gram-negative pathogenic bacteria (Chau et al. 2021). Chauhan (2021) reviewed the distinctive benefits of ceramic-based hybrid nanoparticle as a drug delivering system.

3.3.1.4 Silica Nanoparticles

Because of large surface area, ease of functionalization and biocompatibility, silica nanoparticles are commonly used in drug delivery applications. The mesoporous silica nanoparticles (MSN) are the porous variant that confers amenities and have been recently demonstrated as a powerful drug delivery tool for combating bacterial infections (Şen et al. 2018; Martínez-Carmona et al. 2018; Bernardos et al. 2019; Selvarajan et al. 2020). Synthesis of silica nanoparticles is carried out by Stober's method (Stober et al. 1968) and the microdilution method. Modifications in Stober's process have been performed to suit user-specific requirements such as usage of low-cost precursor (sodium silicate solution instead of tetraethyl orthosilicate) (Zulfiqar et al. 2016a, b). Another method, the microdilution, involves the formation of oil-in-water (O/W) micelles and water-in-oil (W/O) reverse micelles (Arturo Lopez-Quintelá 2003) stabilized using surfactants (twins or pluronics) acting as nanoreactors to synthesize nanoparticles depending upon the nanoreactor volume (Selvarajan et al. 2020). As peptides can be loaded using silica, Kwon and his team used the tandem peptide cargo made of lactoferrin and a synthetic bacterial toxin $_{D}$ $[KLAKLAK]_2$ for treating *Pseudomonas aeruginosa* infection in lungs (Kwon et al. 2017). Stewart et al. (2018) reported a lower drug release rate for a longer period compared to the initial burst release of the conventional drug formulation using co-assembly of an antimicrobial drug (octenidine dihydrochloride, OCT) and silica with the loading efficacy of 35%. Similarly, a nanoantibiotic system made of MSN loaded with levofloxacin (LEVO) was designed with anti-biofilm activity against *S. aureus* resulting in cell destruction (Pedraza et al. 2018). Further, effective penetration of LEVO-loaded MSN grafted with poly(propyleneimine) dendrimer of third generation (G3) in the cellular membrane of *E. coli* was reported with excellent anti-biofilm activity (González et al. 2018).

3.3.2 Liposome-Based

Liposomes are composed of lipids. Due to their similar structure and composition of the cell membrane, they are used for bacterial cell targeting that can carry both hydrophobic and hydrophilic antimicrobials and thus offering a wider choice of antimicrobial candidates to be loaded. Liposomes show fusogenicity property as they have a phospholipid bilayer structure which upon fusion with antimicrobials is directly available inside a bacterium. The most important factor of liposomes in in vivo investigations is the diameter, so to avoid rejection of liposomes by the reticuloendothelial system and allowing penetration through water channels in infectious biofilms, they should preferentially have a diameter in the range of 100–200 nm (Ferreira et al. 2021). Realization of biofilm targeting from the blood circulation, penetration and accumulation over the entire thickness of an infectious biofilm, associated with deep killing in the biofilm, are some of the challenges in the development of liposomal antimicrobial nanocarriers (Wang et al. 2020). Sanches et al. (2021) demonstrated the potential use of rhamnolipid-based liposomes as nanocarriers against *E. coli* and *S. aureus* with high haemolytic activity and negligible cytotoxicity (highest concentration of 1.3 mmol L^{-1}) to HepG2 cells. Liposomes have also been identified as one of the major antimicrobial agent (meropenem, PEG, triclosan, benzyl penicillin, zinc citrate) delivery systems for treating bacterial biofilm-mediated infections (Wang 2021).

3.3.3 Quantum Dots (QDs)

The ultra-small size semiconductor nanocrystals, with the average size in the range of 1.5–10 nm, are defined as the quantum dots and are synthesized from group II–VI elements in the periodic table depending on their conductive properties and high surface to volume ratios. Due to their unique physical and chemical properties of QDs such as high stability, exceptionally narrow range of emission and high quantum yield, they are used in biosensors, real-tracking, multipolar labelling and imaging (Jahangir et al. 2019; Wang et al. 2019). Polymer-functionalized QDs give QD a promising feature with higher antibacterial activity. Based on structural dimensions (spherical, pentagonal and hexagonal) and size, QDs can be tuned with the ligands and polymer, and thus modified GQDs facilitate the attachment of GQDs to bacterial membrane. For example, PEGylated GQDs exhibited 100% growth inhibition for *S. aureus* and *P. aeruginosa* following 8 h of incubation (Habiba et al. 2015). Reports on antibiotics conjugated with QDs (ceftriaxone conjugated to CdTe QDs) with increased antibiotic efficiency have demonstrated the synergistic antimicrobial effect against *E. coli* (Luo et al. 2011). Recently, gentamicin (GEN)-loaded mesoporous silica nanoparticle sealed with acid-decomposable 3-mercaptopropionic acid capped-ZnS QDs (MPA-ZnS QDs) resulted in controlled release of GEN drug against *E. coli* (strain 0157:H7) and *S. aureus* (strain ATCC:25923) (Mandani et al. 2021).

3.3.4 Biopolymeric Nanomaterials

Polymers derived from living organisms are said to be biopolymers and are made up of several monomeric units forming macromolecular polymer structures with covalent bonds. Rational selection of biopolymers is the most important challenge in controlled drug delivery systems which necessitate a comprehensive understanding of surface and bulk characteristics of biopolymers to achieve optimum therapeutic efficacy. Chitosan (CS) is the most common linear polysaccharide derived from naturally occurring chitin and is mainly extracted from crustacean shellfish and certain fungi. Chemically, it consists of N-acetylglucosamine and glucosamine joining together with the beta-1-4 linkage, giving a positive charge under acidic pH (Kumar 2000; Rinaudo 2006). Chitosan is often chemically modified at amino or hydroxyl groups to make them more effective and widen their medical applications (Rabea et al. 2003; Verlee et al. 2017; Sahariah and Másson 2017). Antimicrobial chitosan is prepared mainly via quaternarization and carboxylation to improve its solubility and antimicrobial activity with the maintenance of its biodegradability and biosafety. Essential oils such as rosemary essential oil when nanoencapsulated on chitosan/polyglutamic acid nanoparticles resulted in a significant increase of the antibacterial activity against *B. subtilis* (Lee et al. 2019a). Bacterial cellulose combined with ZnO-NPs was analysed for the healing property (Mihai et al. 2019).

3.3.5 Dendrimers

Dendrimers are synthetic polymers with a large number of exposed anionic, neutral or cationic functionalities on the surfaces formed by the branched repeating units that emerge from a focal point (Lyu et al. 2019). Carbon, nitrogen and phosphorus as central atoms of dendrimer play an important role in determining the structure, branches and cavities (Elsabahy and Wooley 2012; Kulthe et al. 2012; Fox et al. 2018). Further, the structural specificity of dendrimers allows attachment of compounds and drug molecules to the outer surfaces of dendrimers with final inclusion inside the cavities, which helps in encapsulation and conjugation (Pandurangan et al. 2016; Kim et al. 2018).

Dendrimers can be used in combination with traditional drugs, besides their structures can be formulated based on the pharmacodynamics and pharmacokinetics of the drug (Authimoolam and Dziubla 2016). In an interesting study, poly(amidoamine) (PAMAM) dendrimers conjugated with fluoroquinolones (nadifloxacin and prulifloxacin) showed enhanced antimicrobial activity and water solubility (Kuwahara et al. 2005; Cheng et al. 2007). Further studies on nanodendrimers conjugated with erythromycin significantly showed delivery of erythromycin with four times lesser minimum inhibitory concentration (MBC) against *P. aeruginosa*, 2 times lower against *S. aureus* and 16 times lower against *S. epidermis* (Xue et al. 2013).

