Chapter 11
Cationic Amphiphilic Molecules as Bactericidal Agents

Koyeli Das, Vickramjeet Singh, and Ramesh L. Gardas

Abstract Cationic amphiphiles belong to the large as well as assorted category of antimicrobial agents, which has emerged as a sizzling topic of discussion among scientists these days. These antibacterial molecules are being evaluated preclinically and clinically for the treatment of infection caused by drug-resistant bacteria. Due to the widespread application of the cationic amphiphilic molecule (CAM), it's vital to know the effects and detailed chemistry related to the solid surfaces, degrees of confinement on aggregation morphologies, plus chemical kinetics in the self-assemblies of cationic amphiphilic systems. This chapter has included the points described above and phase transitions exhibited by CAMs in the peptides. CAM offers a new tool designed for scientific research with various industrialized applications required for bacterial membrane permeabilizations by optimizing the goal of antibacterial activity, reaching the target drugs, and thereby compromising their structural integrity by cell rupture and death. These results revealed that the varied supramolecular morphologies of CAMs could be controlled by tuning ionic-hydrophobic, hydrophobic-hydrophobic, ionic-hydrophilic, and charge-transfer interactions.

Keywords Amphiphiles · Aggregation morphology · Antibacterial activity · Antimicrobial agent · Bacterial agents · Bacterial membrane permeabilizations · Cationic amphiphilic molecule · Cationic amphiphilic drugs · Cell rupture · Charge-transfer interactions · Diverse self-assemblies · Dispersion medium · Equilibrium · Food industries · Foodborne diseases · Gonorrhea · Hydrophilic and hydrophobic side moiety · Methicillin-resistant *Staphylococcus aureus*

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Abbreviations

CAD	Cationic amphiphilic drug
CAM	Cationic amphiphilic molecules
MRSA	Methicillin-resistant *Staphylococcus aureus*
SWNT	Single-walled nanotubes

11.1 Introduction

Amphiphilic molecules usually include surfactants, ionic liquids, block copolymers, and other essential bioactive molecules, composed of at least two discrete groups, hydrophilic and hydrophobic. Unique structural designs of the amphiphiles may cause different aggregation morphology at the interfaces as well as diverse self-assemblies in the solutions.

As a result of the unique performances of amphiphiles, they can be extensively utilized in the material, chemicals, food industries, and petroleum products (Ash and Ash 1993). Mainly, self-assemblies in the amphiphiles engage in a crucial role of a biological system, synthesis of varied functional materials. Surfactants or block copolymers are universal templates to direct synthesis of organized nanostructures, while lipids and proteins constitute the main components of the biological membrane. As a result of their structures, amphiphiles possess unique properties (Holmberg et al. 2003; Myers 1999). Strong adsorption in diverse interfaces and self-assemblies in the various solvent (Meleshyn 2009; Sammalkorpi et al. 2008; Ma et al. 2008; Heinz et al. 2008; Jodar-reyes et al. 2008; Gu et al. 2008; Xu et al. 2008; Rodriguez and Laria 2007; Li et al. 2007; Dominguez 2007; Zhang et al. 2007a; Heinz et al. 2007; Zheng et al. 2006; Shah et al. 2006; Israelachvili 1992; Israelachvili et al. 1976). Larson et al. (1985) suggested a lattice model of the self-assembly among amphiphiles in bulk solutions (Larson et al. 1985). Atkin et al. showed adsorption of the amphiphile molecules on silica, graphite, etc., by various experimental techniques (Atkin et al. 2003). Besides adsorption morphologies, surface phase transitions also have essential importance for aqueous surfactants. Surfactant phase transition at the air-water boundary was experimentally discovered (Patti et al. 2007; Ramirez et al. 2007; Hynninen and Panagiotopoulos 2006).

In addition to aggregation on solid surfaces, adsorption of the amphiphiles at various interfaces (Ma et al. 2008; Rodriguez and Laria 2007) in recent years is also studied. With the recent progress of nanotechnologies, studies on the micellization of surfactants in confined systems have turned out to be increasingly important (Chen et al. 2009; Wang 2009; Tummala and Striolo 2009; Angelikopoulos and Bock 2008; Arai et al. 2008; Zhang et al. 2007b; Koopal et al. 2005). Critical micelle concentration (CMC) of amphiphiles is affected through interaction in a surfactant

with a degree of incarceration (Zhang et al. 2007a). Experimentally Wu et al. (2004) compared chains of a sphere, straight cylinders, single helixes, double helices, stack doughnuts, and arrangement of concentric inner shells (Zheng et al. 2007; Yu et al. 2006; Wu et al. 2004). Surfactants have been used as outlines to stimulate orderly nanostructured objects using experimental techniques (Wan and Zhao 2007; Wan et al. 2006; Beck et al. 1992). Carbon nanotubes (SWNTs) are structurally unique, exhibiting mechanical, thermal, electrical, and optical properties, which may offer promises for several novel applications using amphiphiles that would act as a dispersion medium (Wan et al. 2007; Iijima and Ichihashi 1993). Besides adsorption equilibrium, kinetic aspects of amphiphiles at hydrophilic solid surfaces progress rapidly for broad experimental studies (O'Connell et al. 2002). A necessary kinetic process in the case of aqueous surfactant is the micelle/vesicle fission and fusion (Müller et al. 2006; Venturoli et al. 2006; Paria and Khilar 2004). Li et al., in recent studies, investigated the kinetics of collision-based solute exchanges in aqueous phases (Yamamoto and Hyodo 2003).

11.1.1 Bacterial Infection and the Need for Antibacterial Drugs

In this chapter, we have focused on the role of cationic amphiphiles in the environment. Cationic amphiphiles are large as well as various categories of antimicrobial mediators. Though its modes of action are not yet entirely determined, they have emerged as a sizzling topic of discussion among scientists these days as cationic amphiphilic drugs act as a potential candidate in cancer therapy (Geertje et al. 2020; Li et al. 2008). The resistance of antimicrobials (bacteria) against commercially available antibiotic drugs has encouraged scientists to develop alternative safe anti-infection agents (Salta et al. 2013). Emerging multidrug-resistant bacteria have forced the therapeutic community to search for alternative antimicrobial treatments (Omardien et al. 2018). Antimicrobials successfully treat and control different infectious diseases and save several lives (Gunasekaran et al. 2019). Treatment of infections by fighting against infection-causing microbial agents is becoming challenging as per WHO (Zhang et al. 2018), and these infections are tuberculosis, foodborne diseases, gonorrhea, pneumonia, and throat infections (Wahab et al. 2021).

Ever since the discovery of penicillin, various antibiotics have been used for the treatment of infections (Díaz et al. 2012). However, with the widespread use and misuse of antimicrobial agents, various multidrug-resistant bacteria have become a global threat (Santajit and Indrawattana 2016). These superbugs are emerging as a severe concern to pharma industries and pose a significant threat to the human population (Liscovitch and Laviey 1991). Many drug-resistant pathogenic bacteria, the so-called "ESKAPE" bacteria group, include *Staphylococcus aureus*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas*

aeruginosa, and *Enterobacter* (Indoria et al. 2020; Gunasekaran et al. 2019; Kim et al. 2017). Ever since the report of methicillin-resistant *S. aureus* (MRSA) in 1960 (Gunasekaran et al. 2019; Santajit and Indrawattana 2016), it has been identified commonly as a drug-resistant bacteria (Gunasekaran et al. 2019; Liscovitch and Laviey 1991). Various antimicrobial agents inspired by nature have been developed and are still being explored to overcome these resistant pathogens' challenges (Wahab et al. 2021; Omardien et al. 2018; Salta et al. 2013). These antimicrobial agents can be organic or inorganic compounds; nanoparticle-based formulations (Zhang et al. 2018; Anderson and Borlak 2006), antimicrobial coatings, fabrics, textiles, cationic amphiphilic peptides (Indoria et al. 2020), and composite materials have been tested as antimicrobial agents. The antimicrobial drugs, either derived from natural microbes or synthesized in a lab, either destroy the bacteria or hinder bacterial growth, and the bactericidal drugs can kill the bacteria (Kim et al. 2017; Penta 2015). These antimicrobial agents can work by targeting any one of these: (a) translational machinery, (b) cell wall, or (c) DNA replication (Zou et al. 2021; Montazer and Harifi 2020). Various interactions (may cause genetic or enzymatic interference) can occur between the antimicrobial drug molecules and targeted bacteria; among these, hydrophobic and electrostatic interactions occur when cationic amphiphilic (surfactant) disintegrates the membrane of bacteria (Zhou and Wang 2020; Ciumac et al. 2019); however, excessive use of such agents can cause bacterial defiance (Zhou and Wang 2020; Ciumac et al. 2019). Thus, there is a need to improve the current treatment method or develop new biocides and antimicrobial drugs (Zhou and Wang 2020; Ciumac et al. 2019).

11.1.2 Multidrug-Resistant Bacteria and the Search for New Therapeutic Antibacterial Drugs Based on Cationic Amphiphilic Molecules

Novel categories of macrocyclic amphiphilic molecules are achieving progressive interest in the field of nanomedicine because of their basic aspects of molecular identification and robust assemblies. Cationic amphiphilic drugs (CADs) have common physicochemical properties such as a hydrophilic side moiety with a cationic group attached to a hydrophobic part (hydrophobic ring structure or alkyl group) (Vater et al. 2017; Halliwell 1997). Thus, an amphiphilic character is due to a combination of hydrophilicity and hydrophobicity. The former arises due to ionizable amine groups, which are hydrophobic alkyl chains or aromatic ring structures (Vater et al. 2017; Santajit and Indrawattana 2016). The physicochemical properties of CAD molecules are responsible for the distribution pattern of CAD drugs within interacting biological systems; thus, their clinical efficacy involves a complicated interplay of pharmacokinetics and pharmacodynamics (Vater et al. 2017; Halliwell 1997). The CAD-based drugs include different classes such as antipsychotics, tranquilizers, antidepressants, and antiarrhythmics (Vater et al. 2017; Halliwell

1997). CAD led to a morphological change to cells as CAD can accumulate into intracellular compartments (Vater et al. 2017; Halliwell 1997). The intracellular distribution behavior of CAD can be monitored by radio-labeling but may have associated adverse effects due to the random distribution of radioactive tracers into the neighboring sections (Vater et al. 2017). CAD molecules showing ability to act as antidepressants, local anesthetics, neuroleptics, or antiarrhythmics can occur due to their tendency to cause lipidosis (Halliwell 1997).