3.3.6 Photothermally Activated Nanomaterials (PANs)

PANs are the broad spectrum of nanoparticles that convert absorbed light into heat. Resonance oscillation of the surface electron (surface plasmon) or energy of band transition gives the thermal effect to the nanoparticles. These nanoparticles produce thermal relaxation which leads to temperature increase, and their effect depends on many factors such as irradiation intensity, wavelength, the concentration of nanoparticles and photothermal conversion efficacy (Borzenkov et al. 2019). In a recent study, a chitosan-based hydrogel with embedded gold nanorods under low-power diode laser irradiation showed antimicrobial activity against both Gram-positive and Gram-negative bacteria including MDR strains (Bermúdez-Jiménez et al. 2019). Another study on the photothermal effect of phospholipid-coated gold nanorods loaded into a poloxamer 407 hydrogel resulted delivery of poloxamer 407 in ≈4.5–5 log cycle reduction of *P. aeruginosa biofilm* (Al-Bakri and Mahmoud 2019).

3.3.7 Carbon-Based Nanomaterials

3.3.7.1 Graphene-Based Nanomaterials

Graphene is the thinnest two-dimensional crystal sheet of single-layer sp^2 carbon (Goenka et al. 2014). Graphene nanomaterials are comprised of graphene oxide (GO), reduced graphene oxide, single layer, bi-layer graphene and multilayer graphene. Graphene-based nanostructures have wide applications including antimicrobial coatings, cellular targeting, biosensor, wound dressings, etc. The antimicrobial activity of GO increases after the reduction of sheet area. As GO is also a semiconductor material, hence it can be utilized for catalytic disinfection once exposed to UV-visible irradiation. Functionalization of GO with antibiotics, metallic compounds, immunoglobulins, chemotherapeutics, metallic nano-compounds and other organic/inorganic functionalities such as amine and carboxyl is comparatively easy because of its chemically reactive oxygen groups (carboxylic acid, hydroxyl and epoxy groups) (Sun et al. 2018a; Zarafu et al. 2018). Sharp edges of GO make it capable of killing bacteria through direct contact interactions. This mechanism of killing bacteria is called ‘trapping’ and ‘nanoknife’ mechanisms. DNA aptamer-conjugated magnetic graphene oxide (Apt@MGO) for rapid eradication of MRSA superbugs via generation of heat and cell death (~78%) under NIR laser irradiation considering them as biocompatible and light-activated photothermal agent for efficient ablation of MRSA (Ocsoy et al. 2021). Antibacterial activity of three-dimensional porous self-assembled graphene-based composite and VA-laden RGO-nHA composite scaffold (VA@RGO-nHA) against *S. aureus* with controlled release of vancomycin was reported using the *S. aureus*-infected bone by Weng et al. (2017).

3.3.7.2 Carbon Nanotubes (CNTs)

The size and surface area of carbon nanotubes are inversely proportional to each other which enhances the cell damage and subsequent cell death (Wang et al. 2016; Costa et al. 2020). Functionalization and modification help CNTs to improve their biocompatibility and dispersibility and to optimize their antimicrobial property (Rebelo et al. 2016). Enhanced antimicrobial activity of multiwall layer CNTs (MWCNTs) has been observed when functionalized with amino acids such as lysine and arginine. Antimicrobial activity of antibiotic ciprofloxacin can also be improved when coated with the single-wall CNTs (SW-CNTs) resulting in increased bactericidal activities against *S. aureus* and *P. aeruginosa* by 16-fold and *E. coli* by 8-fold, compared to ciprofloxacin alone (Assali et al. 2017).

3.3.7.3 Fullerenes

Fullerenes are ball-shaped molecules, C60 being the most common fullerene. Amphiphilic fullerenes are widely used as drug nanocarriers because of their biocompatibility and cage-like structure (Tan et al. 2017). Fullerene has also being used in PDT to treat drug-resistant bacteria, for instance, against *P. aeruginosa* in the form of its derivatives like fulleropyrrolidinium salts and sulfobutyl fullerene (Hamblin 2016). Photochemical activity and antimicrobial activity of fullerenes as drug carriers upon exposure to light via ROS have been studied in Gram-positive bacteria such as *Streptococcus pyogenes* (Kazemzadeh and Mozafari 2019).

3.3.7.4 Carbon-Based Nanodots

Carbon nanomaterials, such as graphene quantum dots and carbon nanodots with zero-dimensional, are celled as carbon-based nanodots (Manisha et al. 2019). Carbon quantum dots are electrically conductive materials and hence can be used with various antimicrobial materials (Miao et al. 2015). Carbon nanodots synthesized via top-down or bottom-up approaches with a diameter <10 nm have been investigated for loading ciprofloxacin hydrochloride for their antimicrobial activity. These ciprofloxacin hydrochloride-loaded carbon nanodots exhibited enhanced antimicrobial activity against both Gram-positive and Gram-negative bacteria (Thakur et al. 2014). Recent reports on enhanced antimicrobial activity of CDs via green synthesis medicinal turmeric leaves (*Curcuma longa*) against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Klebsiella pneumoniae* resulted in effective delivery of phytochemicals and reactive oxygen species (ROS) production leading to cell death (Nair et al. 2020a; Saravanan et al. 2021).

3.3.7.5 Carbon Nitride Nanomaterials

Graphite C_3N_4 (g-C_3N_4) is a metal-free photocatalyst. A study on strong mesoporous g-C_3N_4 which were manufactured with the cyanimide as raw material and silica as a template showed good inactivation of *E. coli* under visible irradiation (Huang et al. 2014). Modification of graphite 'carbonitrides' with other antimicrobial agents such as aerobic conditions (caused by photocatalytic oxidative inactivation) and under anaerobic circumstances (caused by photocatalytic reductive inactivation), co-rapping of g-C3N4 and reduced graphene oxide sheets have been reported to destroy bacteria (Wang et al. 2013). Graphitized carbonitride (g-C3N4) nanosheets with embedded AgNPs improved the generation of photoelectrons and thus proved to be effective antibacterial agents (Bing et al. 2015).

3.4 Antimicrobial Agents and Their Inhibitory Mechanisms

Antimicrobial agents destroy bacteria by interfering with their bacterial growth/survival/reproduction mechanisms. Various antimicrobial agents such as antibiotics/drugs, AMPs, phytochemicals and metal-based nanomaterials are used as or in delivery systems to treat microbial infections (Patra et al. 2018). These antimicrobial agents show specific inhibition mechanisms against bacteria as illustrated in Fig. 3.1 and Table 3.1.

3.4.1 Antibiotics

Antibiotics represent the most common antimicrobial agents that exert their effects by targeting major bacterial mechanisms such as cell wall synthesis, DNA synthesis, protein synthesis, DNA damage and mRNA synthesis and can be classified into various groups based on the mode of action (bacteriostatic or bactericidal) and their origin, route of administration, range of action (broad-spectrum or narrow-spectrum) and chemical structure (Table 3.2). β-Lactam antibiotics are the bactericidal agents that contain β-lactam ring in their molecular structures and interrupt bacterial cell wall formation by binding covalently to penicillin-binding protein (PBP) enzyme involving the terminal step of peptidoglycan cross-linking in both Gram-positive and Gram-negative bacteria (Bush and Bradford 2016) and include penicillins, cephalosporins, carbapenems and monobactams. Penicillins further can be broadly classified into four different groups: natural penicillins, aminopenicillins, extended-spectrum penicillins and penicillinase stable penicillins. Cephalosporins like penicillins are β-lactam antibiotics developed from cephalosporin C (a natural product of *Cephalosporium acremonium*). Successive modification of cephem ring structure has led to the 'generations' of cephalosporin to be divided into first, second, third, fourth and fifth generations. Carbapenems are derivatives of thienamycin from

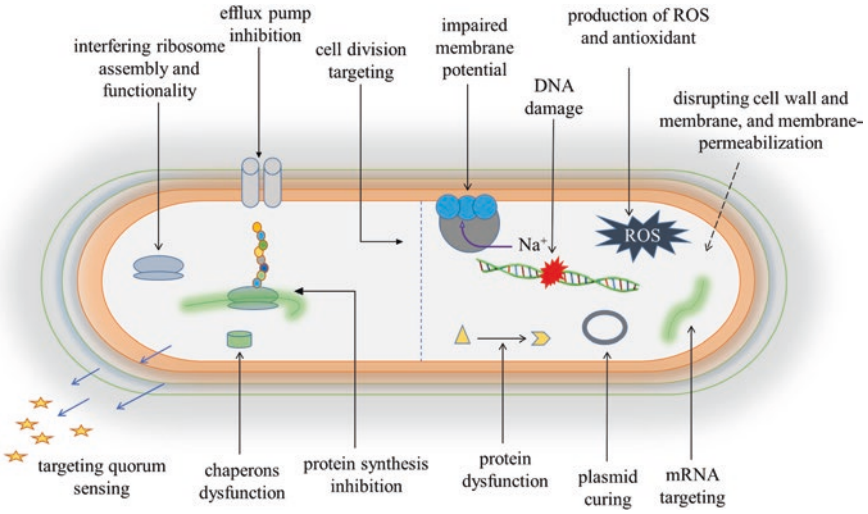

Fig. 3.1 Major mechanism of action displayed by antibiotics, AMPs, phytochemicals and metals

Streptomyces cattleya and differ from penicillins with replacement of sulphur by methylene group in a five-membered ring of β-lactams, further represented by meropenem, doripenem, ertapenem and imipenem. Monobactam is characterized by a non-fused β-lactam nucleus that differs from penicillins, cephalosporins and carbapenems including Aztreonam (Paris 2012). Aminoglycoside antibiotics are bactericidal agents structurally characterized by the presence of amino sugars attached to an aminocyclitol ring by glycosidic bond (Dasenaki and Thomaidis 2017) that include neomycin, amikacin, kanamycin, gentamicin and tobramycin (Shriram et al. 2018). Aminoglycosides inhibit protein synthesis in bacteria by irreversibly binding to the 30S ribosomal subunit, preventing the transfer of aminoacyl-tRNA to the peptidyl site, causing premature termination of the peptide chain and also increasing the frequency of mRNA misreading (Waller and Sampson 2018). Tetracyclines are usually considered as bacteriostatic antibiotics characterized chemically by a linear fused tetracyclic nucleus that inhibits bacterial protein synthesis by binding to 16S rRNA of 30S bacterial ribosomal subunit, arresting translation by interfering with the docking of incoming aminoacyl-transfer RNA (tRNA) at the acceptor site (A site) (Grossman 2016; Markley and Wencewicz 2018). Tetracycline antibiotics are broad spectrum in activity, spanning a wide range of Gram-positive and Gram-negative bacteria, obligate intracellular bacteria, protozoan parasites, chlamydia, mycoplasma, rickettsia and spirochetes and are represented by tetracycline, minocycline, demeclocycline and doxycycline. Streptogramins (pristinamycin, mikamycin, virginiamycin and quinupristin-dalfopristin) are composed of two structurally different components, A and B. A component (pristinamycin IIA, mikamycin A or dalfopristin, virginiamycin M) is polyunsaturated macrolactones, and B component (pristinamycin IB, mikamycin B or quinupristin, virginiamycin S) is a cyclic hexadepsipeptide (Schwarz et al. 2016).

Table 3.1 Different types of antimicrobial agents and their inhibitory mechanism of action against bacteria

Antimicrobial agent	Origin	Bacteria susceptible to the antimicrobial agent	Effective concentration of antimicrobial agent	Mechanism of antimicrobial action	References
Antimicrobial peptides					
1018 M	Mutant peptide of innate defence regulator (IDR-1018)	Methicillin-resistant *staphylococcus aureus* (MRSA)	32 μg/mL	Inhibition of biofilm formation, bacterial cell wall destruction, disruption of genomic DNA and regulation of the expression of ppGpp metabolism and biofilm-forming-related genes	Jiale et al. (2021)
Scolopendin 2	*Scolopendra subspinipes mutilans*	*Enterococcus faecium*, MRSA, *Escherichia coli* O157, *Salmonella typhi* and *Pseudomonas aeruginosa*	6.3–25.0 μM	Membrane permeabilization and formation of pores in the cell membrane	Lee et al. (2015)
PrAMP Bac5(1-17) derivatives	Bovine proline-rich cathelicidin	*K. pneumonia*, *E. coli* and *A. baumannii*	4 μM	Membrane permeabilization and inhibition of bacterial protein synthesis	Mardirossian et al. (2019)
P7	Derivative of cell-penetrating peptide	*Escherichia coli* ATCC25922, *Salmonella typhimurium* CMCC50013, *Staphylococcus aureus* ATCC25923, *Shigella dysenteriae* CMCC51302 and *Listeria monocytogenes* CMCC54002	4–32 μM	Pore formation, interfering with normal DNA replication and cell cycle by binding genomic DNA in *E. coli* plus decreased expression of DNA replication genes	Li et al. (2015)
Rhesus macaque θ-defensins	*Rhesus macaques*	*Staphylococcus simulant* and *S. aureus*	0.5–6 μg/mL	Membrane impairment and activation of the autolytic enzyme	Wilmes et al. (2014)
Phytochemicals					

Eugenol	Commercialized from the Shanghai Yuanye Biotechnology Co., Ltd. (Shanghai, China)	Carbapenem-resistant *Klebsiella pneumoniae* (CRKP)	0.2 mg/mL	Damaged to cell membrane coupled with enhanced membrane permeability and inhibition of biofilm formation and biofilm-associated gene expression	Qian et al. (2020)
Andrographolide (Andro)	*Andrographis paniculata*	*Staphylococcus aureus*	100 μg/mL	Inhibition of intracellular DNA biosynthesis, biofilm formation and protein synthesis	Banerjee et al. (2017)
Carnosol	*Rosmarinus officinalis* L.	*Staphylococcus aureus*	5 μM	Inhibition of *S. aureus* agr (operon controlling quorum sensing in *S. aureus* called as accessory gene regulator) gene expression	Nakagawa et al. (2020)
Conessine	*Holarrhena antidysenterica*	*P. aeruginosa* PAO1 strain K767 (wild-type), K1523 (MexB deletion) and K1455 (MexAB-OprM overexpressed)	40 mg/L when used alone and 20 mg/L when combined with antibiotics	Inhibition of MexAB-OprM efflux pump in *P. aeruginosa*	Siriyong et al. (2017)
8-Epidiosbulbin E acetate (EEA)	*Dioscorea bulbifera* L.	*Enterococcus faecalis*, *Escherichia coli*, *Shigella sonnei* and *Pseudomonas aeruginosa*	25–200 μg/mL	Antibiotic resistance plasmid (R plasmid) curing	Shriram et al. (2008)

(continued)

Table 3.1 (continued)

Antimicrobial agent	Origin	Bacteria susceptible to the antimicrobial agent	Effective concentration of antimicrobial agent	Mechanism of antimicrobial action	References
Berberine and palmatine	*Berberis vulgaris*	*Pseudomonas aeruginosa*	250–1000 μg/mL and 50–100 μg/mL, respectively	Inhibition of *Pseudomonas aeruginosa* MexAB-OprM efflux pumps	Aghayan et al. (2017)
ε-Viniferin	*Paeonia lactiflora*	*Escherichia coli* O157:H7	10 μg/mL	Inhibition of bacterial biofilm formation	Cho et al. (2013)
Carvacrol and eugenol	Commercialized from Sigma Aldrich, UK	*Pectobacterium* species	250 μM	Downregulation of genes related to quorum sensing	Joshi et al. (2016)
4-Diphenylamino 3-iodo coumarin (4-DPA3IC)	Traditional drug formulations	*S. aureus*	10 μg/mL	Bacterial DNA gyrase inhibition	Sareena and Vasu (2020)
Metals					
Nickel		*E. coli*	8 μM	Inhibition of fructose-1,6-bisphosphate aldolase (FbaA), a class II aldolase through binding to the noncatalytic zinc site	Macomber et al. (2011)
Copper		*Escherichia coli* (ATCC 23724)	4–8 mM	Nonenzymatic oxidative damage of membrane phospholipids that led to the loss of membrane integrity and resulted in cell death	Hong et al. (2012)
Chromium		*Escherichia coli* MTCC 40 and *Bacillus subtilis*-industrial strain 168	1–10 μg/mL	Membrane damage caused by ROS production followed by DNA damage	Fathima and Rao (2018)
Metal complexes					