Owing to various interactions, CAD can accumulate into acidic intracellular components such as lysosomes or endosomes (Salata et al. 2017). The physicochemical properties and structure of CAD, dose, duration of dose, inter- and intraspecies susceptibility, and the mechanism by which CAD shows its action can influence their accumulation in lysosomes, which may take a few minutes or hours (Halliwell 1997; Salata et al. 2017). The intracellular accumulation of phospholipids induced by drugs shows adverse side effects, but the association between drug-based phospholipid accumulation and adverse effects cannot be explained (Liscovitch and Laviey 1991). Mazzaglia et al. (2003), studied an amino-group customized and amphiphilic cyclodextrin complex, which produced aggregation with porphine ligand, a widely used in water-soluble photosensitization (Mazzaglia et al. 2003). Consoli et al. (2018), reported polycationic calix(4) are new amphiphiles, forming assemblies in aqueous solutions (Granata et al. 2017; Bari et al. 2016). Cationic amphiphiles and supramolecules are speedily cleared by circulation and show a greater ability to uptake cells (Blanco et al. 2015). There are specific challenges for the development of these amphiphilic drug delivery systems. Firstly, rare models tested stabilities in addition to target abilities in vivo. Secondly, long-term toxicities of macrocyclic cationic amphiphiles are still now not discovered. On the way to deal with these above concerning facts, interdisciplinary research in all scientific disciplines is needed.

11.2 Cationic Amphiphilic Molecules (CAMs)

CAM is designed to conflict speed rise in drug-resistant bacteria. The design targets the structural integrities of the bacterial membrane, leading towards cell rupture and death. The discrete characteristics of CAMs were wide-ranging; structural activity relations were executed to direct rational designs on potential antimicrobials by desired selectivity and cytocompatibility. Mainly, the effects of CAMs show conformational flexibilities, hydrophobic domain flexibilities, as well as hydrophobic domain architectures. So, CAMs' influences on the antimicrobial efficiencies of Gram-positive and Gram-negative bacteria were determined; the safety profile was created via their impact on the mammalian cells. Every CAM has various potential activities against bacteria, hydrophobic sphere rigidity, and structural designs that contribute to their specificities (Kobisy et al. 2021; Dahlin et al. 2021).

Several therapeutically effective as well as clinically valuable drugs are possibly categorized as CAM drugs**.** Their classifications are based on physicochemical

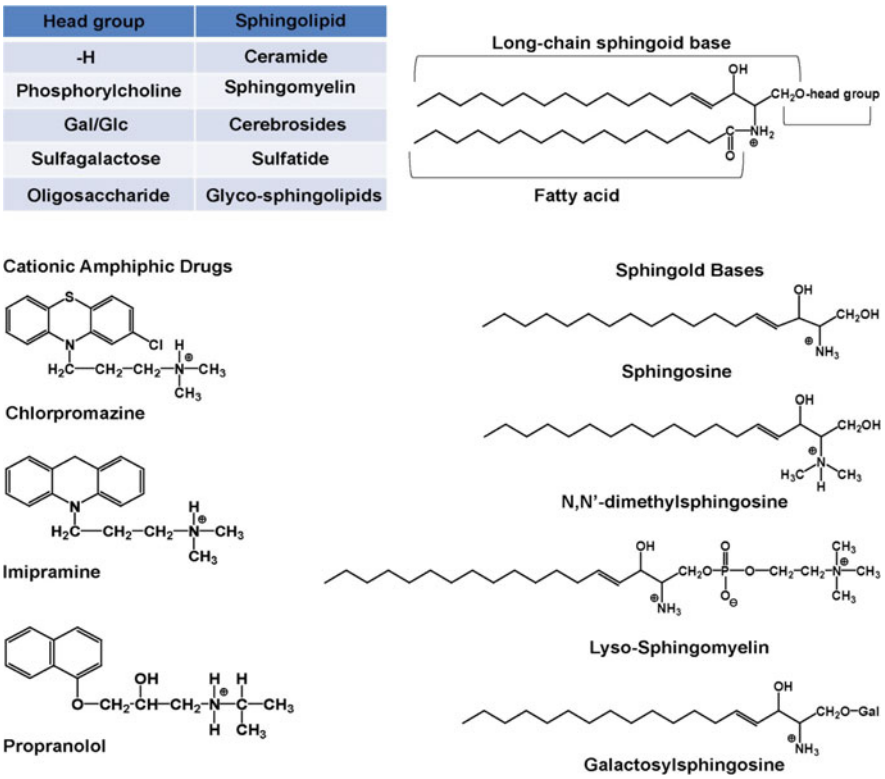

Fig. 11.1 Structures of innovative cationic amphiphilic drugs (CADs). (Liscovitch and Laviey 1991)

properties. In a group, CAM drugs are divided into two specific domains: hydrophobic (i.e., aromatic) spheres with ionizable nitrogen, which is capable of being converted into positive charge atoms (Fig. 11.1).

11.2.1 Natural Cationic Amphiphilic Molecules

Naturally occurring CAM and associated ionic liquids form diverse antibacterial agents, currently validated for preclinical and clinical treatment via antimicrobial resistive bacteria (Kundu 2020). Several studies with cyclic, diastereomers, linear CAM maintained hypotheses with physicochemical properties that are dependable for microbiological activities. It is assumed topologies of CAM are vital for insertion as well as disruption of cytoplasmic membranes. Particularly, the ability to kill bacteria and the difficulties in which bacteria develop resistance make CAMs an attractive target in drug development. However, therapeutic uses in CAMs are hampered due to high manufacturing rates, poor pharmacokinetics, and low bacterial

effectiveness in animal studies. Sequentially, to surmount the problems, various novel and structurally varied CAMs which mimic amphiphilic topologies have in recent times developed. Cationic peptide amphiphiles are a promising stage for the development of novel antimicrobials which can toil as the nanocarriers can be used in synergistic antibacterial therapy (Tague et al. 2019; Almeida et al. 2019; Weeks et al. 2019). In 2014, Kabir-Ud-Din et al. (Yaseen et al. 2014) studied the binding interaction of CAM, which acts as a drug with DNA; absorption studies proved the stabilization of energy levels. In 2018, Joris et al. (2018) demonstrated that cationic amphiphiles (CAM) acting as drugs could be repurposed for the stimulation of lysosomes for siRNA in cancer cells (Joris et al. 2018). Many compounds display finer pharmacokinetics and lower in vitro toxicities by preserving strong antibacterial activities that are hostile to resistant and nonresistant bacteria.