Complexes of 3-(trifluoromethyl)phenylthioureas with Cu(II)	*Staphylococcus aureus* and *Staphylococcus epidermidis*	1–4 μg/mL	Bacterial biofilm and topoisomerase inhibition	Bielenica et al. (2018)
Mixed-ligand copper(I) halide complexes bearing 4,5-bis(diphenylphosphano)-9,9-dimethyl-xanthene and N-methylbenzothiazole-2-thione	*Escherichia coli*, *Xanthomonas campestris*, *Bacillus subtilis* and *Bacillus cereus*	5–15 μl	DNA degradation, generation of ROS and bacterial membrane damage	
Metal nanoparticles				
Biosynthesized silver nanoparticles	*Escherichia coli* and *Pseudomonas aeruginosa*	4.5 and 2.7 μg/mL	Altered cell membrane permeability and membrane damage associated with ROS production	Ramalingam et al. (2016)
Zinc oxide nanoparticles	Vancomycin-resistant *S. aureus* (VRSA)	10 mg/mL	Limiting of bacterial biofilm formation	Jasim et al. (2020)

Table 3.2 Classes of antibiotics and their mechanism of action

Antibiotic class				Examples	Effective against	Mechanism of action	References
β-lactam	Penicillins	Penicillinase sensible	Natural penicillins	Penicillin VK and penicillin G	*E. coli*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, *streptococcus pneumonia*, *Haemophilus influenza*, *Bacteroides fragilis*, *Neisseria gonorrhoeae* *Klebsiella* spp. and *Enterobacter* spp.	Inhibition of cell wall synthesis	Graber et al. (1981), White et al. (1979), and Wise and Andrews (1982)
			Aminopenicillins	Ampicillin and amoxicillin			
		Penicillinase-stable penicillins		Methicillin, nafcillin and oxacillin			
		Extended-spectrum penicillins	Ureidopenicillins	Piperacillin, azlocillin, and mezlocillin			
			Carboxypenicillins	Carbenicillin, ticarcillin			
	Cephalosporins	First generation		Cephaloridine, cephacetrile, cephapirin, cefadroxil cephalexin, cephadrine and cephalothin	*Haemophilus influenza*, *Moraxella catarrhalis*, *Streptococcus pneumonia*, *Streptococcus pyogenes*, *MRSA*, *E. coli* and *Klebsiella* spp.		Jones et al. (2007), Morrissey et al. (2009), and Sader et al. (2014, 2015)
		Second generation		Cefotetan, cefaclor, cefoxitin, cefamandole, cefonicid, cefmetazole, cefuroxime and cefuroxime axetil			
		Third generation		Cefoperazone, cefetamet, cefpodoxime, cefixime, cefovecin, cefsulodin, cefotaxime, ceftiofur and ceftriaxone. Cefdinir, ceftizoxime, ceftazidime and ceftizoxime proxetil			
		Fourth generation		Cefepime, cefpirome and cefquinome			
		Fifth generation		Ceftaroline and ceftolozane			
	Carbapenems			Meropenem, doripenem, ertapenem imipenem and tomopenem	*E. coli*, *Pseudomonas aeruginosa*, *MRSA*, *Acinetobacter baumannii*, *Aeromonas* spp. and multiple β-lactamase (TEM, SHV, CTX-M, OXA, CMY types)-producing *E. coli*		Castanheira et al. (2009), Davies et al. (2008), Jones et al. (2005), and Koga et al. (2008)
	Monobactam			Aztreonam	*E. coli*, *Klebsiella pneumonia*, *Serratia marcescens*, *Pseudomonas aeruginosa* and *Enterobacteriaceae*		Shibl (1989) and Van Laethem et al. (1984)
No lactam	Glycopeptides			Oritavancin, vancomycin, telavancin, dalbavancin and teicoplanin	*Clostridium difficile*, *Clostridium innocuum*, *MRSA*, methicillin-resistant *S. epidermidis* (MRSE) and *enterococci*		Bartoloni et al. (1990) and Biavasco et al. (1991)
	Others			Isoniazid, colistin, polymyxin B and daptomycin	Methicillin-resistant *Staphylococcus aureus*, methicillin-resistant *S. epidermidis*, vancomycin-intermediate-susceptible *S. aureus* and vancomycin-resistant *enterococci*		Rybak et al. (2000)

Antibiotic class	Examples	Effective against	Mechanism of action	References
Amino-glycosides	Neomycin, amikacin, kanamycin, gentamicin, tobramycin, dactimicin and plazomicin	Carbapenem-resistant *Enterobacteriaceae*, *Proteus mirabilis*, *Pseudomonas aeruginosa* and *Acinetobacter* species	Inhibition of protein synthesis	Castanheira et al. (2018)
Tetracyclines	Petracycline, minocycline, demeclocycline, doxycycline, tigecycline, omadacycline and eravacycline	*Moraxella catarrhalis*, *Mycobacterium abscessus*, *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium mucogenicum*, *Mycobacterium immunogenum*, methicillin-resistant *Staphylococcus aureus*, *Streptococcus pneumonia*, *β-hemolytic streptococci*, *Enterococcus* spp., *Haemophilus influenza*, *Escherichia coli*, *Klebsiella oxytoca*, *Enterobacter cloacae*, vancomycin-resistant *enterococci* (VRE), penicillin-resistant *S. pneumoniae* (PRSPN) and extended-spectrum β-lactamase-producing *E. coli*		Brown-Elliott and Wallace (2021), Carvalhaes (2019), and Sun et al. (2021)
Oxazolidinones	Tedizolid and linezolid	Methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, *Streptococcus anginosus* group, *Streptococcus agalactiae* and *enterococci*		Barber et al. (2016), Keel et al. (2012), and Pfaller et al. (2016)
Streptogramins	Quinupristin-dalfopristin	*Vancomycin*-resistant *S. aureus* (VRSA), *Bacteroides fragilis*, vancomycin-resistant *E. faecium*, methicillin-susceptible or methicillin-resistant *S. aureus*		Betriu et al. (1999), Cha et al. (2003), and Dowzicky et al. (1998)
Chloramphenicol		*Haemophilus influenza*, *S. aureus*, *Streptococcus pneumoniae* and *Neisseria meningitides*		Rahal and Simberkoff (1979)
Macrolides	Erythromycin, roxithromycin, troleandomycin, clarithromycin, telithromycin and maridomycin	*Mycobacterium smegmatis*, *M. avium*, *Streptococcus pneumonia*, MRSA, *Neisseria gonorrhoeae* and *Vibrio cholerae*		Champney and Burdine (1998), Doucet-Populaire (1998), Farrell et al. (2004), and Kondo et al. (1973)
Lincosamides	Lincomycin, clindamycin and pirlimycin	*Porphyromonas gingivalis*, *Prevotella intermedia*, *Clostridium perfringens*, *Peptostreptococcus magnus*, *Bacteroides fragilis*, *B. vulgatus*, *B. oralis* and *Eubacterium lentum*		Kondo et al. (1973) and Miyake et al. (1995)

Table 3.1 (continued)