In conclusion, CAM promises soon to provide a novel source of diverse antibacterial compositions. The sphingoid base with amino bases constitutes strength in every sphingolipid (shown in Fig. 11.1). Natural CAMs, also known as sphingoid bases, vary in isomeric configurations, the occurrence of a double bond, the extent of aliphatic chains, and N-methylation group existence. Hopefully, this application can stimulate more research by naturally and synthetically exploring further biochemical processes affected by CAM drugs.

The activity of sphingoid bases in biological modifiers was adequately demonstrated in the latest researches, to appreciate the metabolism of sphingoid bases and their task in cell physiology along with cell pathology (Santajit and Indrawattana 2016).

11.2.2 Synthetic Cationic Amphiphilic Molecules

We present here in this chapter new versatile synthetic strategies for CAM which show tunable amphiphilicity. It is derived from reactive crosslinked precursor molecules, which provide a stage for secondary functionalization by hydrophilic and hydrophobic particles. Since hydrophilic moiety with changeable amphiphilicity instigates from the same precursor, it, therefore, shows related particle size, size distribution, and homogeneous morphology. Consequently, our explanation represents an innovative type of CAM nanocarrier that combines with biocompatible hydrophilic moieties to transport the hydrophobic cargoes (Charrueau and Zandanel 2016; Mura et al. 2013). In 2020, Anje Dong et al. (Zhao et al. 2020) showed how CAM polymers that mimic antimicrobial peptides show excellent antibacterial activity. In 2017, Mark W. Grinstaff et al. (Prata et al. 2018) highlighted the role of size, charge, hydrophobicity, and compaction in the binding of DNA-CAM polyester dendrimer complexes, resulting in improved transfection efficiency. In 2021, Herve Javelot et al. (Xu et al. 2021) proposed that antihistamines and CAM together show varied protective effects against SARS-CoV-2 in patients with mental health disorders. In 2021, Fangong Kong et al. (Yuan et al. 2021) studied lignin-based CAM surfactant properties by amine methylation, ketamine condensation with

alkali lignin acting as raw material. Concluding, alkali lignin can be used as a CAM surfactant in W/O emulsifiers. Therefore, lignin-based CAM surfactants will show immense application prospects shortly soon. Further, Jingcheng Hao et al. (Sarkar et al. 2021) showed the amphiphilicity of the copper nanocluster by tuning the electrostatic interactions with CAM will find applications in light-emitting diodes (LEDs).

Presently, much attention is paid to the organic synthesis catalyzed by ionic liquids (ILs) (Pajuste et al. 2011; Mantarosie et al. 2008; Navajas et al. 2008). According to literature, numerous pyridinium ILs are successfully used as catalysts in various reactions (Wei et al. 2015; Hyvönen et al. 2002). Physicochemical properties of pyrimidine-based CAM were analyzed for their antiproliferative plus antitubercular behavior (Samarkina et al. 2017; Liu et al. 2007; Haldar et al. 2005). D. H. Dagade et al. (Luczak et al. 2010) studied the influence of protic ionic liquids on peptide solvation based on H-bonding, hydrophobicity, etc. and observed the superior ionic-hydrophobic and hydrophobic-hydrophobic interactions. Gabdrakhmanov et al. (Palermo et al. 2012) studied the cationic amphiphiles' behavior with imidazole-based ionic liquids, showed their aggregation properties, and proved their potential in the field of biotechnologies. Fridman (Grenier et al. 2012) reported cationic amphiphiles in the presence of light-induced isomerization could act as antimicrobial drugs. Among various CAMs, surfactants from the imidazolium group deserve special attention. Adjacent to that, imidazolium-based CAM is appropriate for various biotechnological uses: their antibacterial property is reported in the literature (Kunal et al. 2021; Mohammadi et al. 2015) in addition to successful attempts at production of sustainable nanocontainers. CAM drugs engaged clinically to treat a range of disorders; the prospect arises of exogenously controlled sphingoid bases (as well as their synthetic derivatives), which also show comparable therapeutic results. In support of evident reasons, research in pharmacokinetics in vivo is still below structural modifications (Santajit and Indrawattana 2016). CAM drugs that target the enzymes involving whichever sphingolipid hydrolysis or else sphingoid base utilize possibilities towards clinical benefits.