Antibiotic class	Examples	Effective against	Mechanism of action	References
Fluoroquinolones	Norfloxacin, ciprofloxacin, levofloxacin, sparfloxacin, clinafloxacin, moxifloxacin, trovafloxacin, besifloxacin, sarafloxacin, enrofloxacin and temafloxacin	*Ciprofloxacin-resistant MRSA*, *Mycobacterium tuberculosis*, *Pseudomonas aeruginosa*, *S. aureus*, *S. epidermidis*, *Streptococcus pneumonia*, *Haemophilus influenza*, *Aeromonas salmonicida*, *E. coli*, *Mycobacterium avium* complex, *Streptococcus pyogenes*, *Legionella pneumophila* and *Listeria monocytogenes*	Inhibition of DNA topoisomerase	Abdi-Ali et al. (2006), BARNES et al. (1991), Cherubin and Stratton (1994), Cremades et al. (2011), Haas et al. (2010), Jacobs (1991), Jones et al. (1999), Mizunaga et al. (2005), and Stein et al. (2008)
Quinolones	Nalidixic acid			
Sulfonamides	Sulfisoxazole, sulfasalazine, sulfamethoxazole and Ag sulfadiazine	Carbapenem-resistant *Acinetobacter baumannii* (CRAB), *Neisseria meningitides* and *Haemophilus influenza*	Inhibition of folic acid synthesis	McGowan et al. (1976), Nepka et al. (2016), and Neuharold and Feldman (1973)
DHFR inhibitors	Pyrimethamine, trimethoprim			
Nitroimidazoles	Tinidazole and metronidazole	*Obligate anaerobic bacteria* and *Bacteroides fragilis*, *Clostridium difficile* and *Peptostreptococcus anaerobius*	DNA damage	Jokipii and Jokipii (1977) and Jokipii and Jokipii (1987)
Rifampicin		*Mycobacterium tuberculosis*, *Neisseria meningitides*, *Neisseria gonorrhoeae*, *Haemophilus influenzae* and *Listeria monocytogenes*	Inhibition of mRNA synthesis	Hu et al. (2015), Simmons et al. (2000), and Thornsberry et al. (1983)

Component A interferes with polypeptide elongation by preventing binding of aminoacyl-tRNA to ribosome whereas component B destabilizes the peptidyl-tRNA resulting in enhanced bactericidal activity (Lee 2006).

Macrolides are a different group of compounds that has a lactone ring (14–16 atoms) bonded to one or more deoxy sugar and classified according to the number of carbon atoms in the lactone ring; 14 membered includes erythromycin, roxithromycin, troleandomycin, clarithromycin and dirithromycin, whereas 15 membered includes azithromycin and 16 membered includes spiramycin, josamycin, midecamycin and spiramycin (Kuruvilla 2018). Macrolide antibiotics inhibit protein synthesis by targeting bacterial ribosomes, further binding at nascent peptide exit tunnel and partially occluding it. Thus macrolides are viewed as 'tunnel plugs' that stop protein synthesis (Vázquez-Laslop and Mankin 2018). Another class of antimicrobial agents, the lincosamides, are derived from *Streptomyces* spp. Lincosamide structure consists of three components: an amino acid (L-proline substituted by a 4′-alkyl chain), a sugar (lincosamide) and an amide bond connecting these two moieties (Kwon 2017). Lincosamides inhibit protein synthesis by binding to 50S subunit at a site that overlaps both P and A sites on the bacterial ribosome, preventing charged tRNA docking and their movement through the peptidyl transferase centre (Sauberan and Bradley 2018). Lincomycin, clindamycin and pirlimycin are three antibiotics present in the lincosamide group.

Besides macrolides, antibiotics and lincosamides, the quinolones are another family of synthetic antimicrobial drugs that have been reported to be effective against various bacterial infections. The first quinolone reported, nalidixic acid, was introduced in 1964, and its further chemical manipulation and advancements resulted in the development of fluorinated quinolones (fluoroquinolones) that includes danofloxacin, difloxacin, marbofloxacin, orbifloxacin, enrofloxacin, ciprofloxacin, moxifloxacin and levofloxacin. The major mechanism involved in the inhibition of topoisomerase II (DNA gyrase and topoisomerase IV), regulates under-winding and over-winding of DNA. The binding of quinolones to enzyme-DNA complex results in the conformational changes of enzyme further inhibiting relegation of broken DNA strands leading to the bactericidal effect. Besides quinolones, sulfonamides are one of the oldest groups of antibacterial agents introduced into medical practice even before the discovery of penicillin and have broad-spectrum use concerning both Gram-negative and Gram-positive microorganisms. Sulfonamide drugs are the structural analogs of para-aminobenzoic acid (PABA), an essential component in the folic acid pathway. Sulfonamides inhibit the bacterial dihydropteroate synthetase (DPS) enzyme of the folic acid pathway, blocking bacterial nucleic acid synthesis. Sulfonamides also contribute in preventing the conversion of PABA to dihydrofolic acid by substituting competitively for PABA. Combinations with trimethoprim have also shown an excellent bactericidal effect. Trimethoprim inhibits dihydrofolic acid reductase thereby preventing the subsequent conversion of dihydrofolic acid to tetrahydrofolic acid thus blocking two successive steps in the folic acid pathway and exhibiting enhanced bactericidal effect (Ahern and Richardson 2012). Metronidazole and tinidazole are the main representatives of nitroimidazoles. Metronidazole is active against some anaerobic

bacteria (e.g. *Clostridium difficile*), protozoan infections and microaerophilic bacteria (*Gardenia vaginalis* and *helicobacter pylori*). Metronidazole first diffuses across the membrane and then gets reduced by intracellular protein under anaerobic conditions, hence exerting its effect through cytotoxic intermediate and free radical's formation that provoke DNA damage (Bury-Moné 2014).

Apart from the wide-spectrum activity and fast-action advantages of antibiotics, they face some disadvantages such as side effects, hypersensitivity, drug interaction and toxicity and negative effect on commensal microflora (Weledji et al. 2017). In addition to injudicious usage of conventional and commonly available antibiotics in human health, veterinary agriculture further adds to the evolution, persistence and spread of AMR with emergence of new drug-resistant bacterial strains at a frightening rate resulting in the inefficacy of existing drugs with very few or no solutions in sight. Therefore, to successfully combat the escalating problem of AMR, novel and effective antimicrobial agents are recommended such as phytochemicals, metal, metal-based complexes, metallic nanoparticles and AMPs.

3.4.2 Antimicrobial Peptides (AMPs)

AMPs are broadly defined as 'naturally occurring polypeptide sequences of 12–15 residues comprising cationic and hydrophobic amino acid with direct antibacterial activity' (Li et al. 2021). AMPs are produced by all organisms ranging from bacteria, plants, invertebrates and vertebrates and have a wide range of inhibitory effects against fungi, bacteria, viruses and parasites (Kumar et al. 2018a). AMPs have several advantages over conventional antibiotics showing the multifunctional mechanism of antibacterial action altering cell membrane and also attacking specific targets that take part in the development of different intracellular processes such as bacterial cell wall formation, transcription and translation that has antimicrobial activity against multidrug-resistant pathogens (León-Buitimea et al. 2020).

AMPs are found to be highly effective against Gram-negative bacteria which are more challenging to treat than their Gram-positive counterparts because of the outer membrane composition in the earlier that makes them impermeable to most of the conventional antibiotic drugs. AMPs are often introduced in literature as a 'promising alternative to antibiotics' and 'potential to address the growing problem of antibiotic resistance' and 'hold promise to be developed as novel antibiotics' (Li et al. 2021) because of a non-specific mechanism involving membrane target, oxidative damage, damage to intracellular molecules, potent microbicidal activity in the micromolar range and rapid drug action increasing difficulty in resistance development because of limited time for extensive mutation and growth (Koo and Seo 2019). In addition, AMPs are also known as host defence peptides (HDPs) as they can also enhance immune response highlighting the clinical potential of AMPs to stimulate innate immunity (Li et al. 2021). AMPs such as HPA3P (*Helicobacter pylori*-derived AMP) loaded onto a gold nanoparticle-DNA aptamer (AuNP-Apt) conjugate (AuNP-Apt-HPA3P^{His}) when utilized against *Vibrio vulnificus* resulted in

HPA3P^{His}-induced bacterial cell death via disruption of membrane integrity and 100% survival rate in *Vibrio vulnificus*-infected mice resulting in complete inhibition of *Vibrio vulnificus* colonization, hence displaying effective drug delivery of AMPs (Lee et al. 2017).