The development of bacteria-resistant strains is of global concern regarding health issues. Scheming antibiotics limiting the rise of pathogen resistance is therefore necessary to treat pathogenic infections. Self-assembling CAMs are a fascinating platform to treat pathogens owing to their capacity to interrupt bacterial membranes and function like drug nanocarriers. Specially designed peptides (CAMs) that form micelles, twisted ribbons, nanofibers, etc., aim to perceptive antimicrobial activities at the supramolecular level. It has been studied by scientists that micelle-forming CAM peptides possess brilliant antimicrobial activities against a variety of Gram-positive and Gram-negative pathogens, for example, MRSA, multidrug-resistant *Klebsiella pneumonia*, and *Pseudomonas aeruginosa* with (MICs) range 1–8 μg/mL, in contrast to the nanofiber which has (MIC>32 μg/mL). All reported records suggest that antimicrobial activities in CAM peptides depend on morphologies, length of alkyl chains, amino acid sequence, and overall hydrophobicity. Various experimental and spectroscopic techniques using MRSA and *E. coli* showed CAM increases cell membrane permeability plus dislocates

integrity of the pathogen membrane, which leads to cellular lysis and, finally, death. (CAMs) peptides are the most promising platforms to build novel antimicrobials that might act like nanocarriers to develop synergistic antibacterial therapies.

11.3 Antibacterial Actions of the CAM Drug Molecules and Mechanism

CAM is generally evaluated for its antibacterial efficacy adjacent to both Gram-positive and Gram-negative bacteria. MIC determines antibacterial activities of the test agent against a specific bacterium (Darya et al. 2017). Assays are carried out by the micro broth dilution technique, and the lowest concentration of the subjected CAM results is noted by seeing the bacterial growth. According to the literature, most CAMs show MICs in proper therapeutic ranges between 15 and 50 μg/mL (Darya et al. 2017; Lind et al. 2015; La Dow et al. 2011; Rotem and Mor 2009; Delcour 2009; Brogden 2005). Conformational flexibilities of cationic head group have less influence on the antibacterial efficacy in experimented pathogens. The increased flexibility of CAM may result in electrostatic repulsions, thereby avoiding simultaneous interactions with a negative charge constituent of the bacterial membranes. So, these results indicate CAM membrane disruption is ruled by electrostatic interaction at the short-charged linker length while at the long linker length; hydrophobic interaction controls hydrophobic domain flexibility (Palermo et al. 2012; Shai 2002; Dagan et al. 2002; Wieprecht et al. 1997; Chikindas et al. 1993). Vemula et al. (Sunnapu et al. 2020) suggested a simple model membrane with a high concentration of antibacterial headed for membrane damages. It provided a preliminary estimation of the potential effectiveness of the studied CAM. The authors (Petaccia et al. 2016) mentioned that liposome-based forms could be used for future studies to improve understanding of the interaction between membranes and CAM (Zana and Xia 2003); one of the leading emergent parts of CAM is the Gemini surfactant in pharmaceutical applications. Interactions of CAM with oppositely charged cell membranes have been acknowledged for several years (Kronberg et al. 2014). However, CAM Gemini surfactants curved to be incredibly capable as bacterial and antimicrobial agents (Mittal and Bothorel 1986). Furthermore, current research in this area indicates the cancerostatic phenomenon of CAM Gemini, during selective interactions in CAM Gemini surfactant by cancer cells (Sharma and Ilies 2014; Misra et al. 2013; Moroi 1992; Porter 1991). An additional revolutionary area in research of CAM Gemini interaction with oppositely charged electrolytes like DNA has importance with respect to gene transmissions through the cell membrane to attain therapeutics within the nucleus (Tague et al. 2019; Pietralik et al. 2015; Hoque et al. 2014; Paniak et al. 2014; Silva et al. 2014; Badr et al. 2010; Moroi 1992; Taft 1952).

(CAM) drugs, also known as cationic amphiphilic drugs (CAD), interrelate with the cell membrane and gather inside the acidic medium intracellular compartments,

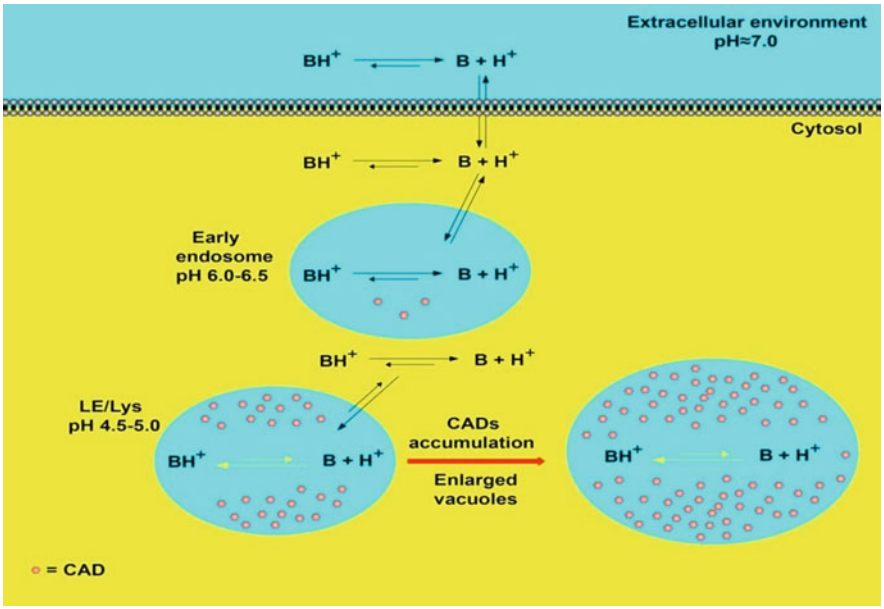

Fig. 11.2 Lysosomal trapping of CADs acting as weak bases (B) as well as cumulates in the intracellular acidic section since lysosomal membranes are to a large extent lesser permeable to protonated base (BH+) in comparison to the uncharged structure. Growths in CADs within late endosomes/lysosomes (LE/Lys)) induce arise in organelles, thereby creating large vacuoles. (Salata et al. 2017)

such as late endosomes or late lysosomes (LE/Lys). So, cellular uptake methods vary among different CADs. Indeed, they collect in (Lys) specific time intervals following in vitro cell exposition, resulting in more diverse kinetics from chemical to physical distinctiveness of the particles. The amine group of CAD is mostly unprotonated at physiological pH. The molecules turn out to be protonated inside the acidic medium of (LE/Lys), since CAD can't further permeate the membrane; they are rapt within the organelle (shown in Fig. 11.2). Many CADs illustrated stimulating phospholipidosis therapeutically, on significant concentrations following chronic treatment (Salata et al. 2017). Though CADs in clinical use are endured, changes in cells are held as a result of the interaction among CADs by the membrane phospholipids. Abilities of precise CAD induced phospholipidosis erstwhile connected with the potency of (drug/phospholipid) interaction. Thus CADs also cross multiple cell membranes to arrive at their target site via catalytic reaction by degrading phospholipid. So, we can find CADs screen to the polar–apolar section of the membrane. At a definite pH, the positive group on the CAD is catalyzed by acid hydrolysis. So, the entire processes, from CAD adsorption to the controlled drug release inside the micelles, occur lying on the particular time-balance by in vivo diffusion rate. So, this process may act significantly on CAD transport (Baciu et al. 2006).

Many researchers have already reported in vitro special antimicrobials (shown in Table 11.1), but less information is known regarding in vivo toxicities. So, further in vivo studies are required sequentially towards understanding (CADs) therapeutic efficacies. Another concerning point in the development of antimicrobial studies is the deficiency of standard experimental procedures. This permits consistent clinical studies to provide information on coating stability and its efficacies, which will cause myriads of innovations (Li et al. 2018; Huang et al. 2016; Hsu and klibanov 2011).

11.4 Synthetic Cationic Amphiphiles in Combination Therapy

Antibiotic resistance is a serious global issue which, without delay, needs efficient solutions. Though small molecules (CADs) are protecting us for almost a century, the emergence of a novel class of antimicrobial drugs also known as synthetic antimicrobial polymers has driven advances in the polymerization as well as the ability to mimic the natural occurrence of antimicrobial peptides which could play a vital role in fighting multidrug-resistant bacteria at future. In exploiting the abilities by controlling chemical as well as structural properties of polymers, the synthetic antimicrobial polymeric materials formed initially from (CADs) could be strategically used in the combination therapies of diverse antimicrobial co-agents with the diverse format to capitulate extra powerful (synergistic) results (Judzewitsch et al. 2018, 2020; Namivandi-Zangeneh et al. 2020; Chandna et al. 2020; O'Neill 2020; Song et al. 2012). Acceptance of the combination therapies in other settings suggests recital efforts by academicians, research funding bodies, international health agencies, governments, regulators, and pharmaceutical manufacturers makes it available at affordable prices worldwide. It is expected that widespread use of the combination pills with routine modifications can bring about substantial risk reductions in several diseases (mainly heart problems). Healthcare systems require deploying strategies efficiently. If implemented, these combination therapy strategies could thereby avoid millions of fatal as well as non-fatal events.

11.5 Challenges and Future Perspectives

Synthetic small-molecule antibacterial peptidomimetics (AMPs) represent a promise in the innovative field of potent antibiotics. AMPs are found in a broad assembly of organisms that protect against pathogens. They are naturally CAMs, which have essential amino acids and hydrophobic side chains. The cationic group shows electrostatic attraction with anionic bacterial membranes, whereas the hydrophobic group gets inserted into the lipophilic core; this eventually leads to the disruption of the bacterial membrane and cell death (Chen et al. 2021; Tague et al. 2021; Mauceri

Table 11.1 Categories of cationic surfactants (CAM) identified in the literature and bacteria involved show various applications presently under preclinical and clinical trial phase