AMPs are commonly known for non-receptor-mediated membrane-lytic bactericidal activity. Membrane-targeting mechanisms of AMPs can be described through pole and carpet models, barrel-stave models and toroidal pore models (Fig. 3.2). In the toroidal-pore model, the initial binding of the peptide to the membrane is followed by cascade aggregation of incoming monomer units, causing the lipid moieties of inner and outer membranes to fold inward, forming continuous channels lined by multiple peptide units and thus tightly associating lipid head groups of membrane phospholipids with peptides. A typical example of this model includes magainin 2, lacticin Q, arenicin and melittin (Huan et al. 2020). However, the barrel-stave model differs from the toroidal pore model by the peptide monomers inserted into the membrane arranged parallelly to phospholipid molecules of the membrane. Besides membrane penetration and pore formation, AMPs have another mechanism of action which includes inhibition of protein synthesis by affecting transcription, translation, protein folding and assembly of newly synthesized proteins. For example, PR-39, a proline, and arginine-rich AMP isolated from pigs' small intestine were found primarily to penetrate rapidly into *E. coli* outer membrane that led to protein synthesis inhibition and degradation of the protein (Boman et al. 1993). Following penetration, inhibition of nucleic acid biosynthesis occurs by affecting the key enzymes of DNA synthesis or inducing degradation of the nucleic acid molecule. By inhibiting the DNA replication, DNA damage response (SOS response), causing chromosomal separation failure blocking cell cycle, and inhibiting cell division is the process of AMPs. Cruz et al. (2020) identified 40-amino acid residue MciZ as an effective inhibitor of bacterial cell division, Z-ring formation and localization. Histatin, eNAP-2 and indolicidin were also found to have strong protease inhibition mechanisms (Huan et al. 2020). Similarly, investigations on NP-6 from Sichuan pepper seeds showed inhibition of beta-galactosidase activity in *E. coli* (Hou et al. 2019). These multifunctional mechanisms of antibacterial action thus highlight the AMPs as a promising alternative to antibiotics.

3.4.3 Phytochemicals

Plants produce a wide array of phytochemicals that have been utilized for centuries in ethnomedicine or folk medicines. Phytochemicals are compounds that occur naturally in plants as secondary metabolites (Bai et al. 2011) and can be classified into many major classes depending upon the chemical structure (alkaloids, polyphenols(flavonoids and non-flavonoids), terpenoids, sulphur-containing phytochemicals), biosynthetic pathways, biological pathways and botanical origins (Górniak et al. 2019; Belščak-Cvitanović et al. 2018). Two major sub-classes of phenolic acid include hydroxybenzoic acid (e.g. gallic acid, vanillic acid,

protocatechuic acid, salicylic acid, syringe) and hydroxycinnamic acid (e.g. chlorogenic acid, coumaric acid, caffeic acid, ferulic acid curcumin, caftaric acid, cinnamic acid) (Flamini and De Rosso 2018). Similar to phenolic acids, tannins are a group of structurally complex polyphenols comprising condensed (proanthocyanidins) and hydrolyzable tannins that can form complexes with proteins by non-specific interactions. Therefore, displaying antimicrobial activity may be associated with their potential to denature microbial transport protein, adhesins and microbial enzymes preventing microbial growth through deprivation of metal ions and substrates (Gupta and Pandey 2019). Bacterial cells can be affected by phytochemicals in several ways due to the greater diversity displayed by phytochemicals. The major mechanism of phytochemicals action includes membrane permeabilization, cell membrane disruption, EP inhibition, inhibition of biofilm formation and quorum sensing, targeting resistant plasmid, inhibition of cell division and DNA and protein synthesis (Table 3.1) (Navarro-Martínez et al. 2005; Gradišar et al. 2007; Domadia et al. 2008; Wu et al. 2008; Boulet et al. 2018). For instance, studies have shown enhanced bactericidal activity of thymol against *S. aureus* and *E. coli* by encapsulating thymol in hollow mesoporous silica sphere with cell membrane disruption as an inhibitory mechanism of action, thus highlighting enhanced resistance reversal potential antimicrobial agent when combined with nanocarriers (Liu et al. 2021a) that could speed up the successful application of antimicrobial agents in clinical settings.

Similarly, essential oils are known for their broad-spectrum antimicrobial potentials mainly attributable to their abilities of targeting major determinants of drug resistance, pathogenicity and spread, which include EPs, cell membrane, quorum sensing, resistant plasmids and biofilms. Recent reports confirm that essential oils show both direct killing (bactericidal) or re-sensitizing (or resistance-reversal) potentials providing effective solutions for tackling AMR and the potential to rejuvenate or replace otherwise fading antibiotic arsenal (Yu et al. 2020). Recent years have witnessed the use of nanomaterials as synergistic agents with essential oils as well as their carriers. Montmorillonite nanosheet-based (MMT-based) drug nanoplatform involving antibacterial metal copper ions, quaternized chitosan (QCS) and antibiotic 5-fluorocytosine (5-FC) [QCS/MMT/5-FCCu] strongly inhibited *S. aureus*, *E. coli* and *Candida albicans* with high drug-loading capacity, excellent wound healing and good biocompatibility in a mouse model infected with wound demonstrating enhanced killing effect against both bacteria (Sun et al. 2019). Similarly, cinnamaldehyde-loaded liposomes decorated with chitosan also showed strong antibacterial efficacy against *S. aureus* by damaging cell membrane integrity, causing cell death by leakage of intracellular components (Wang et al. 2021).

3.4.4 Metals, Metal-Based Complexes and Metallic Nanoparticles

Since ancient times, antimicrobial activities of metals such as silver (Ag), gold (Au), copper (Cu) titanium (Ti), mercury (Hg) and tellurium (Te) consisting of different properties defining the spectrum of activity and potencies are known that are used as antimicrobial agents because of their microbiocidal activity at extremely low concentration. Previous reports on *E. coli* and *S. aureus* treated with $AgNO_3$ resulted in losing their replication ability and protein inactivation resulting in strong antibacterial activity of metals (Woo et al. 2008). The major mechanism of antibacterial action of metals includes production of ROS, impairing membrane function, interfering with nutrient assimilation, inducing genotoxicity, protein dysfunction and loss of enzyme activity (Lemire et al. 2013). For example, tellurite (TeO_3^{2-}) toxicity in *E. coli* by treatment of K_2TeO_3 in *E. coli* leads to superoxide formation (Pérez et al. 2007). Similar results with loosening of cell walls, cytoplasmic aggregation and cell wall rupture were observed when *Erwinia carotovora* subsp. *atroseptica* was treated with aluminium chloride resulting in increased mortality (Yaganza et al. 2004). Further, as there is a chemical similarity between iron (Fe) and gallium (Ga), Ga can substitute Fe in a different biological system and inhibits Fe-dependent processes, for example, inhibition of growth, biofilm formation and death of *P. aeruginosa* by Ga-induced reduced uptake of Fe and reduced expression of genes involved in Fe uptake suggesting the importance of Ga in interference of nutrient assimilation. In addition, since Ga is FDA approved for *intravenous* (*IV*) administration suggesting Ga as potentially promising therapeutics in the dearth of new antibiotic development (Kaneko et al. 2007).

Treatment of *E. coli* (lacking copper homeotic system) with copper metal resulted in rapid inactivation of isopropyl malate dehydratase (an iron-sulphur cluster enzyme in the pathway of branched-chain amino acid synthesis) damaging essential enzymes of biosynthetic pathways (Macomber and Imlay 2009). In addition to this, metals when used in nanoformulations or complexed with other antimicrobial agents such as phytochemicals, antibiotics and synthetic metal complex show greater inhibitory effects against bacteria compared to their free ligand, exhibiting potent broad-spectrum antimicrobial activity, with low toxicity (Lemire et al. 2013). For example, when a metal complex of Ga and flavonoid quercetin (metal complex 1) and H2bbppd and Cu(II) (metal complex 2) were evaluated against *Staphylococcus aureus* (ATCC SP 25923), *Escherichia coli* (ATCC SP 11229), *Enterococcus faecalis* (ATCC SP 19433) and *Pseudomonas fluorescens* (ATCC SP 13525), both metal complex showed greater inhibitory effects as compared to their ligand with lower MIC $\leq$250 μg/ml, confirming broad-spectrum strong antibacterial activities.