Sl no	Cationic surfactants	Microorganisms involved
1	Rhamno lipids, Vicosin (Araújo et al. 2018; Yazdany and Kazi 2016)	*Pseudomonas aeruginosa, Pseudomonas fluoroscens, Pseudomonas* sp *DSM 2874, Pseudomonas aeruginosa Strain BS2, Pseudomonas aeruginosa DS 10-129 4.31*
2	Trehalose lipids (Ratnikova and Titok 2020; Varjani et al. 2020; Nikolova et al. 2020; Mawgoud and Stephanopoulos 2017)	*Arthrobacter* sp., *Mycobacterium, Corynebacterium, Rhodococcus erythropolis*
3	Glucose lipids (Li et al. 2021)	*Bacillus subtilis*
4	Glycolipids Glycolipids (Pentasaccharide lipids) Sucrose and Fructose Glycolipids (Jana and Kulkarni 2020; Vacca 2017; Brundish et al. 1966)	*Alcanivorax borkumensis, Pseudomonas cepacia, Streptococcus thermophilus, B, Rhodococcus aurntiacus, Rhodococcus* sp. *Strain H13A, Rhodococcus aurantiacus (or R. aurantiacus), Nocardia coryne bacteroides, Arthrobacter paraffineus*
5	Triacylglycerols, steryl esters and wax esters: Neutral lipids, fatty acid + neutral lipids Fatty acids (Holert et al. 2020; Kalscheuer et al. 2007)	*Clostridium pasteurization Corynebacterium salvonicum SFC Nocardia erythropolis Corynebacterium lepus*
6	Acyl glucoses (Haozhe et al. 2020)	*Corynebacterium diphtheriae*
7	Surfactin peptides (Wu et al. 2019)	*Bacillus subtilis*
8	Iturin peptides (Zhao et al. 2021)	*Bacillus subtilis*
9	Fengycin peptides (Yaseen et al. 2018)	*Bacillus subtilis*
10	Viscosin peptides (Bonnichsen et al. 2015)	*Pseudomonas fluorescens*
11	Lichenysin peptides (Coronel et al. 2017)	*Bacillus licheniformis*
12	Serrawettin peptides (Zhang et al. 2021)	*Serratia marcescens*
13	Streptofactin peptides (Crnovčić et al. 2018)	*Streptomyces tandae*
14	Lipo peptides (Sardar et al. 2021)	*Bacillus subtilis, Bacillus licheniformis JF2, Bacillus licheniformis 86, Serratia marcescens, Bacillus subtilis 2.7, Bacillus subtilis ATCC 21332, Bacillus subtilis LB5a*
15	Phospholipids Protein phospholipids (Noba et al. 2019)	*Corynebacterium lepus, Acinetobacter* sp., *Corynebacterium insidiosum*
16	Gramicidins Gramicidin S (deca peptide) (Wenzel et al. 2018)	*Brevibacillus brevis*
17	Polymixins Polymyxin D (deca peptide) (Galea et al. 2017)	*Bacillus polymyxa*
18	Antibiotic TA (Heil et al. 2021)	*Myxococcus xanthus*
19	Corynomicolic acids (Aisaka et al. 2007)	*Corynebacterium insidibasseosum*
20	Emulsan based CAM Lipoteteropolysaccharide (Amani and Kariminezhad 2016)	*Acinetobacter calcoaceticus Acinetobacter calcoaceticus RAG – 1*

(continued)

Table 11.1 (continued)

21	Alasan-based CAM (Navon-Venezia et al. 1995)	*Acinetobacter radioresistens*
22	Liposan-based CAM (Steinmassl et al. 2018)	*Acinetobacter calcoacetices*
23	Lipomanan-based CAM (Steinmassl et al. 2018)	*Acinetobacter calcoacetices*
24	Vesicle-based CAM (Villalón et al. 2019)	*Acinetobacter calcoaceticus*
25	Microbial whole-cell biosensors (MWCBs) (Michael Moraskie et al. 2021)	*Cyanobacter*
26	Phosphatidyl ethanolamine CAM (Tsubaki et al. 2021)	*Acinetobacter* sp.
27	Lipopolysaccharides (Nikolay et al. 2010)	*Acinetobacter* sp.
28	Polysaccharide-protein-based CAM, Protein-lipid-carboxy-based CAM, Sucrose ester -based CAM (Li et al. 2019)	*Corynebacterium hydrocarboclastus*
29	Corynomycolic acid, fatty acid (Cooper et al. 1979)	*Corynebacterium lepus*
30	Ornithin-based CAM (Nigro Di Gregorio et al. 2017)	*Pseudomonas rubescens, Thiobacillus thiooxidans*
31	Trehalosedimycolates (Zhang and DeBosch 2020), Trehalose (mono and di) corynomycolate, Phosphatidyl ethanolamine	*Rhodococcus erythropolis*
32	Rubiwettins R1 and RG1 (Matsuyama et al. 1990)	*Serratiarubidae, Serratiarubidoea*
33	Protein Carbohydrate complex (Ghosh et al. 2019)	*Pseudomonas fluorescens*
34	Methyl mannosylerythritol lipid (Okuhira et al. 2020; Mohamed et al. 2018)	*Streptococcus bovis*, *Fibrobacter succinogenes*, *Ruminococci, Megasphaera elsdenii*, *Selenomonas ruminantium, Succinivibrio dextrinosolvens*
35	Gemini surfactant Gemini pyrimidine CAM (SPYRIT 68, SPYRIT 7) (Koziróg et al. 2017; Zhao and Wang 2017)	*Gram-positive* sp *(S. aureus)*, *Asaia* sp.
36	Methyl imidazolium-based CAM (mim-based IL), Dicationic imidazolium surfactant (Daniel et al. 2021; Liu et al. 2016)	*Escherichia coli, Staphylococcus aureus, P. aeruginosa, S. epidermidis*
37	Lauryl isoquinolinium-based CAM (Yu et al. 2021)	*Escherichia coli*, *B. cereus*
38	Quaternary ammonium-based CAM (QASs) (Borkowski et al. 2018)	*Escherichia coli*
39	Nucleotides, nucleosides, nucleolipids, amino acids, lipo–amino acids, diterpenoids (i.e., natural CAM) (Borkowskia et al. 2018)	*Bifidus* sp., *E. coli, P. gingivalis, Streptomyces Iysosuperficus, Pseudopedobactersaltans, Cyanobacteria*
40	Pyrimidinophanes, pyrimidinocyclophane, multiuracilophane, cryptand-like uracilophane, pyrimidinicamphiphiles (Kumar et al. 2021)	*Escherichia coli, Bacillus subtilis, Mycobacterium tuberculosis (MTB), Neisseria meningitides*

(continued)

Table 11.1 (continued)

41	Gemini lipoaminoacids alkylated lauryl arginine-based liposomes (Gemini analogs) Lysine-based lipoaminoacids Serine-based lipoaminoacids (Azimullah et al. 2020; Pavlov et al. 2020)	*Escherichia coli, Salmonella typhimurium, Azospirillum lipoferum 4B, Bacillus subtilis*
42	Cholesterol (Chol)-based CAM (Araya et al. 2019; Jameson and Wilkinson 2017)	*Escherichia coli, Bacillus subtilis*
43	Arginine-based QACs (Cairns 1980), Alkylated arginine (LAM), Gemini alkylated arginine (C6(LA2) micelles, C9(LA2), C12 (LA2) vesicles, diacylglycerol Arg vesicles (Elwakeel et al. 2018; Savoini et al. 1984)	*Enterobacter lignolyticus, Escherichia coli*
44	Alanine (Gemini-ester-QAC-surfactant) (de Camargo et al. 2017)	*Pseudomonas striata 63, Salmonella typhimurium, Streptococcus faecalis, Staphylococcus aureus, Bacillus stearothermophilus*
45	Lysine-CAM in liposomes (Uyeda et al. 2016)	*E. coli*
46	Serine-gene delivery CAM systems (Mukherjee et al. 2019)	*E. coli, Aeromonas salmonicida, Vibrio alginolyticus*
47	CTAB for insulin delivery (Robeson et al. 1983)	*Escherichia coli, Streptococcus mutans*
48	Di-oleoyl-phosphatidyl-ethanol-amine (DOPE) (Wu et al. 2016)	*Escherichia coli*
49	Di-acyl-glycerol-arginine (Brunello and Marshall 2018)	*Staphylococcus aureus*
50	Di-palmitoyl-phosphatidyl-choline (DPPC) (Thanh et al. 2018; Apisarnthanarak et al. 2017)	*Acinetobacter baumannii, Staphylococcus aureus, Bacillus cereus, Brochothrix thermosphacta*
51	Di-dodecyl-dimethyl- ammonium-bromide (DDAB) (Laalami et al. 2021; Zhou et al. 2020)	*E. coli, Bacillus subtilis*
52	Cetylpyridinium chloride (Pardini et al. 2005)	*Staphylococcus aureus*
53	Diamidequat-based CAM (Im et al. 2019)	*Bdellovibrio bacteriovorus HD100*
54	4-Vinyl-benzyl-phospholipids, Dexamethasone-21-di-sodium-phospholipids (Konuray and Erginkaya 2018)	*Bacillus coagulans*
55	Benzalkonium chloride, Cetalkonium chloride (Forbes et al. 2019)	*Enterococcus faecalis, Escherichia coli*
56	Dopamine hydrochloride acetylcholine chloride, 1-Tetradecyl-3-methylimidazolium bromide (Mahajan et al. 2012)	*K. pneumonia, Bdellovibrio bacteriovorus HD100, Vibrio fischeri*
57	Tryptophan-213-based CAM (Huang et al. 2012)	*E. coli*, *B. cereus*
58	Di-myristoyl-phosphatidyl-choline (DMPC) (Taleb et al. 2016)	*E. coli, S. aureus*

(continued)

Table 11.1 (continued)

59	Bola-form analogue CAM (Orellana et al. 2017)	*Enterobacter lignolyticus*
60	1,4-Di-aza-bicyclo(2.2.2)octane-based CAM (DABCO-n series) Quinuclidine (Q-Nuc-n) (Burilova et al. 2018)	*E. coli, B. aureus*
61	Di-alkyl-amino and nitrogen analogue of hexa-decyl- phospho-choline (Amino and Suzuki 2017; Kurosawa et al. 2017)	*Enterobacter lignolyticus*
62	Di-butyl-amino-based analogue of CTAB (Taleb et al. 2016)	*E. coli, S. aureus*

et al. 2020). There are certain limitations in AMPs because of their in vivo toxicity, high industrialized costs, and susceptibility to the metabolism of proteases. Latest developments in the small molecular AMPs eliminate all limitations; for example, LTX-109, via Lytix Biopharma has already finished (Phase 2) clinical trials of MRSA. Small molecular AMPs show a positive correlation between antibacterial activities and cytotoxicity for on-selective disrupting membrane abilities, suitable for antimicrobial drugs. Further elucidation of vital constituents can cover a broad spectrum of antibacterial efficacy and membrane selectivity, thereby designing potent, selective small AMP mimics in chemotherapeutic agents.

Among the reported antimicrobial (CAM) compounds with high drug-resistant pathogenic activity, some can cause minor damage to the membranes of mammalian cells. The cases presented in this assay suggest synthetic antimicrobial (CAM) may ultimately be highly effective and safer for treating topical, systemic infections; however additional studies are required to attain this goal.

11.6 Conclusions

Bacterial infections can cause various life-threatening diseases and have been developed into severe public health problems by drug-resistant strains. As a result, novel antibiotics with brilliant antibacterial activity and low cytotoxicity are urgently required. Electrostatic interactions caused by the cell membrane of bacteria interference are trailed by cellular component leakage and cell death. Due to bacterial remarkable cell damage, AMPs emerged as valuable against drug-resistant bacteria proved more effective than other classical antibiotics in definite cases. Moreover, structural complexity deprived pharmacokinetic property; low antibacterial activity of AMPs hinders progress in their development. So, researchers took more interest in the modification of it and synthetic AMPs.

Nevertheless, it is crucial to build up complex carriers which are tunable and simpler for industrial scale. To expand application in a domain for specified delivery, two essential factors are required: (1) synthetic peptides to influence pathogens and (2) through design prevention of the production of toxic synthetic peptides.

Together, these two factors can develop novel technologies for synthesis and innovative design strategies at a small price. Therefore, it is necessary to enhance the discovery of potent antimicrobial therapeutic peptides for target bacteria, fungi, viruses, helminths, and protozoa.

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