3.5 Nanomaterial-Based Antimicrobial Delivery Targeting Drug-Resistant Determinants

3.5.1 Bacterial Cell Membrane

The first line of defence in bacteria is the cell membrane that maintains the necessary osmotic balance between the outer environment and the cytoplasm (Yeh et al. 2020). Various nanomaterials have been found interacting with the bacterial cell membrane to increase the membrane permeability via the generation of ROS and production of radicals [singlet oxygen ($^1O_2$), electrons (e^-), hydroxyl radicals (●OH) and superoxide radicals ($O_2^{\bullet-}$)] (Wang et al. 2017). As an alternative to traditional antibiotics, photothermally active nanomaterials have emerged as a potential drug delivery system to target bacterial drug-resistant determinants (Borzenkov et al. 2020; Kaur et al. 2021). Multifunctional drug delivery nanoparticle (MDD-NP) and crystalline ruthenium polypyridine nanoparticles (Sph-Ru-MMT@PZ) consisting of adhesive and surface-anchoring properties, under 670 nm red irradiation therapy (R-IT), resulted in bacterial destruction and cell lysis of *E. coli* via ROS production (Yin et al. 2021). Further in vivo studies in mice revealed synergistic anti-infective effects of nanoparticles, hence promoting wound healing. Vancomycin-encapsulated, pH-responsive, surface charge-switching poly(D,l-lactic-co-glycolic acid)-*b*-poly(l-histidine)-*b*-poly(ethylene glycol) (PLGA-PLH-PEG) nanocarriers demonstrated pH-sensitive NP binding to bacteria (pH 6.0) and drug delivery to bacterial cell membrane of *S. aureus* causing cystic fibrosis with an 1.3-fold increase in MIC (Radovic-Moreno et al. 2012). A study on controlled release of drug at the injection site was conducted with kanamycin-loaded TiO_2 nanotubes (NTs) under NIR irradiation via disrupting the bacterial cell membrane integrity by damaging bacterial cell wall and radical-induced inflammation and cytotoxicity resulting in ≥99.9% reduction in *E. coli* (Xu et al. 2021). Similar results were observed in eco-friendly chitosan-based nanoantibiotic system (LD@CN/DA) for potential delivery of linezolid (LD) with 3,5-dinitrosalicylic acid (DA) as antimicrobial agents with 98.4% drug release efficiency against MRSA, *E. coli* and *E. faecalis* resulting in the formation of ROS and enhancing pathogen-specific activity (Teaima et al. 2020).

3.5.2 Biofilms

Human infections can be caused by bacteria that are in the form of biofilms, planktonic cultures and intracellular residence depending on their surroundings and growth parameters (Yeh et al. 2020). Biofilms are well-organized community of bacteria that adhere to the host cells to protect themselves from the harsh environmental, physiological conditions and action of antibiotics (Sharma et al. 2019). Recent reports on worldwide human infections caused by biofilms have crossed

60% making them the primary cause of various treatment failures in medicine (Huang et al. 2021). Therefore, biofilms have emerged as one of the major resistance mechanisms and spreading AMR. Recent years have witnessed the successful applications of nanomaterials in eradicating biofilms as well as in carrying effective anti-biofilm agents.

Endophthalmitis is defined as the bacterial infections caused by various microorganisms inside the eye vitreous and aqueous humour (Durand 2013). Chen et al. (2019) studied the eradication of *E. coli*, *S. aureus* and MRSA biofilms causing endophthalmitis using ammonium methylbenzene blue-loaded pH-responsive zeolitic imidazolate framework-8-polyacrylic acid (ZIF-8-PAA) modified with $AgNO_3$ and secondary modification of vancomycin/NH_2-polyethylene glycol (Van/NH_2-PEG) composite nanomaterial (ZIF-8-PAA-MB@AgNPs@Van-PEG). Further in vitro retinal pigment epithelium cellular experiments and in vivo mice endophthalmitis models resulted in effective drug release, biocompatibility and antibacterial efficiency of composite nanomaterial against biofilm-causing bacteria (Chen et al. 2019). *Pseudomonas aeruginosa*, another pathogen found in adult patients infected with cystic fibrosis (CF), is the major biofilm-forming bacteria (Davies 2002). The development of novel aerosolized ciprofloxacin-loaded poly(lactic-co-glycolic (PLGA) acid) nanocarriers onto the in vitro model of *Pseudomonas aeruginosa* biofilm-infected human bronchial epithelial cells resulted in the eradication of planktonic bacteria and reduced biofilm fraction by log 6 revealing their potential avenues in preclinical studies (Juntke et al. 2021).

Nitric oxide has emerged as a promising agent for disrupting biofilms and promoting wound healing (Englande and Friedman 2010). Hasan et al. (2019) developed polyethyleneimine/diazeniumdiolate (PEI/NONOate)-doped PLGA nanoparticles (PLGA-PEI/NO NPs) against MRSA biofilm of diabetic wounds resulting in binding of NPs to biofilm matrix facilitating NO delivery and enhanced anti-biofilm activity. Further in vivo studies in MRSA biofilm-infected wounds in diabetic mice accelerated healing via biofilm binding NO release from NPs (Hasan et al. 2019). Amikacin and ciprofloxacin drugs encapsulated in liposomes have shown their effective penetration abilities in *P. aeruginosa* biofilms (Zhang et al. 2018; Chalmers et al. 2021). Besides liposomes, AMP-based nanocarriers have greatly enhanced their medicinal benefits by improving stability, solubility and in vivo half-life in various pulmonary, gastrointestinal and wound infections (Song et al. 2021) (Table 3.3).

3.5.3 Efflux Pumps (EPs)

Extrusion of therapeutically relevant antimicrobial agents/drugs from inside cells to the extracellular environment via EPs has been frequently involved in microbial antibiotic resistance and spreading AMR (Alav et al. 2018). Investigations have identified several EP genes in chromosomes and plasmids of different bacterial species that mediate drug resistance (Li and Nikaido 2009). EPs are also found to play

Table 3.3 List of nanocarriers conjugated with antimicrobial agents as delivery systems in microbes

Antimicrobial agent/drug	Nanocarrier	Drug resistance determinant target	Observation/action mechanism	Name of microorganism	Experiment model	References
Vancomycin	Vancomycin-loaded solid lipid nanoparticles (VM-ATS-SLN)	Biofilm formation	VM release in response to acidified pH and lipase enzyme with biofilm growth inhibition	MRSA	Skin-infected mice model	Ibrahim et al. (2021)
Microcin J25 (MccJ25)	Chitosan nanoparticles (CNs)-antimicrobial peptide microcin J25 (MccJ25) conjugates (CNMs)	Cell membrane	Binding to outer membrane protein A (OmpA) and lipopolysaccharide (LPS) of bacteria causing membrane damage	*E. coli* K88 and MRSA	Human embryonic kidney cells (HEK293T)	Yu et al. (2021a)
Folic acid	Nanoscale metal-organic frameworks (NMOFs) encapsulating the antibacterial ligand (lysine carbon dots, Lys-CDs) and targeted drug (folic acid, FA)	Biofilm formation	Sharp increase of reactive oxygen species (ROS) inside the bacterial cells by FA functionalizing NMOFs	*S. aureus* and *E. coli*	In vitro NIH-3 T3 mouse fibroblast cell	Yu et al. (2021b)
Piper betle aqueous extract	Piper betle-based silver nanoparticles (PbAgNPs)	Quorum sensing	Inhibition of QS-mediated virulence factors such as prodigiosin, protease, biofilm formation, exopolysaccharides and hydrophobicity productions with downregulation of fimA, fimC, flhD and bsmB genes	*Proteus mirabilis* and *Serratia marcescens*	*Caenorhabditis elegans*	Ho et al. (2020)

Antimicrobial agent/drug	Nanocarrier	Drug resistance determinant target	Observation/action mechanism	Name of microorganism	Experiment model	References
Quercetrin and afzelin	Quercetrin and afzelin capped silver nanoparticles (AgNPs)	Biofilm formation	Reduced cell surface hydrophobicity, decreased surface adherence loss of membrane potential	*Salmonella typhimurium*	Zebrafish infection model	Lotha et al. (2018)
Gentamicin	Silica-gentamicin nanohybrids (SiO2-G)	Biofilm formation	Holistic ultrastructural deformation of the *E. coli* biofilms in the form of an utter deterioration of cell shapes and apt damage and wrinkling of their cell walls	MRSA and *E. coli*	Zebrafish embryos	Mosselhy et al. (2018)
Cinnamaldehyde (CA)	CA-loaded mesoporous silica-coated gold nanorod (CA@AuMN-HA)	Cell membrane	On-demand release of CA under NIR irradiation with enhanced antibacterial activity	MRSA and drug-resistant *E. coli*	MRSA-infected mice wound model and *C. elegans*	Sun et al. (2018b)
In-house-designed potent USAMP named RBRBR	RBRBR encapsulated chitosan-based nanoparticles (CS-NPs)	Cell membrane and biofilm formation	98% (5-log reduction) biofilm bacterial reduction at 10 mg/mL formulation	MRSA	Mammalian Vero cell line	Almaaytah et al. (2017)

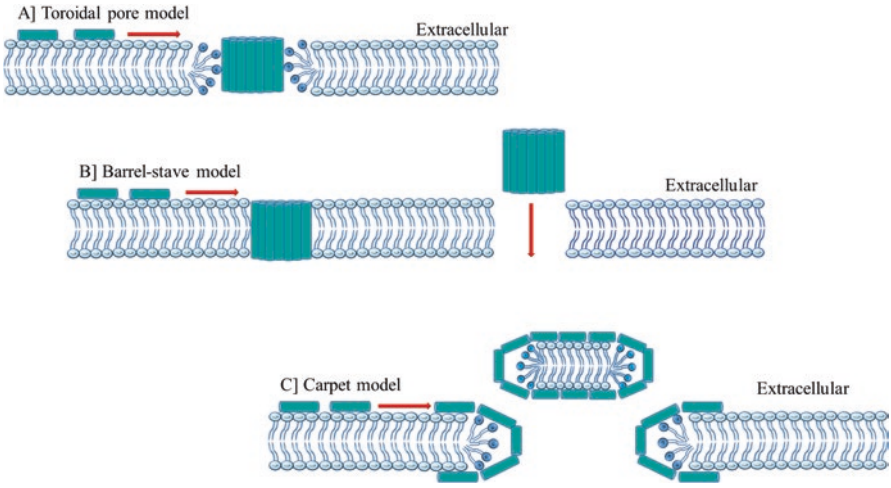

Fig. 3.2 Membrane-targeting mechanism of antimicrobial peptides (AMPs)

key roles in biofilm formation by extruding quorum sensing molecules and quorum quenchers that mediate the formation of biofilm matrix, thus promoting surface adhesion (Ugwuanyi et al. 2021). EPs have been characterized as one of the major drug-resistant determinants. Numerous nanomaterials for delivering antimicrobials to EP target sites have been investigated using in vivo and in vitro models as a potential tool for treating bacterial infection (Prasher et al. 2021). A recent study has reported on the synergistic effects of ciprofloxacin with embelin-loaded chitosan-gold nanoparticles against environmental MDR *P. aeruginosa* and *E. coli* strains by inhibiting EPs by interacting with PA-r (MexA, MexB and OprM) and EC-r (AcrA, AcrB and TolC) active sites (Khare et al. 2021). Further advancements in the microfluidic assembly of pomegranate-like hierarchical microspheres and meropenem-loaded porous silica (MCM-48), for efflux regulation in oral drug delivery against *S. aureus* and *P. aeruginosa*, demonstrated reduced efflux of MER back into the gastrointestinal lumen (Raza et al. 2021). One of the recent innovative strategies includes the application of combinations of different antibiotics on nanomaterials to combat MDR bacteria. Khameneh et al. (2015) investigated the antibacterial activity of co-loaded piperine and gentamicin nanoliposomes in MRSA resulting in EP inhibition with MIC of 32 and 100 μg/mL, respectively. Similarly, liposome-encapsulated phenylalanine-arginine β-naphthylamide (PAβN), an EP inhibitor (EPI), has been proven a cost-effective and worthwhile delivery system against MDR *P. aeruginosa* in lung infections (Ray et al. 2021). However, deeper studies are much further required in this field.

3.5.4 *Quorum Sensing*

The communication mechanism between the bacteria cells with each other that entails the synthesis, detection and autoinducer extracellular signalling molecules is defined as quorum sensing (QS) (Rutherford and Bassler 2012). Molecular mechanisms involving acyl-homoserine lactones, peptide autoinducers and autoinducer 2 are the major QS systems present in bacteria involved in intercellular signalling during human bacterial infections (Irie and Parsek 2008). As a result, there is an increasing demand for viable, non-toxic/anti-QS agents exhibiting dual actin modes addressing both biofilm formation and QS in bacterial infections. In recent years, nanomaterials as antimicrobial agents/drug delivery systems have been reported as an effective tool for QS elimination and treating microbial infections. Bueloni et al. (2020) developed vanadium-nalidixic acid complex (V-NA) nanoencapsulated into myristyl myristate nanostructured lipid carriers (NLCs), and polymeric nanoparticles of Eudragit NE 30D (EuNPs) with enhanced antibacterial and anti-quorum sensing properties against *P. aeruginosa* and *Chromobacterium violaceum* resulted in controlled release of V-NA (30–40% for 3 days) with 59.3 and 129.9 μM MIC values, respectively. Similar results were observed in chitosan-gum acacia gold nanocomposite (CS-GA-AuNC) against MDR *P. aeruginosa* with a greater reduction in Las-R gene expression levels majorly involved as a virulence factor in biofilm formation and QS (Raja Namasivayam et al. 2020). Further in vivo studies on murine macrophage cell line revealed their excellent biocompatibility, an excellent property for drug delivery systems. Recently, the formulations of AMP dendrimers and QSIs (anti-MvfR compounds) for treating burn wound infections caused by *P. aeruginosa* were developed that inhibited the MvfR virulence pathway in the QS system of the bacteria (Jafari et al. 2021). Similar results in tobramycin antibiotic and alkylquinolone quorum sensing inhibitor (QSI)-loaded squalenyl hydrogen sulphate nanoparticles (SqNPs) in in vitro models of pulmonary *P. aeruginosa* infections were observed with improved biofilm penetration and enhanced antimicrobial efficiency (Ho et al. 2020).

3.6 Conclusion and Future Perspectives

Biocompatibility, cost-effectiveness, controlled drug release, deep penetration, target specificity and sustainability properties of nanocarriers make them ideal drug carriers, for delivering wide-ranging antimicrobial agents. However, despite the seemingly large corpus of research and development of a nanomaterial-based delivery system of antimicrobial agents, numerous hurdles need to be overcome before nanomaterial-based approaches for the optimum treatment of drug-resistant bacterial infections may be successfully translated to clinical settings. Silver-oxide and zinc-oxide nanomaterials being approved by the FDA have increased the likelihood of clinical settings among the current leads. Antimicrobial agents such as phytochemicals, AMPs, antibiotics and metallic complexes comprising great

biocompatibility and enhanced antimicrobial activity in conjugation with nanocarriers such as liposomes, nanoparticles, nanocomposites and dendrimers are the emerging promising tools for prolonged and regulated release of drugs/antimicrobial agents against microbial infections. These nanomaterial-based drug delivery systems are proven to be targeting key drug-resistant determinants (cell membrane, EPs, biofilm formation, QS) in pathogenic and threatening bacteria. Nanoliposomes are been already employed in clinical settings for delivering antimicrobials to biofilm-forming bacterial infections. PLGA NPs and GO-NPs have the broadest drug delivery range including AMPs that are found to target biofilms and QS systems. However, deeper research is still required in the field of nanomaterial-based delivery of antimicrobials targeting specific EPs, drug release kinetics, biodegradation, pharmacokinetics and their clearance. For their development, research necessitates multidisciplinary clinical and industrial collaborations for fighting these human microbial infections and making them available from bench to bedside.

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